

Telavancin

Briefing Document

Telavancin for the Treatment of Complicated Skin and Skin Structure Infections

Anti-infective Drugs Advisory Committee

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Theravance, Inc.

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ABBREVIATIONS USED

AE	adverse event
AM	alveolar macrophages
APD	action potential duration
ARF	acute renal failure
ATCC	American Type Culture Collection
AT Population	all-treated population
AUC	area under the concentration-time curve
BMI	body mass index
BUN	blood urea nitrogen
CDC	Centers for Disease Control and Prevention
CE Population	clinically evaluable population
CI	confidence interval
CFU	colony forming unit
CoNS	coagulase-negative staphylococci
COPD	chronic obstructive pulmonary disease
CrCl	creatinine clearance
cSSSI	complicated skin and skin structure infections
DNR	do not resuscitate
ECG	electrocardiograph
ELF	epithelial lining fluid
EOT	end-of-therapy
HAP	hospital-acquired pneumonia
HIV	human immunodeficiency virus
hVISA	heterogenous vancomycin-intermediate <i>Staphylococcus aureus</i>
IND	Investigational New Drug (application)
IV	intravenous
LOS	length of stay
MAT Population	modified all-treated population
ME Population	microbiologically evaluable population
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
MSSA	methicillin-sensitive <i>Staphylococcus aureus</i>
NDA	New Drug Application

ABBREVIATIONS USED (CONT'D)

PK/PD	pharmacokinetic/pharmacodynamic
PCS	potentially clinically serious
PVL	Panton-Valentine leukocidin
R	resistant
S	susceptible
SAE	serious adverse event
SAP	statistical analysis plan
TOC	test of cure
TLV	telavancin
US	United States
VAN	vancomycin
VISA	vancomycin-intermediate <i>Staphylococcus aureus</i>
VRE	vancomycin-resistant enterococci
VSE	vancomycin-susceptible enterococci
VRSA	vancomycin-resistant <i>Staphylococcus aureus</i>
VSSA	vancomycin-susceptible <i>Staphylococcus aureus</i>

SUMMARY

Telavancin is a bactericidal lipoglycopeptide antibiotic with a unique multifunctional mechanism of action that includes inhibition of bacterial cell wall synthesis and disruption of the functional integrity of the bacterial membrane. Telavancin was developed in response to the need for novel antimicrobial agents to address the challenge of treating resistant Gram-positive bacteria – specifically methicillin-resistant *Staphylococcus aureus* (MRSA).

The telavancin discovery program focused on identification of a compound with a novel mechanism of action, greater potency than glycopeptides, activity against Gram-positive pathogens resistant to or with reduced susceptibility to available antibiotics, and a convenient dosing regimen. The initial indication for telavancin is complicated skin and skin structure infections (cSSSI), to be followed by hospital-acquired pneumonia (HAP), due to Gram-positive pathogens. The current submission is for cSSSI, which is the primary focus of this Briefing Document.

Telavancin is active against nearly all clinically relevant Gram-positive pathogens: staphylococci (including methicillin-resistant and vancomycin-intermediate strains), streptococci (including multidrug-resistant pneumococci), enterococci (including many vancomycin-resistant strains), Gram-positive anaerobes such as clostridia (including *C. difficile*), and other less commonly encountered pathogens. Telavancin also retains activity against strains of *S. aureus* and *Enterococcus* spp. that are nonsusceptible to daptomycin or linezolid.

To date, neither in vitro passaging studies nor evaluation of clinical isolates from patients exposed to telavancin for as long as 21 days have revealed evidence of the development of resistance to telavancin. These data indicate that there is a low potential for the emergence of resistance to telavancin, possibly as a result of the multifunctional mechanism of action. Although some vancomycin-resistant enterococci have reduced susceptibility to telavancin, there is no known cross-resistance between telavancin and other classes of antibiotics.

Telavancin exhibits linear, predictable pharmacokinetics, with good penetration into skin and lung tissue. The potency, half-life, and postantibiotic effect of the drug allow for once daily

dosing. Telavancin is cleared primarily by the kidneys. Therefore, dosage adjustment is recommended for patients with renal impairment (creatinine clearance \leq 50 mL/min).

The cSSSI Phase 3 program consisted of two randomized, multinational, double-blind studies conducted under identical protocols. Combined, the studies enrolled a total of 1867 adult patients, 719 of whom were infected with MRSA. The design of these studies followed applicable regulatory guidance, meeting the requirements for a suitable control agent and for assuring that patients had cSSSI. The telavancin program included the largest subset of patients infected with MRSA to date.

The studies demonstrated that telavancin 10 mg/kg IV q 24 hours for 7 to 14 days is as effective as a current standard of care, vancomycin, in treating patients with cSSSI caused by susceptible strains of Gram-positive pathogens. The results of the primary efficacy endpoint, Clinical Response at the Test-of-cure (TOC), in the coprimary All-treated (AT) and Clinically-evaluable (CE) analysis populations consistently showed that telavancin is noninferior to vancomycin in patients with cSSSI, using a noninferiority margin of 10%. The lower bound of the 95% confidence interval (CI) of the treatment difference between telavancin and vancomycin in both coprimary analysis populations in each study was greater than -6%. When data for the two studies were pooled, the lower bound of the 95% CI for the treatment difference was greater than -4% in both the AT and CE populations (Figure 9). A prespecified objective of the cSSSI program was to analyze the pooled data from Studies 0017 and 0018 to test whether telavancin 10 mg/kg is superior to vancomycin in the treatment of cSSSI due to MRSA. In this analysis, telavancin did not demonstrate statistical superiority over vancomycin. However, the clinical, microbiologic, and overall therapeutic response rates were consistently numerically higher in the telavancin group in both analysis populations.

Two additional Phase 3 trials of telavancin, conducted in patients with hospital-acquired pneumonia (HAP), have been completed. Preliminary data have been submitted to the FDA. Like the cSSSI studies, the two HAP studies were conducted under identical protocols and were large, randomized, multinational, multicenter, double-blind, and active-controlled, comparing telavancin administered at a dose of 10 mg/kg IV every 24 hours (or at a reduced dosage in patients with moderate or severe renal impairment) with vancomycin. As in the cSSSI studies, the primary endpoint in the HAP studies was clinical response at TOC in the

AT and CE populations. A total of 1503 patients were enrolled and treated. Each of the HAP studies demonstrated noninferiority of telavancin compared with vancomycin. These data are also supportive of the safety of telavancin. The focus of this briefing document is on the studies in cSSSI. Where relevant and available, limited data from the HAP studies have been referenced to provide information on an additional population of patients treated with telavancin.

In the cSSSI studies, common adverse events were almost always mild or moderate in severity. Like vancomycin, telavancin is associated with renal adverse events. While renal adverse events were infrequent in the cSSSI studies, they occurred in more patients receiving telavancin (3.4%) than vancomycin (1.2%) and were associated with the presence of baseline comorbidities (e.g., heart failure, abnormal blood pressure, kidney disease, etc.) that increase the risk for renal impairment. Renal function should be monitored in all patients receiving telavancin. In considering the use of telavancin in patients with moderate or severe renal impairment or with underlying conditions predisposing to kidney dysfunction, the possible risks of telavancin should be weighed against the potential benefits.

Telavancin also causes a QT prolongation, but the prolongation is half of that observed in a controlled comparison with another drug (moxifloxacin) that is indicated for cSSSI and for other, less serious infections.

In nonclinical developmental studies there were minor fetal effects. After reviewing the data from all developmental studies, an independent expert concluded that the primary evidence of an adverse developmental effect was a reduction in litter weight in a study in rats and that there was no clear evidence of teratogenicity in any of the developmental studies. After evaluating the few observed limb defects, he noted that there was no embryologically coherent mechanism by which a common malformation syndrome could be postulated to have been caused by telavancin. Proposed labeling for the product advises that there are no adequate and well-controlled studies in pregnant women and that telavancin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Telavancin offers an important addition to the therapeutic armamentarium for the treatment of serious infections due to resistant Gram-positive pathogens, particularly MRSA. With appropriate consideration of the potential risks in individual patients and the use of renal

function monitoring in all patients, benefits of telavancin outweigh the risks for the treatment of cSSSI caused by susceptible strains of the following Gram-positive microorganisms: *S. aureus* (including methicillin-resistant strains [MRSA]), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius* and *S. constellatus*), and *Enterococcus faecalis* (vancomycin-susceptible isolates only).

Regulatory History of the Application

An NDA for telavancin for the treatment of cSSSI was submitted in December 2006. In October 2007 FDA issued an Approvable Letter citing the following: unresolved regulatory compliance issues at the product's contract manufacturing facility, outstanding financial disclosure forms for three investigators, several points impacting the benefit to risk assessment of the product, a request for information regarding isolates with differential sensitivity to telavancin and vancomycin, and a request for comment on the appropriate use of telavancin in pregnant women. In January 2008, Theravance submitted a response to the issues cited, and the response was accepted as complete in March 2008. The additional information provided in that response has been included in this Briefing Document in the respective sections.

Review of telavancin by the Anti-infective Drugs Advisory Committee was previously scheduled for February 2008. That meeting was cancelled in order to allow the FDA to complete an assessment of the integrity of clinical data submitted in the NDA prior to FDA presentation of those data to the Advisory Committee. That assessment was completed in September 2008 and, based on a simultaneous re-auditing of investigative sites by Theravance, Theravance was instructed to delete the efficacy data from three clinical sites (73 patients) and QTc data from two sites (66 patients). The analyses presented in this Briefing Document reflect these deletions. The deletions did not change the outcome of the primary endpoint or any of the study conclusions.

1 MRSA – A GROWING PROBLEM

MRSA infections are a common cause of significant morbidity and mortality

The global emergence of Gram-positive pathogens with decreased susceptibility to available therapies has become a major public health problem, with *S. aureus* being of particular concern. Nosocomial *S. aureus* infections are an unfortunately common occurrence. An analysis of US hospital data from 2000 and 2001 found that 1% of all patients admitted acquired *S. aureus* infections, for a total of 300,000 cases and 2.7 million excess patient-days of hospitalization per year (Noskin GA, et al. Arch Intern Med. 2005;165(15):1756–1761). Most *S. aureus* infections in hospitalized patients are now due to methicillin-resistant strains. In 1974, methicillin-resistant *S. aureus* (MRSA) accounted for only 2% of healthcare-associated *S. aureus* reported to the Centers for Disease Control and Prevention (CDC). Today, MRSA accounts for more than 60% of *S. aureus* infections in healthcare settings (CDC).

In recent years, MRSA has become increasingly prevalent in the community. MRSA is now the most common cause of skin and soft tissue infections diagnosed in US emergency departments (Moran GJ, et al. N Engl J Med. 2006;355(7):666-674). Moreover, MRSA accounted for approximately 40% of all outpatient *S. aureus* infections in 2006 (Styers D, et al. Ann Clin Microbiol Antimicrob. 2006;5:2).

MRSA infections are associated with significant morbidity and mortality. Data from 2005 in a recent report from the CDC (Klevens RM, et al. JAMA. 2007; 298(15):1763-1771) described an active, population-based surveillance for invasive MRSA infections in nine centers from July 2004 through December 2005. A case of invasive MRSA infection was defined by the isolation of MRSA from a normally sterile body site in a resident of the surveillance area, including residents institutionalized in long-term care facilities, prisons, etc. There were 8987 observed cases of invasive MRSA and 1598 in-hospital deaths among patients with MRSA infection reported during the surveillance period. Cellulitis (along with bacteremia and pneumonia) was one of the most common conditions associated with invasive MRSA disease. The findings further documented that invasive MRSA disease does occur in persons without established health care risk factors, is associated with strains of both community and health care origin strains, and is associated with significant mortality. An accompanying editorial noted: “The rate of invasive MRSA was an astounding 31.8 per

100,000. To put this number into context, the estimated rate of invasive MRSA is greater than the combined rate in 2005 for invasive pneumococcal disease (14.1 per 100,000), invasive group A streptococcus (3.6 per 100,000), invasive meningococcal disease (0.35 per 100,000), and invasive *H. influenzae* (1.4 per 100,000). If the projection on the number of deaths (18,650) is accurate, these deaths would exceed the total number of deaths attributable to human immunodeficiency virus/AIDS in the United States in 2005.”

Compared with infections caused by MSSA, MRSA infections have also been associated with higher mortality, longer hospital stays, and increased cost of care. Engemann and colleagues reported that MRSA in surgical wounds caused a 12-fold increase in mortality versus noninfected patients and a 3-fold increase versus patients with MSSA (Engemann JJ, et al. *Clin Infect Dis.* 2003;36(5):592-598). In patients with nosocomial bacteremia, the total excess cost associated with MRSA versus MSSA has been reported to be \$29,867 per patient (Cosgrove SE, et al. *Infect Control Hosp Epidemiol.* 2005;26(2):166–174).

Methicillin-resistant *S. aureus*, especially community-acquired MRSA, is increasingly a problem in pregnant women and in the postpartum period. Laibl et al found that the rate of MRSA infections in pregnant women increased 10-fold over a 5-year period from 2000–2004 (Laibl VR. *Obstet Gynecol.* 2005;106:461–5). Nearly half the cases occurred in the second trimester, but 18% of cases occurred in the postpartum period. Almost all of the cases were skin and soft tissue infections. An increase in the prevalence of MRSA causing postpartum mastitis, often requiring hospitalization, has been reported (Reddy P et al. *Emerg Infect Dis* 2007;2:298-301; Stafford I et al. *Obstet Gynecol* 2008;112: 533-7). Postpartum infections due to MRSA are often serious and potentially life-threatening, such as wound abscess, septicemia, septic thrombophlebitis, septic pulmonary emboli, iliopsoas pyomyositis, and necrotizing pneumonia following an episiotomy infection (Stumpf PG, et al. *Am J Perinatol.* 2008;25:413-5; Sokolov KM, et al. *Obstet Gynecol.* 2007;110:535-8); Asnis D, et al. *Obstet Gynecol.* 2007;110:188; Rotas M, et al. *Obstet Gynecol.* 2007;109:533-6).

Continued evolution of drug resistance complicates management of MRSA infection

Despite the availability of approved treatments with activity against MRSA, drug resistance is a continuing concern. There are now at least seven recognized strains of MRSA that are resistant to vancomycin (VRSA) (Sievert, et al. Clin Infect Dis. 2008;46:668). More alarming are the numerous reports of vancomycin intermediate (VISA) and heteroresistant (hVISA) strains with an incidence in some centers of nearly 10% of clinical isolates (Tenover FC, Moellering RC. Clin Inf Dis. 2007;44:1208–15; Maor Y, et al. J Clin Microbiol. 2007;45:1511-1514), and widespread reports of increasing vancomycin MICs among MRSA (Steinkraus G, et al. J Antimicrob Chemother. 2007;60:788–794).

Given this vancomycin “MIC creep” among isolates of MRSA, recent data are available describing the achievability of the pharmacodynamic target for vancomycin (AUC/MIC = 345) that is associated with successful treatment of serious infections. Investigators assessed the FDA-approved dose (1 g IV q 12 hours) and a 50% higher dose (1 g IV q 8 hours) (Kuti JL, et al. Clin Microbiol Infect. 2008;14:116–23). The cumulative target attainment rate for MRSA with MICs ranging from 1 to 4 µg/mL was 25% for the standard regimen and 45% for the high-dose regimen. For organisms with MIC ≥ 2 mg/mL, the target attainment rate was zero. Dose escalation of vancomycin to 4 g per day or more has been associated with increased rates of nephrotoxicity (Lodise TP, et al. Antimicrob Agents Chemother. 2008;52:1330–36).

Finally, resistance among MRSA and enterococci has already emerged to some of the more recently introduced antibacterial agents, such as daptomycin (Boucher H, Sakoulas G. Clin Infect Dis. 2007;45:601-8) and linezolid (Besier S, et al. Antimicrob. Agents Chemother. 2008;52:1570–1572; Arias CA. J Clin Microbiol. 2008;463: 892–896).

The important need for additional antibiotics effective against MRSA

The increasing incidence and severity of MRSA infections, the frequency of treatment failure and recurrence, and the continuing evolution of drug resistance all reinforce the important need for additional antibiotics that have demonstrated effectiveness against MRSA. Over time, the need has outpaced drug development, making a treatment that is enduringly effective against resistant and insensitive strains an elusive target. To date, resistance has

emerged to each new treatment option before adequate alternatives have become available. There is a growing need for new treatments for resistant strains.

2 MRSA IN cSSSI

Complicated skin and skin structure infection caused by Gram-positive bacteria are of particular epidemiological and clinical importance because of their capacity to cause serious and life-threatening diseases in both healthy and debilitated individuals. Failure of treatment is common and is associated with significant clinical and economic burden.

Current treatment of cSSSI where MRSA is suspected or confirmed

Agents currently approved in the United States for cSSSI due to MRSA include vancomycin, daptomycin, linezolid, and tigecycline. Vancomycin is the most frequently prescribed first-line therapy for severe infections where MRSA is suspected or documented.

Failure of initial treatment for cSSSI is common. A retrospective assessment of 47,219 hospitalized patients with cSSSI in 2003 and 2004 found evidence of failure of initial antibiotic therapy in 22.8% of cases. Treatment failure was associated with a 3-fold increase in mortality, an additional 5.4 days of hospitalization and incremental per patient charges of \$5285 (Edelsberg J, Berger A, et al. Infect Control Hosp Epidemiol. 2008;29:160–169).

Recurrent infections with MRSA are also common. Miller and colleagues prospectively studied disease recurrence in patients previously treated for community-acquired MRSA skin infections. At Day 30 of follow up, the reinfection rate was reported at 33%. By Day 120, the rate exceeded 50% (Miller L, et al. Clin Infect Dis. 2007;44:483–492). Colonization likely contributes to the problem of recurrent infections. Huang and colleagues assessed the 18-month risk of MRSA infection among 209 adults identified as harboring MRSA (Wang SS, Platt R. Clin Inf Dis. 2003;36:281-5). They found that 29% of patients developed subsequent infections, of which, 80% of those patients developed infections at new sites. Notably, the half-life of MRSA colonization has been reported to be as long as 40 months (Sanford, Widman, et al. Clin Infect Dis. 1994;19:1123–28).

3 TELAVANCIN TARGET INDICATION: cSSSI

Complicated skin and skin structure infection was chosen as the initial indication for telavancin, with a focus on the most common pathogen, MRSA.

Telavancin is intended to be used for:

Treatment of patients with complicated skin and skin structure infections caused by susceptible strains of the following Gram-positive microorganisms: *S. aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius* and *S. constellatus*), and *Enterococcus faecalis* (vancomycin-susceptible isolates only).

4 TELAVANCIN – DEVELOPMENT TARGET, CHEMISTRY, MICROBIOLOGY, PHARMACOKINETICS

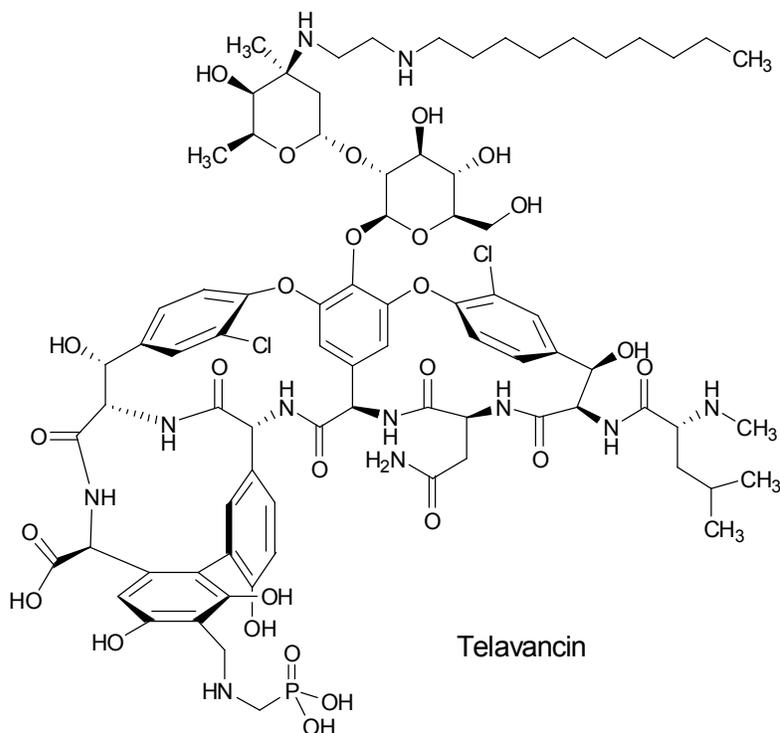
4.1 Development Target

The telavancin discovery program focused on identification of a compound with a novel mechanism of action, greater potency than glycopeptides, activity against Gram-positive pathogens resistant to or with reduced susceptibility to available antibiotics, and a convenient dosing regimen.

4.2 Chemistry

Telavancin hydrochloride is a purified, semisynthetic lipoglycopeptide antibiotic that has the chemical structure shown in Figure 1.

Figure 1: Chemical Structure of Telavancin



4.3 Preclinical Safety Evaluation

The nonclinical program to evaluate the potential toxicity of telavancin included safety pharmacology studies, single- and multiple-dose toxicity studies of up to 6 months in duration, genotoxicity studies, developmental and reproductive toxicity studies, and ex vivo assays to evaluate the hemolytic potential. Additional studies performed included a 6-week study in male rats to assess potential gonadal toxicity, a 6-week study to evaluate potential for immunotoxicity, studies to assess the potential for local irritation of the skin and eye, and a study to assess the potential of telavancin to cause phototoxicity. This program identified potential effects on cardiac repolarization, renal toxicity and reproductive toxicity as issues with potential relevance to the clinical use of telavancin.

4.3.1 Renal

The nephrotoxic potential for telavancin has been characterized in dogs and rats in exploratory studies and in repeated-dose studies of up to 6 months in duration.

After 2 weeks of dosing, an increase in renal tubular vacuolization that was considered indicative of minimal nephrotoxicity was observed in rats at 25 mg/kg/day, but not in dogs at this dose. At this dose and duration, the minimal morphological change was not associated with changes in urea nitrogen or creatinine.

Administration of telavancin at 50 mg/kg/day for 4 weeks caused minimal increases in blood urea nitrogen (BUN) and creatinine in rats and dogs and slightly increased urine volumes in dogs. Mild renal tubular injury was observed microscopically in rats (minimal focal to multifocal renal tubular degeneration) at 25 and 50 mg/kg/day and in dogs (renal cortical tubular dilatation) at 50 mg/kg/day. Both the changes in clinical chemistry and urinalysis parameters and the microscopic lesions exhibited reversibility at the end of the 4-week recovery period.

Administration of telavancin to rats for 13 weeks resulted in slight (less than 2-fold) increases in BUN and creatinine at 50 and 100 mg/kg/day. The elevated BUN values generally returned toward control values after 4 weeks of recovery, whereas the creatinine concentrations remained slightly elevated in males. Similar and reversible elevations in urea nitrogen and creatinine were noted following 6 months of dosing in rats at 50 mg/kg/day. Dogs dosed for 13 weeks at 25 and 100 mg/kg/day exhibited slight increases in BUN and urine volume. These values returned towards control values after 4 weeks of recovery. Clinical pathology changes in the 13-week rat and dog, and 6-month rat studies were associated with histopathological findings of renal proximal tubular degeneration. Microscopic examination revealed evidence of partial reversibility of the renal damage in the rat and dog 1 month after cessation of treatment.

Thus, the renal toxicity observed with telavancin in rats and dogs is relatively mild and shows evidence of reversibility, based on a return towards baseline values for BUN and creatinine and a reduction in histopathology severity scores. These effects were detected at exposures (based on AUCs) similar to those measured in clinical studies.

4.3.2 Potential Effects on Cardiac Repolarization

The safety pharmacology program included in vitro receptor binding assays, exploratory and GLP studies on the potential of telavancin to interfere with hERG potassium channel currents and action potential duration in canine and ovine Purkinje fibers, single-dose studies evaluating the potential of telavancin at doses up to 50 mg/kg to cause cardiovascular and respiratory changes in anesthetized dogs and a multiple-dose study to evaluate potential cardiovascular effects in conscious dogs at doses up to 100 mg/kg/day.

Although no notable receptor/ion channel binding or inhibition of enzyme activity was observed in receptor binding studies, telavancin did cause a decrease in hERG potassium ion channel currents in an exploratory (non-GLP) assay. Although inhibition of hERG potassium channel currents was also noted in the GLP assay, 50% inhibition could not be obtained up to 600 µg/mL, a concentration approximately 60-fold higher than the observed free plasma concentration in humans at 10 mg/kg/day (C_{max} in humans = 97 µg/mL, approximately 90% protein bound). The effects of telavancin on action potential duration (APD) were also evaluated in canine and sheep Purkinje fibers. In canine Purkinje fibers, a slight prolongation in APD₆₀ and APD₉₀ (7 to 11%) was observed at concentrations of 50 and 150 µg/mL and a stimulation frequency of 1 Hz. These increases were not dose dependent and were not observed at the other stimulation frequency (0.5 Hz). At concentrations of 5, 50, and 150 µg/mL, telavancin had no effect on any of the cardiac action potential parameters measured in sheep Purkinje fibers.

Studies in anesthetized and conscious dogs, which included qualitative and quantitative assessments of electrocardiograms (measurement of RR, PR, QRS, QT, and QTc intervals and evaluation of ST segment elevation/depression) failed to demonstrate an effect on QTc intervals even after repeated dosing at 100 mg/kg/day. Using the average plasma concentration of 389 µg/mL (approximately 90% protein binding) at 100 mg/kg in the conscious dog study, exposure to the free fraction at this dose is estimated to be approximately 4-fold higher than the observed free plasma concentration in humans at 10 mg/kg/day. Based on separate toxicokinetic data, exposure of the free fraction at this dose (C_{max} = 477 µg/mL, approximately 90% protein bound) is estimated to be approximately 5-fold higher than the observed free plasma concentration in humans at 10 mg/kg/day (C_{max} = 97 µg/mL, approximately 90% protein bound).

Electrocardiograms were also evaluated in dogs in the 2-week, 4-week, and 13-week toxicity studies. In none of these studies was a change in QTc noted, even after 13 weeks of treatment at 100 mg/kg/day.

Although the *in vivo* assays failed to detect an effect on cardiac repolarization, the observation of effects in two of the *in vitro* studies (hERG and canine Purkinje fiber) suggested that a prolongation of the QTc interval in man is possible.

4.3.3 *Fetal Development*

The safety of telavancin in pregnant women was not evaluated in clinical studies. Because lower fetal weights in rats and a low incidence of limb defects in several species were noted, an independent expert review was requested of Dr. Anthony Scialli (a Board-certified obstetrician-gynecologist with subspecialty training in reproductive and developmental toxicology) in order to assess the importance of these findings. Dr. Scialli's review of the embryofetal development studies in rats, rabbits and minipigs is provided in Appendix 1. Key findings from his assessment are summarized below.

In rats, decreases in mean maternal body weight, mean maternal body weight gain and food consumption in the mid- and/or high-dose groups (approximately 1.1- and 1.6-fold, respectively, the plasma exposures of patients) indicated that there was maternal toxicity at these doses, consistent with appropriate dose selection. There was a decrease in fetal weight in the mid and high dose groups. This effect was not pronounced and was only detected using the fetus rather than the litter as the experimental unit. Two fetuses with malformations were noted. One fetus in the mid dose group had protruding tongue, "brachymelia" of the left hindlimb, syndactyly of the left hindlimb, and anophthalmia. One fetus in the high dose group had "brachymelia" of the left hindlimb. Although the study author indicated that the "brachymelia" (short limb) noted on external examination in one high-dose and one mid-dose fetus was considered treatment-related, our independent consultant, Dr. Scialli, disagreed with this conclusion because the observation of short limb on external examination is nonspecific and potentially unreliable. In this study, for instance, the mid-dose fetus with "brachymelia" had no long-bone abnormalities on skeletal examination, calling into question whether there was a limb malformation at all and the high-dose fetus with "brachymelia" was not evaluated skeletally, because it was selected by coin

toss for visceral evaluation. Therefore, no actual limb abnormalities were documented in this study. Dr. Scialli also noted that the report author had chosen to use the term “brachymelia” rather than the more commonly used term, “micromelia.” Micromelia is identified in historical data bases, leading to the conclusion that this finding was within the historical control range. Therefore, we conclude that it is not clear that either of the fetuses in this study truly had a treatment-related limb-shortening abnormality.

In the embryofetal toxicity study in rabbits, maternal toxicity characterized by decreases in body weight, body weight gain, and food consumption was also noted at the highest dose tested indicating that the study was designed appropriately. No effects were noted on fetal weight nor were there statistically significant increases in external, visceral, or skeletal malformations. A number of fetal abnormalities were noted, including:

- ◆ One fetus in the high-dose group with limb abnormalities consisting of absence of the ulna and absence of one digit. This fetus also had gastroschisis, diaphragmatic hernia, and gallbladder agenesis.
- ◆ Another high-dose fetus from a different litter with an umbilical hernia.
- ◆ Three additional fetuses from three different high-dose litters with fusion of the sternbrae
- ◆ One additional fetus in a separate litter with a bipartite vertebral centrum, fusion of a pair of ribs, and forking of a rib.

Dr. Scialli noted that although the sternbral, vertebral, and rib abnormalities were considered malformations, their clinical significance is doubtful. Fused sternbrae, a malformation that occurs spontaneously in control litters and that has been associated with maternal toxicity in rat and rabbit studies, was isolated to one litter. While the report author considered 75 mg/kg/day an effect level based on the number and severity of fetal malformations seen at this dose level, Dr. Scialli disagreed with this conclusion. The basis for Dr. Scialli’s opinion was that clinically significant malformations in this study were limited to one fetus in the control group with cardiomegaly, one fetus in the high-dose group with multiple malformations, and one fetus in a separate litter with umbilical hernia. Given the

diverse nature of these malformations, it was not possible to conclude that there was a treatment-related effect.

The findings in the study in minipigs included fetuses with limb abnormalities in one of the control groups, in the low-dose group, and in the mid-dose group, but none in the high-dose group. The limb abnormalities were primarily polydactyly, which is known to occur spontaneously in the minipig. Polydactyly was seen in one fetus in the control group, four fetuses in three litters in the low-dose group, and five fetuses in three litters in the mid-dose group. One of the fetuses with polydactyly in the mid-dose group appeared to have a misshapened leg due to absence of the radius. Another mid-dose fetus, in a litter not otherwise affected, had syndactyly. The report author indicated that because these abnormalities occur spontaneously in the minipig and because the high-dose group was not affected, the abnormalities were not treatment related. While Dr. Scialli noted difficulties in interpretation of the minipig study due to poor reproductive performance, he was in agreement with the author that the highest dose tested, 75 mg/kg/day was a no-effect level.

Dr. Scialli concluded that the primary evidence of an adverse developmental effect was a reduction in litter weight in a study in rats and that there was no clear evidence of teratogenicity in any of the developmental studies. After evaluating the few observed limb defects, he noted that there was no embryologically coherent mechanism by which a common malformation syndrome could be postulated to have been caused by telavancin.

4.4 Microbiology

Telavancin is a semisynthetic lipoglycopeptide antibiotic active against Gram-positive bacteria, including pathogens commonly associated with complicated skin and skin structure infections (cSSSI). Minimum inhibitory concentrations (MICs) for telavancin are lower than glycopeptide comparators (vancomycin and teicoplanin). Organisms resistant to other classes of antibiotics, including oxacillin, daptomycin, and linezolid, remain susceptible to telavancin at the proposed MIC breakpoints. Cross-resistance with telavancin appears to be limited to organisms expressing acquired VanA-type vancomycin resistance.

The bactericidal action of telavancin results from a mechanism that includes inhibition of cell wall synthesis and disruption of bacterial membrane function. Telavancin inhibits cell wall synthesis by binding to late-stage peptidoglycan precursors in a manner similar to

vancomycin. Telavancin also binds to bacterial cell membrane and disrupts membrane barrier function. Unlike lipopeptides, telavancin does not bind to mammalian cell membranes. Bacterial resistance to telavancin has not been detected in either in vitro or clinical studies.

Telavancin exhibits concentration-dependent bactericidal activity and induces a prolonged postantibiotic effect. In vitro drug interaction studies identified limited instances of synergy between telavancin and other antibiotics. No antagonism was observed. In vivo pharmacology studies showed that telavancin is efficacious, and demonstrates bactericidal activity in multiple animal models including soft tissue infections. The area under the concentration-time curve (AUC)/MIC ratio is the definitive pharmacodynamic correlate. In animal models of infection using vancomycin, nafcillin, or linezolid as comparators, the efficacy of telavancin was comparable or statistically superior (Section 4.4.5).

4.4.1 Mechanism of Action

Telavancin exerts its bactericidal action through a mechanism that combines inhibition of cell wall synthesis and disruption of bacterial membrane function (Table 1). Telavancin inhibits cell wall synthesis by binding to late-stage peptidoglycan precursors, including lipid II, in a manner similar to vancomycin (Higgins DL, et al. Antimicrob Agents Chemother. 2005;49:1127–34). This activity prevents both the polymerization of precursor into peptidoglycan and subsequent cross-linking events. Telavancin demonstrates >10-fold enhanced potency compared with vancomycin.

Table 1: Inhibition of Cellular Targets in *S. aureus*

Antibiotic	MIC (µg/mL)	Inhibition of Target, IC ₅₀	
		Cell Wall ^a	Bacterial Membrane ^b
Telavancin	0.25	0.26	3.6
Vancomycin	1	3.0	>64

Source: Theravance, Inc. data on file

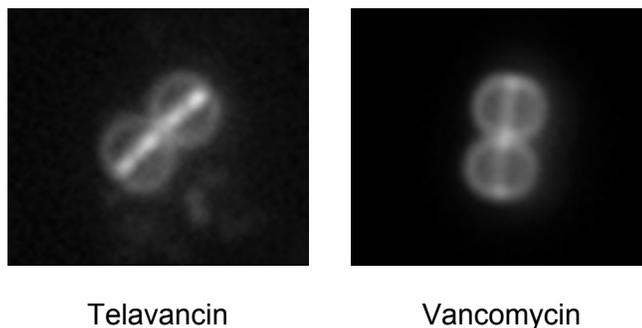
^aInhibition of peptidoglycan biosynthesis, µg/mL

^bDepolarization of bacterial membrane, µg/mL

In addition to inhibiting cell wall synthesis, telavancin also binds to the bacterial membrane, disrupting membrane barrier function (Higgins DL, et al. Antimicrob. Agents Chemother. 2005;49:1127–34). Vancomycin lacks this mechanism. Telavancin-induced membrane

effects are observed at concentrations that are higher than the telavancin MIC, but well below clinically achievable plasma levels. Binding of telavancin to the bacterial membrane is lipid II dependent. Relative to vancomycin, telavancin possesses enhanced affinity for lipid II versus cell wall (Breukink, et al. 46th Intersci Conf Antimicrob Agents Chemother. 2006; Abstr. C1-678.). This affinity differential translates into preferential binding to the division septum, the site of active cell wall synthesis (Theravance, Inc. data on file). Analysis of bacteria stained with fluorescent-conjugates of telavancin and vancomycin shows that telavancin targets the division septum more efficiently than vancomycin (Figure 2). Potent inhibition of cell wall synthesis, combined with the disruption of bacterial membrane function, results in the enhanced antibacterial potency of telavancin relative to vancomycin. Unlike other classes of antibiotics that target the cell wall (e.g., beta-lactams), telavancin is bactericidal without causing cell lysis, thereby avoiding the release of unsecreted cellular toxins and antigenic cell wall components.

Figure 2: *Staphylococcus aureus* Cells Stained with Fluorescent Conjugates of Telavancin and Vancomycin



4.4.2 Resistance Studies

The only known resistance mechanism that affects telavancin activity is VanA-type vancomycin resistance. Non-VanA-type vancomycin-resistant organisms are typically susceptible to telavancin (MIC ≤ 1 $\mu\text{g/mL}$) (Krause KM, et al. Antimicrob Agents Chemother. 2008;52:2647; Draghi DC, et al. Antimicrob. Agents Chemother. 2008;52:2383; Draghi DC, et al. J Antimicrob Chemother. 2008;62:116). There is no known cross-resistance between telavancin and other classes of antibiotics. Both single-step and serial passage in vitro experiments failed to generate resistant mutants in target organisms (Theravance Inc. Study Report 05-6424-MB-01, 2006; Sahm, DF, et al. 2006. Abstr. C1-0681. Abstr. 46th Intersci Conf Antimicrob Agents Chemother.; Krause K., 2003. Abstr. C1-1810 43rd Intersci Conf

Antimicrob Agents Chemother.; Krause K, 2005.; Abstr. P-1762 15th European Congress of Clinical Microbiology & Infectious Diseases). During clinical trials, there was no evidence of resistance developing to telavancin (Theravance, Inc. data on file). Resistance development during therapy with telavancin was determined by comparing the susceptibility of patient isolates recovered at baseline to those recovered after the last dose of telavancin. Results indicate that telavancin MIC values of baseline pathogens did not increase by more than 2-fold, a difference considered to be within the standard error of the MIC assay procedure (i.e., \pm 1-fold to 2-fold dilution).

4.4.3 *In Vitro Spectrum of Activity*

The in vitro activity of telavancin has been assessed in 19 independent survey studies against more than 12,000 bacterial clinical isolates collected from approximately 165 centers worldwide from 2003 to 2006. Among the 19 studies were two prospective surveys, one each conducted in the United States (US) and Europe, that included a total of more than 7000 nonduplicate isolates (Draghi DC, et al. Antimicrob Agents Chemother. 2008;52:2383; Draghi DC, et al. J Antimicrob Chemother. 2008;62:116). Sources of the clinical isolates in these studies included specimens from the bloodstream, respiratory tract, and skin and wound sites. Recently, an additional 10,700 isolates were tested through a prospective international surveillance program, conducted in 2007, that included isolates collected from North America, Europe, Israel, Latin America, and Asia (Fritsche T, et al. 2008; Abstr. C1-148. Abstr. 48th Intersci Conf Antimicrob Agents Chemother.). Collectively, these studies demonstrate the potent in vitro activity of telavancin against the principal species implicated in cSSSI: staphylococci (including methicillin-resistant strains), beta-hemolytic streptococci and enterococci, as well as against other Gram-positive species considered significant human pathogens. Notably, telavancin activity was consistent irrespective of specimen source or geographic region. Overall MIC distributions were narrow for each of the claimed organism groups and reflect the data generated in individual clinical studies. Telavancin activity was not affected by the mechanisms that confer resistance to oxacillin, daptomycin, or linezolid. A summary of telavancin's activity against isolates collected in the US during 2004 and 2005 is provided in Table 2.

Table 2: In Vitro Activity of Telavancin and Comparator Agents against Selected Gram-positive Pathogens from US Surveillance Conducted in 2004/2005

Organism	No. Tested	Agent	MIC (µg/mL)		
			Range	MIC ₅₀	MIC ₉₀
<i>S. aureus</i> (oxacillin-S)	1217	Telavancin	0.03-1	0.25	0.5
		Vancomycin	≤0.25-2	1	1
		Teicoplanin	≤0.12-8	1	2
		Linezolid	≤0.25->4	2	2
		Daptomycin	0.12-1	0.5	0.5
<i>S. aureus</i> (oxacillin-R)	1082	Telavancin	0.06-1	0.25	0.25
		Vancomycin	0.5-2	1	1
		Teicoplanin	≤0.12-8	0.5	1
		Linezolid	≤0.25->4	2	2
		Daptomycin	0.12->1	0.5	0.5
Coagulase-negative staphylococci (oxacillin-S)	100 ^a	Telavancin	0.06-1	0.25	0.5
		Vancomycin	≤0.25-4	1	2
		Teicoplanin	≤0.12-32	2	8
		Linezolid	≤0.5-2	1	1
		Daptomycin	0.12->1	0.5	1
Coagulase-negative staphylococci (oxacillin-R)	272 ^b	Telavancin	0.12-1	0.25	0.5
		Vancomycin	0.5-4	2	2
		Teicoplanin	0.25-32	4	8
		Linezolid	≤0.5->4	1	1
		Daptomycin	0.12->1	0.5	1
<i>S. pyogenes</i>	68	Telavancin	0.015-0.12	0.03	0.06
		Vancomycin	0.25-1	0.25	0.5
		Linezolid	0.5-1	1	1
		Daptomycin	≤0.03-0.25	0.06	0.06
<i>S. agalactiae</i>	45	Telavancin	0.03-0.12	0.06	0.06
		Vancomycin	0.25-0.5	0.5	0.5
		Linezolid	0.5-1	1	1
		Daptomycin	0.12-0.5	0.25	0.25
Other beta-hemolytic streptococci (Group C, F G)	31 ^c	Telavancin	0.03-0.25	0.03	0.06
		Vancomycin	0.25-1	0.25	0.5
		Linezolid	1-2	1	1
		Daptomycin	≤0.03-0.5	0.06	0.25
Viridans Group streptococci	102 ^d	Telavancin	≤0.001-1	0.03	0.12
		Vancomycin	0.12-1	0.5	0.5
		Linezolid	≤0.12-2	1	1
		Daptomycin	≤0.03->1	0.25	1
<i>E. faecalis</i> (vancomycin-S)	429	Telavancin	0.12-2	0.5	1
		Vancomycin	≤0.5-4	1	2
		Teicoplanin	≤0.03-0.5	0.25	0.25
		Linezolid	0.25-32	1	2
		Daptomycin	0.5-2	0.5	1
<i>E. faecium</i> (vancomycin-S)	92	Telavancin	≤0.015-0.5	0.12	0.25
		Vancomycin	≤0.5-2	≤0.5	1
		Teicoplanin	≤0.03-2	0.5	0.5
		Linezolid	≤0.015-4	2	2
		Daptomycin	≤0.015-8	2	4

Table notes on next page.

Table Notes

S, susceptible; R, resistant

Source: Draghi DC, et al. Antimicrob Agents Chemother. 2008;52:2383

^a Includes *S. capitis* (6), *S. epidermidis* (43), *S. haemolyticus* (4), *S. hominis* (1), *S. simulans* (4), *S. warneri* (5), *S. xylosus* (1), unspciated CoNS (36).

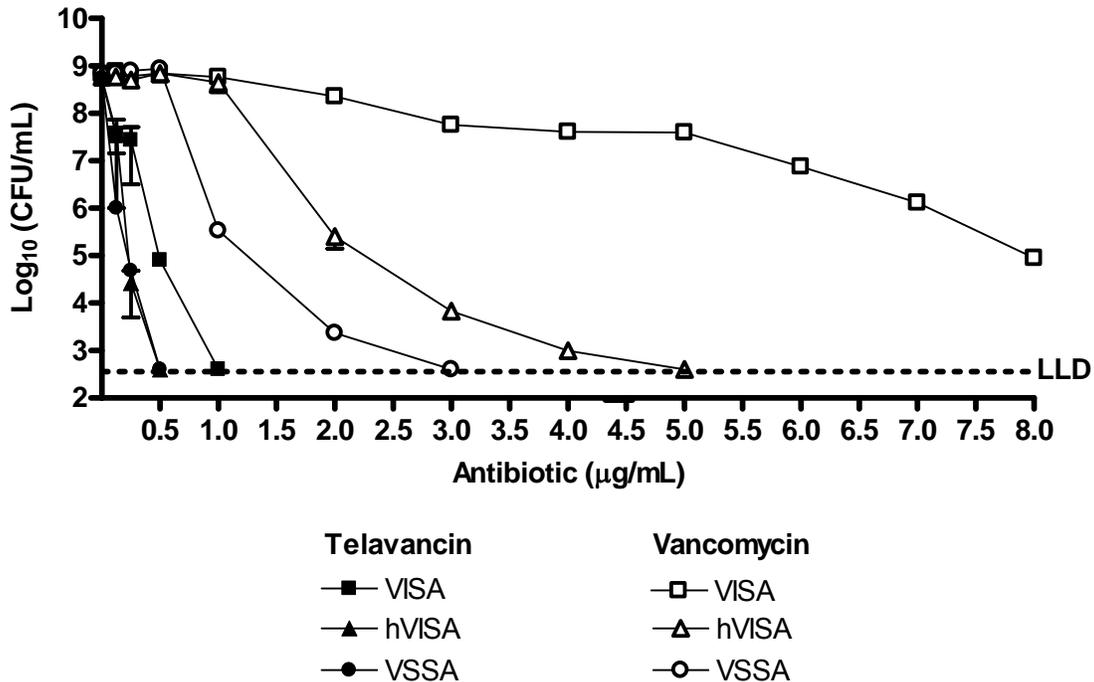
^b Includes *S. capitis* (2), *S. cohnii* (2), *S. epidermidis* (171), *S. haemolyticus* (10), *S. hominis* (12), *S. saprophyticus* (1), *S. sciuri* (2), *S. simulans* (12), *S. warneri* (1), *S. xylosus* (1), unspciated CoNS (58).

^c Includes Streptococci Group C (10), Group F (3), Group G (18).

^d Includes *S. bovis* (1), *S. constellatus* (5), *S. intermedius* (16), *S. mitis* (1), *S. oralis* (1), *S. sanguinis* (1), *Streptococcus* spp. (99)

A number of studies focused specifically on the activity of telavancin against staphylococci with reduced susceptibility to vancomycin. Vancomycin-intermediate *S. aureus* (VISA) and heterogenous VISA (hVISA) were susceptible to telavancin at the proposed MIC breakpoint for this organism (1 µg/mL) (Leuthner KD et al. J Antimicrob Chemother. 2006;58:338; Draghi et al. Antimicrob Agents Chemother. 2008;52:2383). In preliminary studies, subpopulations with reduced susceptibility to telavancin were not detected among hVISA and VISA isolates (Figure 3) (Theravance Inc. Study Report 08-6424-MCB-04, 2008).

Figure 3 Telavancin and Vancomycin Population Analysis Profiles for *S. aureus* ATCC 29213 (VSSA), hVISA Mu3 (ATCC 700698) and VISA Mu50 (ATCC 700699) Isolates



Telavancin is also active against many Gram-positive anaerobic bacteria, with uniformly potent activity against most *Clostridium* species, including *C. perfringens* (n = 27; MIC range, 0.06–0.25 µg/mL) and *C. difficile* (n = 29; MIC range, 0.12–0.5 µg/mL) (Goldstein EJ, et al. Antimicrob Agents Chemother. 2004;48:2149; Finegold SM, et al. 2005; Abstr. E-1750. Abstr. 45th Intersci. Conf. Antimicrob. Agents Chemother.).

4.4.4 Supportive In Vitro Microbiology Studies

Bactericidal Activity

Telavancin exerts concentration-dependent bactericidal activity against Gram-positive organisms (Pace JL, et al. Antimicrob Agents Chemother. 2003;47:3602; Theravance Inc. Study Report 06-6424-MCB-10, 2006). MBC/MIC ratios were ≤ 4 for the majority of staphylococci tested, including hVISA and VISA strains. Concentration-dependent bactericidal effects were demonstrated in time-kill studies against target organisms including MSSA, MRSA, VISA and coagulase-negative staphylococci. Against streptococci, including beta-hemolytic species, telavancin was bactericidal at low multiples of the MIC. Telavancin was bacteriostatic at low multiples of the MIC against vancomycin-susceptible enterococci. However, at higher test concentrations telavancin was bactericidal against these organisms.

Telavancin has also been shown to retain bactericidal activity against slowly growing isolates of *S. aureus* in time-kill assays and in an in vitro model of biofilm infection (Odenholt I, et al. Antimicrob. Agents Chemother. 2007;51:3311; Clouse FL, et al. Antimicrob. Agents Chemother. 2007;51:4521; Gander S, et al. J Antimicrob Chemother. 2005;56:337). In a model of intracellular *S. aureus* infection, telavancin treatment resulted in > 90% reduction in bacterial titers (Barcia-MaCay M, et al. J Antimicrob Chemother. 2006;58:1177). The activity of telavancin was superior to that of vancomycin in each of these studies.

In Vitro Antimicrobial Interactions

In vitro synergy studies detected no antagonistic interactions between telavancin and class-representative antibiotics, which included aztreonam, piperacillin/tazobactam, imipenem, cefepime, amikacin, trimethoprim/sulfamethoxazole, ciprofloxacin and rifampin (Sahm DF, et

al. 2006. Abstr. E-0718. Abstr. 46th Annual Intersci Conf Antimicrob Agents Chemother.; Theravance Inc. Study Report 05-6424-MB-02, 2005). Synergistic interactions against *S. aureus*, including MRSA strains, were observed with some beta-lactam agents.

4.4.5 Preclinical Pharmacology

Pharmacokinetics and Pharmacodynamics

Pharmacokinetic-pharmacodynamic studies in the neutropenic mouse thigh infection model suggest that total exposure (AUC_{0-24}/MIC) is the pharmacokinetic parameter that correlates with efficacy (Hegde SS, et al. Antimicrob Agents Chemother. 2004;48:3043). An AUC_{0-24}/MIC ratio of 219 was required for a 1- \log_{10} reduction in CFU/g against an MRSA strain with an MIC of 1 $\mu\text{g}/\text{mL}$ in the neutropenic mouse thigh model. This was the target chosen to generate estimates of the telavancin doses evaluated in Phase 2 and Phase 3 clinical trials of cSSSI. The results from Monte Carlo simulations for a 750 mg dose (approximately 10 mg/kg for average adult body weight) were found to yield target attainment rates $\geq 99\%$ for organisms with MIC values as high as 2 $\mu\text{g}/\text{mL}$ (Theravance, Inc. data on file).

In Vivo Efficacy in Animal Models of Infection

The in vivo antibacterial efficacy of telavancin has been evaluated in a number of animal models of infection caused by Gram-positive pathogen (Hegde SS, et al. Antimicrob Agents Chemother. 2004;48:3043; Reyes N, et al. Antimicrob Agents Chemother. 2005;49:4344; Reyes N, et al. J Antimicrob Chemother. 2006;58:462; Hegde SS, et al. J Antimicrob Chemother. 2008;61:169; Madrigal AG, et al. Antimicrob Agents Chemother. 2005;49:3163; Stucki A, et al. Antimicrob. Agents Chemother. 2006;50:770; Miro JM, et al. Antimicrob. Agents Chemother. 2007;51:2373; Theravance, Inc. data on file). These studies demonstrated that telavancin was efficacious and displayed dose-dependent bactericidal activity in models of soft-tissue (neutropenic mouse thigh, mouse subcutaneous infection), deep-seated (rat and rabbit endocarditis), systemic (murine bacteremia), lung (murine pneumonia) and central nervous system (rabbit meningitis) infections. When assessed at human equivalent exposures, telavancin was at least as effective as, and more often superior to, comparator agents.

In the neutropenic mouse thigh model of infection, telavancin was efficacious against a variety of Gram-positive pathogens including *S. aureus*, *S. epidermidis*, *E. faecalis*, and *S. pneumoniae* (Hegde SS, et al. *Antimicrob Agents Chemother.* 2004;48:3043). Telavancin was more potent than nafcillin and vancomycin against *S. aureus* (MSSA) and more potent than vancomycin and linezolid against MRSA. In a high-inoculum variation of the neutropenic mouse thigh infection model with MRSA, telavancin was superior to daptomycin (Theravance Inc. Study Report 04-6424-PH-02, 2004). Telavancin had similar potency against MRSA in models of soft tissue infection in immunocompetent (mouse subcutaneous abscess) and immunocompromised animals (neutropenic mouse thigh). In contrast, vancomycin and especially linezolid were substantially less potent in immunocompromised animals, suggesting that immune status has minimal impact on the efficacy of telavancin (Hegde SS, et al. *Antimicrob Agents Chemother.* 2004;48:3043).

4.5 Pharmacokinetic Profile

4.5.1 Pharmacokinetics

Telavancin exhibits predictable, linear pharmacokinetics. In healthy young adults, the pharmacokinetics of intravenously administered telavancin were linear following single doses from 1 to 15 mg/kg and time-independent following multiple doses from 7.5 to 15 mg/kg administered once daily for up to 7 days. Steady-state concentrations were achieved by the third daily dose.

The mean pharmacokinetic parameters of telavancin (10 mg/kg) after single and multiple 60-minute intravenous infusions are summarized in Table 3.

Table 3: Pharmacokinetic Parameters of Telavancin in Healthy Adults, 10 mg/kg

	Single Dose	Multiple Dose
	(n=42)	(n=36)
C _{max} (µg/mL)	93.6 ± 14.2	108 ± 26
C _{min} (µg/mL)	--	8.6 ± 2.8
AUC _{0-∞} (µg·hr/mL)	747 ± 129	--
AUC _{0-24h} (µg·hr/mL)	666 ± 107	780 ± 125
t _{1/2} (hr)	8.0 ± 1.5	8.1 ± 1.5
CL (mL/hr/kg)	13.9 ± 2.9	13.1 ± 2.0
MRT (hr)	10.8 ± 2.1	10.2 ± 1.9
V _{ss} (mL/kg)	145 ± 23	133 ± 24

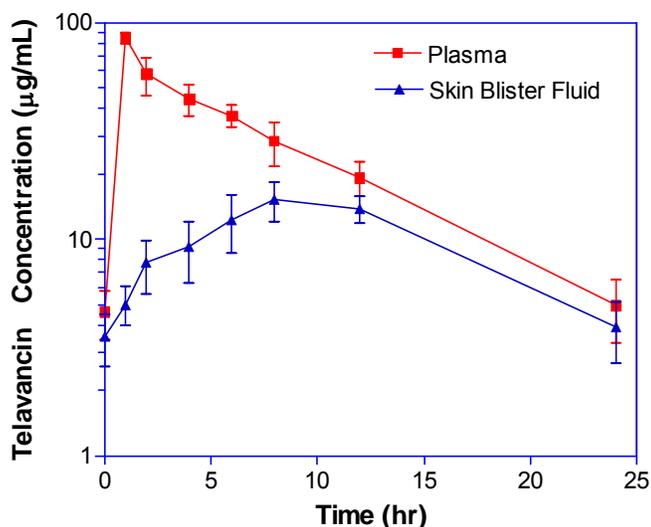
4.5.2 Distribution

Telavancin binds to human plasma proteins, primarily to serum albumin, in a concentration-independent manner. The mean binding is approximately 90% and is not affected by renal insufficiency or moderate hepatic impairment.

Concentrations of telavancin in skin blister fluid in healthy subjects were used as a model to assess drug concentrations at the site of a skin/skin structure infection. Concentrations of telavancin in skin blister fluid were 40% of those in plasma (AUC_{0-24hr} ratio) after three daily doses of 7.5 mg/kg¹ telavancin in healthy young adults (Figure 4) and exceeded the MIC₉₀ (0.5 µg/mL) for clinical isolates of *S. aureus*, including MRSA, for the entire 24-hour dosing interval.

¹ 7.5 mg/kg was the target dose at the time the study was conducted; subsequent data have supported the use of 10 mg/kg once daily

Figure 4: Steady State Concentrations of Telavancin 7.5 mg/kg IV every 24 hours in Plasma and Skin Blister Fluid



Sun HK, et al. Antimicrob. Agents Chemother. 2006;50:788-790

4.5.3 Metabolism

No metabolites of telavancin were detected in in vitro studies using human liver microsomes, liver slices, hepatocytes, and kidney S9 fraction. None of the following recombinant CYP 450 isoforms were shown to metabolize telavancin in human liver microsomes: CYP 1A2, 2C9, 2C19, 2D6, 3A4, 3A5, 4A11. The clearance of telavancin is not expected to be altered by inhibitors of any of these enzymes.

In a mass balance study in male subjects using radiolabeled telavancin, three hydroxylated metabolites were identified, with the predominant metabolite accounting for < 1% of the radioactivity in urine and < 2% of the radioactivity in plasma.

4.5.4 Excretion

Telavancin is eliminated primarily by the kidney. In a mass balance study, approximately 76% of the administered dose was recovered from urine and < 1% of the dose was recovered from feces (collected up to 216 hours) based on total radioactivity.

4.5.5 *Special Populations*

Geriatric Patients:

The impact of age on the pharmacokinetics of telavancin was evaluated in healthy young (range, 21 to 42 years) and elderly (range, 65 to 83 years) subjects. The mean creatinine clearance (CrCl) of elderly subjects was 66 mL/min. Age alone did not have a clinically meaningful impact on the pharmacokinetics of telavancin.

Sex:

The impact of sex on the pharmacokinetics of telavancin was evaluated in eight healthy male and eight healthy female subjects. The pharmacokinetics of telavancin were similar in males and females.

Renal Impairment:

The pharmacokinetics of telavancin were evaluated in subjects with normal (CrCl > 80 mL/min) renal function and subjects with varying degrees of renal impairment following administration of a single dose of telavancin 7.5 mg/kg. At the time the study was conducted, 7.5 mg/kg was the target dose; subsequent data have supported the use of 10 mg/kg once daily. The mean AUC_{0-∞} values were approximately 13%, 29%, and 118% higher for subjects with mild (CrCl > 50 to 80 mL/min), moderate (CrCl 30 to 50 mL/min), and severe (CrCl < 30 mL/min) renal impairment, respectively, compared with subjects with normal renal function. Based on these data, dosing recommendations were developed (Table 4). The effects of peritoneal dialysis have not been studied.

Table 4: Dosage Adjustment in Adult Patients with Renal Impairment

Estimated Creatinine Clearance (mL/min) ¹	Recommended Dosage Regimen of Telavancin
> 50	No dosage adjustment necessary
30 to 50	7.5 mg/kg every 24 hours
< 30	10 mg/kg every 48 hours

¹ Creatinine clearance estimated from serum creatinine with the Cockcroft-Gault formula

Hepatic Impairment:

The pharmacokinetics of telavancin were not altered in subjects with moderate hepatic impairment (Child-Pugh B) compared with healthy subjects with normal hepatic function matched for sex, age, and weight. No dosage adjustment is recommended for moderate hepatic impairment. The pharmacokinetics of telavancin have not been evaluated in patients with severe hepatic impairment (Child-Pugh C).

4.5.6 *In Vivo Drug Interactions*

Midazolam: The IC₅₀ for telavancin to inhibit the CYP3A4/5 isozyme was found to be close to achievable plasma concentrations. Therefore, the impact of telavancin on the pharmacokinetics of midazolam (CYP 3A4/5 substrate) was evaluated in 16 healthy adult subjects following administration of single intravenous doses of telavancin 10 mg/kg, intravenous midazolam 1 mg, and the two in combination. The results showed that telavancin had no impact on the pharmacokinetics of midazolam and midazolam had no effect on the pharmacokinetics of telavancin. Therefore, telavancin is unlikely to alter the pharmacokinetics of drugs metabolized by the cytochrome P450 system to a clinically significant degree.

Aztreonam: The impact of telavancin on the pharmacokinetics of aztreonam was evaluated in 11 healthy adult subjects following administration of single intravenous doses of telavancin 10 mg/kg, aztreonam 2 g, and the two in combination. Telavancin had no impact on the pharmacokinetics of aztreonam and aztreonam had no effect on the pharmacokinetics of telavancin. No dosage adjustment of telavancin or aztreonam is recommended when the two drugs are coadministered.

Piperacillin-tazobactam: The impact of telavancin on the pharmacokinetics of piperacillin-tazobactam was evaluated in 12 healthy adult subjects following intravenous administration of a single dose of telavancin 10 mg/kg, piperacillin-tazobactam 4.5 g, and both. Telavancin had no impact on the pharmacokinetics of piperacillin-tazobactam, and piperacillin-tazobactam had no effect on the pharmacokinetics of telavancin. No dosage adjustment of telavancin or piperacillin-tazobactam is recommended when both drugs are coadministered.

4.5.7 Summary of Pharmacokinetics

- Telavancin has linear, predictable pharmacokinetics, with good penetration into potential sites of infection. Its potency and half-life support once daily dosing. Because telavancin is renally excreted, a dosage adjustment is recommended for patients with moderate or severe renal insufficiency.
- There is no known potential for drug:drug interactions that could modify the pharmacokinetics of telavancin or affect the disposition of other drugs.

5 CLINICAL EFFICACY AND SAFETY STUDIES

The Phase 2 and 3 studies with telavancin focused on demonstrating the efficacy and safety of telavancin for the treatment of cSSSI and hospital-acquired pneumonia (HAP).

The Phase 2 cSSSI program consisted of two randomized, double-blind studies and compared telavancin at intravenous (IV) dosages of 7.5 mg/kg (Study 202a and Study 202b – original protocol) and 10 mg/kg q 24 hours (Study 202b – amended protocol) with standard therapy consisting of the investigator’s prerandomization choice of an antistaphylococcal penicillin (nafcillin or oxacillin 2 g q 6 hours or, in South Africa, cloxacillin 0.5 to 1.0 g q 6 hours) or vancomycin (1 g IV q 12 hours with dosage adjustment permitted by unblinded personnel following the standard procedures of each institution).

The Phase 3 programs each included two studies: Studies 0017 and 0018 (cSSSI), and Studies 0015 and 0019 (HAP). Each of these four studies compared telavancin at a dosage of 10 mg/kg once daily IV with vancomycin (1 g IV q 12 hours with dosage adjustment permitted by unblinded personnel following the standard procedures of each institution). The dose initially selected for study in cSSSI was 7.5 mg/kg q 24 hours. The cSSSI protocols were amended to reflect an increase in the dose to 10 mg/kg q 24 hours after availability of results of the pharmacokinetic/pharmacodynamic (PK/PD) modeling supporting this dose, and of safety data from the Phase 2 studies demonstrating similar safety profiles for the two doses. The Phase 2 and Phase 3 studies did not allow “step-down” therapy to oral antibiotics.

Where relevant, data from the HAP studies have been referenced to provide information on an additional population of patients treated with telavancin at 10 mg/kg q 24 hours.

6 PROGRAM DESIGN – COMPLICATED SKIN AND SKIN STRUCTURE INFECTION STUDIES

The Phase 3 studies (Studies 0017 and 0018) were conducted under identical protocols. Each study was a randomized, double-blind, active-controlled, parallel-group, multicenter, multinational trial with a 7- to 14-day treatment period. The objective of each study was to demonstrate noninferiority of telavancin 10 mg/kg to vancomycin (1 g IV q 12 hours) in the treatment of cSSSI due to Gram-positive pathogens, with a focus on cSSSI due to MRSA, and to establish the safety profile of telavancin. The primary outcome variable was clinical cure based on investigator assessment.

Combined, the studies enrolled total of 1867 patients, 719 of whom were infected with MRSA. Approximately 69% of patients were enrolled in the United States. Clinical sites in South America, Canada, Western and Eastern Europe, Israel, Australia, Asia, and South Africa also enrolled patients in these studies. Enrolled patients had one of the following diagnoses:

- Major abscess requiring surgical incision and drainage
- Deep/extensive cellulitis
- Wound infections (post-surgical or post-traumatic)
- Infected ulcer (excluding chronic diabetic foot ulcers)
- Infected burn (< 20% body surface area)

Enrolled patients must have had severe disease requiring intravenous treatment for at least 7 days. Uncomplicated infections were categorically excluded. To illustrate the severity of disease in the studied population, nearly 75% of the patients were hospitalized at Baseline and the remainder were cared for under outpatient parenteral antibiotic therapy programs; 25% were diabetic, approximately 25% had failed prior antibiotic therapy, nearly 20% of the patients had prior trauma as a source for the infection, and approximately 10% were associated with a prior surgical procedure. The frequency of signs and symptoms indicating more complicated infections were similar to previous studies of complicated skin and skin structure infections. Notably, the average surface area of the infection site was approximately 350 cm², and in patients with abscess, the average surface area was 190 cm². This should be contrasted with a recent publication on the value of antibiotics for uncomplicated cutaneous abscesses where the average surface area was only 19 cm²

(Rajendran PM, et al. *Antimicrob Agents Chemother.* 2007;51:4044–8). The protocol allowed the dosage of vancomycin to be optimized for body weight and/or renal function per site-specific guidelines, including monitoring of vancomycin serum concentrations to account for altered renal function and to ensure adequate serum concentrations. Because the dosing regimens differed, dummy infusions were used to maintain the blind. As noted above, a switch to oral therapy was not allowed; patients were to receive the blinded study drug as long as Gram-positive treatment was required. To mimic standard clinical practice in this regard patients were allowed to receive treatment as outpatients in a clinic setting or under the supervision of home health care service providers.

As the studies were focused on the treatment of MRSA, the comparator selected was vancomycin. In the event MSSA was identified investigators were to continue with the randomized study treatment. Patients could receive concomitant aztreonam or metronidazole for suspected Gram-negative and anaerobic infection, respectively.

An additional prespecified objective was to pool the data from the two studies to test whether telavancin 10 mg/kg was superior to vancomycin in the treatment of cSSSI due to MRSA. The MRSA subgroup analysis was to be conducted only if both individual studies met the overall prespecified noninferiority margin in order to protect the overall alpha level for significance testing. This objective was designed to confirm the results of a Phase 2 study showing that in patients with MRSA as a baseline pathogen, the microbiologic eradication rate was statistically significantly greater among patients treated with telavancin 10 mg/kg compared with standard therapy (92% vs. 68%, $p = 0.043$) (Stryjewski, ME et al. *Antimicrob Agents Chemother.* 2006;50:862–7).

Because changes in cardiac repolarization and renal function were detected in preclinical studies, the Phase 3 program was designed to further assess the importance of these safety findings by not excluding patients receiving drugs known to be associated with QT prolongation or patients with renal impairment. This approach contrasts with recent registrational studies of other drugs for the treatment of cSSSI, which have often excluded such patients. These studies did not stratify randomization on renal function.

Theravance retained contract research organizations to monitor the investigative sites on a periodic basis. All patient data were verified against source documents and site procedures

were reviewed for compliance with applicable local, state and federal regulations, including those related to human subjects' protections. Theravance also audited the conduct and monitoring of these studies, confirming that the investigative sites, contract research organizations and central laboratories complied with Good Clinical Practice. As noted above, following re-auditing of investigative sites by Theravance, Theravance was instructed to delete the efficacy data for patients from three clinical sites (totaling 73 patients) and QTc data for patients from two sites (totaling 66 patients). The analyses presented herein reflect these deletions. The deletions did not change the outcome of the primary endpoint or any of the study conclusions.

Selection of Telavancin Dosage

The selection of the telavancin dosage, 10 mg/kg once daily IV, was based on the results of a PK/PD assessment and of the Phase 2 studies. Data from the neutropenic murine thigh infection model suggested that doses of 750 mg (approximately 10 mg/kg) would result in > 99% probability of AUC target attainment for organisms with MICs as high as 2 µg/mL. This PK/PD assessment was confirmed clinically by the results of the Phase 2 study noted above (Study 202b) in which the microbiologic eradication rate in patients with cSSSI due to MRSA was statistically significantly greater among patients treated with telavancin 10 mg/kg compared with standard therapy. The safety profiles in patients treated with 7.5 and 10 mg/kg were similar.

Choice of Vancomycin as the Comparator

The recent increase in the incidence of MRSA as a pathogen in cSSSI together with vancomycin's activity against other Gram-positive pathogens has led to the increasing selection of vancomycin as the treatment of choice in cSSSI requiring IV therapy. This trend was reflected in the choice by investigators of vancomycin for 93% of the patients randomized to standard therapy in the last of the Phase 2 studies in cSSSI (enrollment period 20 February 2004 to 09 September 2004). Given these data, and that the focus of the Phase 3 studies was on patients with cSSSI due to MRSA, vancomycin was selected as the only comparator in the Phase 3 studies. Vancomycin is cited in the Infectious Disease Society of America's practice guideline as the "parenteral drug of choice" for treatment of skin and soft tissue infections caused by MRSA (Stevens DL, et. al. Clin Infect Dis.

2005;41:1373–406). Additionally, vancomycin has in vitro activity against all of the Gram-positive organisms (including MSSA) known to cause cSSSI, and has been used as the standard in other registration trials for recently approved products (e.g., tigecycline). The vancomycin dosage used in the telavancin studies, (1 g IV every 12 hours), is the labeled regimen for patients with normal renal function. The dosage could be monitored and adjusted according to the standard procedures of each institution.

Noninferiority Margin

The noninferiority margin was prospectively set at 10% in the protocol on the basis of medical judgment and precedent. During the course of the study, FDA issued a guidance requesting that sponsors of trials using the noninferiority design justify their choice of noninferiority margin. Theravance performed a comprehensive search of the published literature and the regulatory literature (e.g., package inserts and medical officer reviews for approved drugs) for information regarding the results of placebo-controlled trials in skin and skin structure infections. Theravance also consulted with experts in the field. These efforts failed to provide any direct evidence of clinical outcomes in patients with cSSSI receiving placebo or no medical treatment. The lack of information regarding placebo controlled trials in cSSSI is not surprising given that cSSSI are associated with considerable morbidity and mortality, making systemic antibiotic treatment essential for resolution of these infections. Thus, it is considered unethical to conduct placebo-controlled studies in cSSSI.

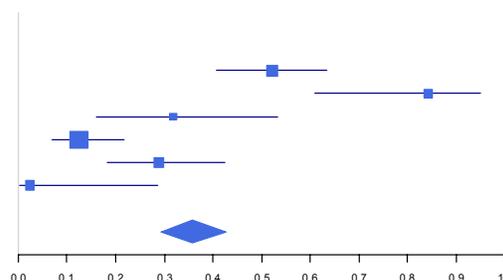
In lieu of historical data on the cure rate for a placebo or no therapy treatment group, data from randomized trials comparing two dosages of antibiotics for treatment of cSSSI, one of which was less than maximally effective, may be inferred to set an upper limit of a placebo cure rate in this condition. In one study, patients receiving a single dose of dalbavancin had a substantially lower rate of clinical success at test-of-cure than those receiving two doses (62% [8/13] vs. 94% [16/17]). In another study, patients receiving tigecycline 25 mg BID had a lower rate of clinical success at test-of-cure than those receiving 50 mg BID (67% vs. 74%). The clinical success rates of 62% to 67% in patients who received the lower dose regimens in these studies suggests that the placebo cure rate in this condition would surely be no higher, and indeed, since it is likely that the lower dose regimens have some activity, also supports a placebo response rate substantially lower than these for cSSSI.

Unfortunately, the sample sizes for these two studies were small, making the variability of the estimates too large to draw meaningful conclusions.

Data from published studies in uSSSI (impetigo) were used to estimate an upper limit on the placebo cure rate for cSSSI. Placebo cure rates for uSSSI can be considered a conservative estimate of placebo cure rates for cSSSI given that cSSSI by definition involve deeper soft tissues, often require surgical intervention, and have a more complicated course. Clinical cure rates for the placebo-treated patients in six reported impetigo investigations were identified and are summarized below. Using the results from these studies, Theravance conducted a fixed-effects meta-analysis to estimate the weighted average placebo cure rate. The cure rate in an ITT population of placebo-treated patients calculated from the meta-analysis was 35.7% with a corresponding 95% CI of 29.3%–42.7% (Figure 5).

Figure 5: Cure Rates for Placebo in Impetigo Studies

Study	Cures/N	Cure Rate	Lower Bound	Upper Bound
ALTABAX	37/71	0.521	0.406	0.634
Eells (1986)	16/19	0.842	0.608	0.948
Gould (1984)	7/22	0.318	0.16	0.534
Koenig (2002)	10/80	0.125	0.069	0.217
Rojas (1985)	15/52	0.288	0.182	0.425
Ruby (1973)	0/20	0.024	0.001	0.287
Summary		0.357	0.293	0.427



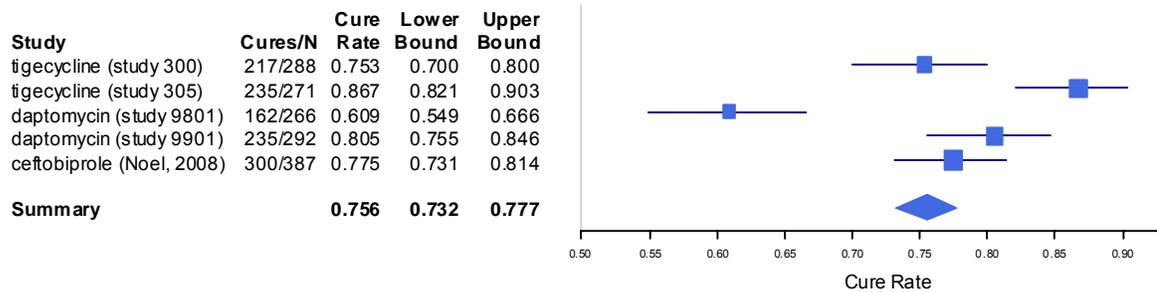
Data Sources ²

To establish the historical cure rate in cSSSI for patients treated with vancomycin, Theravance conducted a separate search of the medical literature. Five studies were identified in cSSSI where the endpoint was clinical cure and vancomycin was used as the

² Eells LD, Mertz PM, Piovanetti Y, et al. Arch Dermatol. 1986;122:1273-1276.
GlaxoSmithKline. ALTABAX Prescribing Information, April 2007.
Gould JC, et al. International Congress and Symposium Series Royal Society of Medicine. 1984;80:85-93.
Koenig S, et al. Br Med J. 2002;324:203-6
Rojas R, et al. The efficacy of Bactroban ointment and its vehicle in the treatment of impetigo: a double-blind comparative study. Proceedings of an International Symposium, Nassau, Bahama Islands, 21-22 May 1984. 1985:96-102.
Ruby RJ, Nelson JD. Pediatrics. 1973;52:854-859

active comparator. Vancomycin cure rates for these studies are shown below. Again using a fixed-effects meta-analysis, Theravance determined the vancomycin cure rate in the ITT population to be 75.6% with a corresponding 95% CI of 73.2%–77.7% (Figure 6).

Figure 6: Vancomycin Cure Rates in Randomized cSSSI Studies



Data Sources:³

Theravance used the resulting meta-analysis estimates of the placebo and vancomycin cure rates to determine the vancomycin vs. placebo treatment effect size (i.e., M1). M1 was calculated by taking the difference between the estimated vancomycin response rate and the estimated placebo rate (75.6% minus 35.7%) and conservatively estimated using the lower bound of the 95% confidence interval of the difference (using the pooled variance). The resulting estimate of M1 was 32.8%. The actual treatment effect size for vancomycin relative to placebo in cSSSI is most likely larger than the estimated M1 of 32.8% because the placebo cure rate used in this calculation is based on cure rates observed in uSSSI. It would be expected that actual placebo cure rates for cSSSI would be much lower than those for uSSSI. Consequently, a lower estimate of placebo cure rate would translate into a larger estimate of the treatment effect size.

The most precise unbiased point estimates of telavancin and vancomycin cure rates are obtained by pooling studies 0017 and 0018 (Table 5). The vancomycin AT cure rate estimate of 75.3% compares very favorably with the historical vancomycin rate of 75.6% from Figure 6. This suggests that the constancy of effect assumption among the historical

³ Noel, GJ, et al. Antimicrob Agents Chemother. 2008;52(1):37–44.
CDER. Tygacil Application 21-821 Medical Review. URL:
http://www.fda.gov/cder/foi/nda/2005/21-821_Tygacil_Medr.pdf.
CDER. Cubicin Application 21-572 Clinical Review. URL:
http://www.fda.gov/cder/foi/nda/2003/21-572_Cubicin_Medr_P1.pdf.

studies is reasonable. Assume that the noninferiority margin (the “ Δ ”) is selected such that it preserves at least 50% of the treatment effect of the active control (relative to a placebo) which translates to: $P_{\text{PLACEBO}} \leq P_{\text{VANCO}} - (2 \times \Delta)$ where P_{VANCO} and P_{PLACEBO} represent the control and placebo population response rates. Thus the vancomycin AT cure rate estimate of 75.3% would imply that the placebo rate should not be more than 55.3% to support a 10% margin for all treated patients. As noted above, the upper bound for placebo cure rates in uncomplicated skin and skin structure infections is 42.7%, and is likely lower in complicated SSSI. This evidence supports the 10% noninferiority margin adopted in the protocol by preserving more than 50% of the imputed placebo effect.

Table 5: Point Estimates of Cure Rate for the Pooled 0017 and 0018 Studies, AT and CE Populations

	0017 + 0018 Post Amendment	
	TLV 10 mg/kg N (%)	VAN N (%)
AT		
Cure	681 (77.0)	685 (75.3)
Not Cured	111 (12.6)	115 (12.6)
Indeterminate	40 (4.5)	36 (4.0)
Missing	52 (5.9)	74 (8.1)
- Total -	884 (100.0)	910 (100.0)
CE		
Cure	631 (88.4)	636 (88.3)
Not Cured	83 (11.6)	84 (11.7)
- Total -	714 (100.0)	720 (100.0)

Study Procedures

Baseline evaluations were performed prior to treatment start and included pertinent medical history, an assessment of the signs and symptoms of the infection, measurement of the primary infection site, Gram’s stain and culture of the primary infection site, blood culture, clinical laboratory tests, an X-ray to rule out osteomyelitis (if clinically indicated), and three 12-lead electrocardiograms (ECGs).

During the treatment phase, patients were evaluated daily for the occurrence of adverse events. Additional daily procedures included an assessment of the clinical signs and symptoms of the infection, measurement of the primary infection site, and blood cultures if baseline blood cultures were positive (or if the investigator suspected a bloodstream

infection post treatment initiation). Blood samples for clinical laboratory tests were collected every 3 days. On Day 4, three ECGs were obtained and PK sampling was conducted at selected clinical sites.

All patients were to have an End-of-therapy (EOT) visit within 3 days following the last dose of study medication and a Follow-up visit within 7 to 14 days after the EOT visit. A Test-of-Cure (TOC) assessment (assessment of signs/symptoms, measurement of infection site, assessment of clinical response) was conducted at the Follow-up visit for patients who had a clinical cure or had an indeterminate outcome at the EOT visit. The investigator was to determine the clinical response by comparing a patient's signs and symptoms at the EOT or TOC evaluation to those recorded at study admission. Additional procedures at the EOT and TOC evaluations were to include measurement of the primary infection site, Gram stain, and culture of the primary infection site (only if a clinically significant lesion and/or drainage persisted), body temperature, assessment of adverse events, and collection of clinical laboratory samples for hematology, serum chemistry, and urinalysis.

Documentation of any significant surgical procedures related to the primary infection site (performed from the first day of study administration through the Follow-up visit) such as routine debridement, incision and drainage, or amputation was performed at each study visit.

Efficacy and Safety Variables

The primary efficacy variable was the clinical response at TOC. The clinical response was assessed by the investigators while blinded to treatment assignment using the following criteria: (1) Cured: resolution of signs and symptoms associated with the skin and skin structure infection present at study admission such that no further antibiotic therapy was necessary; (2) Not Cured: inadequate response to study therapy; and (3) Indeterminate: inability to determine outcome. For purposes of analysis, a clinical response of "Not Cured" at EOT was carried forward to TOC. Other efficacy parameters included By Patient Microbiologic Response, By Pathogen Microbiologic Response, Overall Therapeutic Response, clinical signs and symptoms of infection, duration of treatment with study medication, time to resolution of fever, and size of primary infection site.

Safety parameters included adverse events, clinical laboratory test results (hematology, clinical chemistry, urinalysis), and 12-lead electrocardiogram (ECG).

Statistical Methods

A Statistical Analysis Plan (SAP) was finalized and submitted to FDA before the blind was broken and outcomes were known. Four efficacy analysis populations were prospectively defined as follows: (1) All Treated: The “All-treated” (AT) population was comprised of patients who received any amount of study medication. Patients were grouped for analysis according to the treatment assigned by randomization, regardless of the study drug actually received; (2) Modified AT: The Modified AT (MAT) population was comprised of patients in the AT population who also had a pathogen isolated at baseline from the primary infection site and/or from blood cultures; (3) Clinically Evaluable: The Clinically Evaluable (CE) population was comprised of those patients in the AT population who received the study medication assigned by the randomization schedule, and met the evaluability criteria detailed in the protocol and SAP; and (4) Microbiologically Evaluable: The Microbiologically Evaluable (ME) population was comprised of patients in the CE population who had a Gram-positive pathogen recovered from pretreatment cultures of the primary infection site and/or from blood cultures.

Patients with outcomes of “Indeterminate” or “Missing” for the TOC assessment were excluded from the CE population, and were considered the same as “Not Cured” in the efficacy evaluations of the AT population.

The primary efficacy analysis for each of the two studies was a test for noninferiority of telavancin to vancomycin with respect to clinical response at the TOC assessment. For purposes of assessing clinical noninferiority, the tests in the AT and CE populations were considered coprimary. The efficacy analysis was to test for the clinical noninferiority of telavancin relative to vancomycin, employing a noninferiority Δ criterion of 10%. Proof of noninferiority was defined as the lower bound of the 95% confidence interval for the difference in cure rates (telavancin – vancomycin) being greater than -10%. The confidence intervals on the between-treatment differences were obtained using asymptotic approximations.

For the pooled analysis of Studies 0017 and 0018, the point estimates and confidence intervals for the treatment differences were obtained using asymptotic methods, stratifying by study. These were calculated using the extended Mantel-Haenszel approach. To test for superiority of telavancin versus vancomycin in patients with MRSA from the pooled population, statistical significance was declared at the 1-sided 0.025 level. The analysis was to employ asymptotic normal theory methods and was to stratify on study.

7 EFFICACY

Key findings:

- Telavancin met or surpassed its primary endpoint in both coprimary analyses.
 - The results surpassed the prespecified noninferiority margin of 10% and achieved an even more rigorous margin where the lower bound of the 95% CI of the treatment difference was $> -6\%$ (Sections 7.5 to 7.7).
- Across multiple efficacy endpoints, including clinical response, microbiological eradication, and overall therapeutic response, telavancin was noninferior to vancomycin.
- Telavancin demonstrated efficacy across subgroups in a large, clinically relevant patient population with notable medical complications (e.g., obesity, diabetes peripheral vascular disease, and other concurrent medical conditions) and with cSSSI due to relevant and contemporary pathogens (Sections 7.1 to 7.4).
- The MRSA sub-population for the pooled results of Studies 0017 and 0018 was prespecified for analysis. Results of this analysis demonstrated that while statistical superiority of telavancin over vancomycin was not found, the clinical, microbiologic and overall therapeutic response rates were consistently numerically higher in the telavancin group in patients with MRSA cSSSI (Section 7.8).
- Telavancin was shown to be effective in the treatment of infections due to other Gram-positive pathogens including various streptococci and enterococci, as well as in infections due to *S. aureus* regardless of vancomycin MIC (Sections 7.9 and 7.10).

7.1 Patient Disposition

Table 6 provides the number of patients randomized to each treatment, and summarizes their disposition. Overall, approximately 80% of patients in each treatment group completed treatment with study medication. The most common reason in both groups for not completing treatment was premature discontinuation for an adverse event. Overall, approximately 90% of patients had a follow-up visit and therefore, according to the protocol, were considered to have completed the study.

The mean and median duration of study treatment in each group was approximately 9 days, and the majority of patients received between 7 to 14 days of study medication.

Table 6: Patient who Discontinued Study Drug – Studies 0017 and 0018, AT Population Excluding Study Sites 37004, 38020, and 38091

	0017		0018		0017 + 0018 Post	
	Post Amendment		Post Amendment		Amendment	
	TLV 10 mg/kg N (%) (N=426)	VAN N (%) (N=429)	TLV 10 mg/kg N (%) (N=458)	VAN N (%) (N=481)	TLV 10 mg/kg N (%) (N=884)	VAN N (%) (N=910)
	Number (%) of Patients					
Completed the Intended Course Of Study Therapy	350 (82)	355 (83)	365 (80)	392 (81)	715 (81)	747 (82)
Did Not Complete the Intended Course of Study Therapy	76 (18)	74 (17)	93 (20)	89 (19)	169 (19)	163 (18)
Unsatisfactory Therapeutic Response	14 (3)	13 (3)	10 (2)	8 (2)	24 (3)	21 (2)
Death	2 (<1)	2 (<1)	2 (<1)	3 (<1)	4 (<1)	5 (<1)
Two Consecutive ECGs With QTc > 500 Msec	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Adverse Event	29 (7)	22 (5)	35 (8)	27 (6)	64 (7)	49 (5)
Patient Withdrew Consent	11 (3)	14 (3)	16 (3)	18 (4)	27 (3)	32 (4)
Major Protocol Deviation	1 (<1)	2 (<1)	4 (<1)	1 (<1)	5 (<1)	3 (<1)
Lost To Follow-Up	6 (1)	6 (1)	7 (2)	9 (2)	13 (1)	15 (2)
Infection Due to Gram-negative Organisms Only	2 (<1)	4 (<1)	5 (1)	6 (1)	7 (<1)	10 (1)
Persistent S. Aureus Bacteremia	0	0	1 (<1)	0	1 (<1)	0
Other	11 (3)	10 (2)	12 (3)	16 (3)	23 (3)	26 (3)

7.2 Data Sets Analyzed

Table 7 summarizes the four efficacy analysis populations. In each study, the treatment groups were comparable with regard to the percentage of patients included in each efficacy analysis population (AT, MAT, CE, and ME). Approximately 80% of the AT population was clinically evaluable and > 70% of the CE population was also microbiologically evaluable. The most common reasons for exclusion from the CE population, occurring with similar frequencies in each treatment group, were: indeterminate response for the TOC evaluation (~11%), received non-study prohibited antibiotic (~5%), and received less than the requisite number of days of study therapy (~4%); all other reasons occurred at < 2% frequency.

Table 7: Data Sets Analyzed – Studies 0017 and 0018, Excluding Study Sites 37004, 38020, and 38091

	Study 0017		Study 0018		Total	
	TLV 10 mg/kg	VAN	TLV 10 mg/kg	VAN	TLV 10 mg/kg	VAN
	Number (%) of Patients					
AT	426 (100)	429 (100)	458 (100)	481 (100)	884 (100)	910 (100)
MAT	307 (72)	322 (75)	343 (75)	368 (77)	650 (74)	690 (76)
CE	346 (81)	349 (81)	368 (80)	371 (77)	714 (81)	720 (79)
ME	237 (56)	255 (59)	270 (59)	270 (56)	507 (57)	525 (58)

Percentages are based on number of patients in the AT population.

7.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics were similar for the AT and CE populations. Accordingly, just the results for the AT (or MAT, as appropriate) population are summarized in this section.

The two treatment groups in each study were well-balanced in terms of age, sex, race, weight, and BMI (Table 8). In each of these studies, the majority of patients were < 65 years of age. Overall, of the 884 patients treated with telavancin 10 mg/kg in these Phase 3 studies, 170 (19%) were 65 years or older and the proportion was similar in the vancomycin group. There were more males than females. The majority of patients were white, with reasonable representation of other races. The majority (approximately two-thirds) of patients enrolled in each of these studies were either overweight (BMI 25 to < 30 kg/m²), obese (BMI 30 - 40 kg/m²), or morbidly obese (BMI ≥ 40 kg/m²).

Table 8: Demographic and Baseline Characteristics – Studies 0017 and 0018, AT Population Excluding Study Sites 37004, 38020, and 38091

	Study 0017		Study 0018		Total	
	TLV 10 mg/kg (N=426)	VAN (N=429)	TLV 10 mg/kg (N=458)	VAN (N=481)	TLV 10 mg/kg (N=884)	VAN (N=910)
Age (years)						
Mean	48.9	47.7	49.2	49.9	49.1	48.8
SD	17.3	16.1	16.1	17.0	16.7	16.6
Number (%) of Patients						
Age Distribution						
<65 years	337 (79)	357 (83)	377 (82)	379 (79)	714 (81)	736 (81)
≥65 years	89 (21)	72 (17)	81 (18)	102 (21)	170 (19)	174 (19)
- Total -	426 (100)	429 (100)	458 (100)	481 (100)	884 (100)	910 (100)
Sex						
Male	230 (54)	248 (58)	258 (56)	294 (61)	488 (55)	542 (60)
Female	196 (46)	181 (42)	200 (44)	187 (39)	396 (45)	368 (40)
Race[1]						
Aborigine [2]	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
American Indian / Alaska Native	3 (<1)	2 (<1)	7 (2)	9 (2)	10 (1)	11 (1)
Asian	7 (2)	9 (2)	38 (8)	44 (9)	45 (5)	53 (6)
Black, of African heritage	59 (14)	52 (12)	69 (15)	74 (15)	128 (14)	126 (14)
Hawaiian / Pacific Islander	3 (<1)	9 (2)	4 (<1)	8 (2)	7 (<1)	17 (2)
White	349 (82)	353 (82)	336 (73)	343 (71)	685 (77)	696 (76)
Multi-racial	4 (<1)	3 (<1)	4 (<1)	3 (<1)	8 (<1)	6 (<1)
- Total -	426 (100)	429 (100)	458 (100)	481 (100)	884 (100)	910 (100)
Weight (kg)						
Mean	84.3	83.6	88.0	86.5	86.2	85.2
SD	24.9	21.9	28.5	26.2	26.9	24.3
Body Mass Index (kg/m²)						
Mean	29.4	28.8	30.1	29.9	29.8	29.4
SD	8.5	6.9	9.1	8.8	8.8	8.0
Body Mass Index(kg/m²) Distribution						
Underweight < 18.5 (kg/m ²)	7 (2)	10 (2)	7 (2)	7 (1)	14 (2)	17 (2)
Normal Weight 18.5 - < 25 (kg/m ²)	138 (32)	128 (30)	138 (30)	139 (29)	276 (31)	267 (29)
Overweight 25 - < 30 (kg/m ²)	133 (31)	137 (32)	136 (30)	148 (31)	269 (30)	285 (31)
Obese 30 - < 40 (kg/m ²)	104 (24)	120 (28)	124 (27)	131 (27)	228 (26)	251 (28)
Morbidly Obese - ≥40 (kg/m ²)	44 (10)	34 (8)	53 (12)	56 (12)	97 (11)	90 (10)
- Total -	426 (100)	429 (100)	458 (100)	481 (100)	884 (100)	910 (100)

[1] A patient could indicate more than one racial category.

[2] 'Aborigine' was not a CRF-prompted category but was indicated in the CRF margin.

Baseline renal function is summarized in Table 9. Although the majority of patients had normal renal function (CrCl > 80 mL/min), patients with varying degrees of renal impairment

were represented. Notably, there were more patients in the telavancin group with CrCl < 30 mL/min.

Table 9: Baseline Renal Function – Studies 0017 and 0018, AT Population Excluding Study Sites 37004, 38020, and 38091

	Study 0017		Study 0018		Total	
	TLV 10 mg/kg (N=426)	VAN (N=429)	TLV 10 mg/kg (N=458)	VAN (N=481)	TLV 10 mg/kg (N=884)	VAN (N=910)
Baseline Serum Creatinine (µmol/L)[1]						
Mean	83	81	82	83	82	82
SD	60	79	40	48	51	65
Baseline Creatinine Clearance (mL/min)[2]						
Mean	96	98	93	92	94	95
SD	41	37	36	38	38	38
Number (%) of Patients						
Categories:						
>80 mL/min	274 (65)	291 (69)	279 (63)	286 (62)	553 (64)	577 (65)
>50-80 mL/min	85 (20)	85 (20)	112 (25)	118 (25)	197 (23)	203 (23)
30-50 mL/min	41 (10)	35 (8)	32 (7)	45 (10)	73 (8)	80 (9)
<30 mL/min	21 (5)	12 (3)	17 (4)	16 (3)	38 (4)	28 (3)
- Total -	421 (100)	423 (100)	440 (100)	465 (100)	861 (100)	888 (100)
Missing	5	6	18	16	23	22
Hemodialysis						
Pts on Hemodialysis	6 (1)	4 (<1)	3 (<1)	1 (<1)	9 (1)	5 (<1)

[1] Data from central lab.

[2] Calculated using creatinine data from central lab.

Table 10 summarizes medical conditions and surgical procedures directly associated with cSSSI. Diabetes mellitus and recent trauma were the most frequently occurring conditions across all studies. Approximately 10% of the patients had cSSSI associated with a prior surgical procedure.

Table 10: Medical/Surgical Conditions Associated with cSSSI – Studies 0017 and 0018, AT Population Excluding Study Sites 37004, 38020, and 38091

	Study 0017		Study 0018		Total	
	TLV 10 mg/kg (N=426)	VAN (N=429)	TLV 10 mg/kg (N=458)	VAN (N=481)	TLV 10 mg/kg (N=884)	VAN (N=910)
	Number (%) of Patients					
Any History/Condition[1]	325 (76.3)	327 (76.2)	292 (63.8)	321 (66.7)	617 (69.8)	648 (71.2)
Diabetes mellitus	109 (25.6)	109 (25.4)	113 (24.7)	118 (24.5)	222 (25.1)	227 (24.9)
Recent trauma	115 (27.0)	125 (29.1)	59 (12.9)	65 (13.5)	174 (19.7)	190 (20.9)
Recent surgical procedure	37 (8.7)	42 (9.8)	58 (12.7)	48 (10.0)	95 (10.7)	90 (9.9)
Peripheral vascular disease	42 (9.9)	28 (6.5)	33 (7.2)	49 (10.2)	75 (8.5)	77 (8.5)
Bite	33 (7.7)	50 (11.7)	34 (7.4)	34 (7.1)	67 (7.6)	84 (9.2)
Chronic skin disease	34 (8.0)	25 (5.8)	25 (5.5)	44 (9.1)	59 (6.7)	69 (7.6)
Chronic edema	21 (4.9)	20 (4.7)	21 (4.6)	32 (6.7)	42 (4.8)	52 (5.7)
Thermal burn	7 (1.6)	4 (0.9)	14 (3.1)	10 (2.1)	21 (2.4)	14 (1.5)
Foreign body	5 (1.2)	3 (0.7)	5 (1.1)	6 (1.2)	10 (1.1)	9 (1.0)
Other	62 (14.6)	59 (13.8)	42 (9.2)	57 (11.9)	104 (11.8)	116 (12.7)

[1] More than one condition could be reported.

Infection type and location are summarized in Table 11. The most frequent types of infection were major abscess and deep/extensive cellulitis. Wound infections were also well represented, while there were fewer cases of infected ulcers and even fewer infected burns. Approximately one-half of the infections were in the lower extremities.

Table 11: Type and Location of cSSSI – Studies 0017 and 0018, AT Population
Excluding Study Sites 37004, 38020, and 38091

	Study 0017		Study 0018		Total	
	TLV 10 mg/kg (N=426)	VAN (N=429)	TLV 10 mg/kg (N=458)	VAN (N=481)	TLV 10 mg/kg (N=884)	VAN (N=910)
Number (%) of Patients						
Description of Complicated Skin/Skin Structure Infection						
Major Abscess	179 (42)	193 (45)	196 (43)	204 (42)	375 (42)	397 (44)
Wound Infection	72 (17)	60 (14)	67 (15)	61 (13)	139 (16)	121 (13)
Deep/Extensive Cellulitis	156 (37)	161 (38)	153 (33)	176 (37)	309 (35)	337 (37)
Infected Ulcer	16 (4)	12 (3)	29 (6)	34 (7)	45 (5)	46 (5)
Infected Burn	3 (<1)	3 (<1)	13 (3)	6 (1)	16 (2)	9 (<1)
Location of Primary Infection Site						
Head/Neck	29 (7)	33 (8)	32 (7)	31 (6)	61 (7)	64 (7)
Front Torso	61 (14)	60 (14)	65 (14)	60 (12)	126 (14)	120 (13)
Back Torso	43 (10)	53 (12)	49 (11)	51 (11)	92 (10)	104 (11)
Upper Extremities	84 (20)	99 (23)	60 (13)	65 (14)	144 (16)	164 (18)
Lower Extremities	209 (49)	184 (43)	252 (55)	274 (57)	461 (52)	458 (50)

7.4 Baseline Pathogens

Nearly all (99%) patients in the MAT population had a pathogen isolated from the primary infection site at baseline. The remaining patients had a pathogen isolated from baseline blood cultures. All ME patients had Gram-positive pathogens. Table 12 summarizes the most common pathogens isolated from the primary infection site at baseline. The treatment groups were well balanced in terms of the distribution of baseline pathogens. Most patients (82% of telavancin patients and 85% of vancomycin patients in Studies 0017 and 0018 combined) had *S. aureus* isolated from the primary infection site. In the combined population, 52% of telavancin-treated patients and 53% of vancomycin-treated patients had a *S. aureus* isolate that was methicillin-resistant (MRSA).

Table 12: Most Common Pathogens Isolated from the Primary Infection Site at Baseline – Studies 0017 and 0018, MAT Population Excluding Study Sites 37004, 38020, and 38091

	Study 0017		Study 0018		Total	
	TLV 10 mg/kg (N=307)	VAN (N=322)	TLV 10 mg/kg (N=343)	VAN (N=368)	TLV 10 mg/kg (N=650)	VAN (N=690)
	Number (%) of Patients					
Any Primary Infection Site Pathogen	301 (98)	321 (100)	342 (100)	364 (99)	643 (99)	685 (99)
Primary Infection Site Pathogen Only	287 (93)	314 (98)	329 (96)	356 (97)	616 (95)	670 (97)
Primary Infection Site and Blood Pathogen	14 (5)	7 (2)	13 (4)	8 (2)	27 (4)	15 (2)
	Number (%) of Patients with Any Primary Infection Site Pathogen					
Gram-Positive Pathogens	279 (93)	306 (95)	331 (97)	347 (95)	610 (95)	653 (95)
<i>S. aureus</i> (All)	242 (80)	270 (84)	288 (84)	311 (85)	530 (82)	581 (85)
MRSA	144 (48)	167 (52)	188 (55)	194 (53)	332 (52)	361 (53)
MSSA	102 (34)	105 (33)	100 (29)	118 (32)	202 (31)	223 (33)
<i>Enterococcus faecalis</i>	15 (5)	18 (6)	15 (4)	25 (7)	30 (5)	43 (6)
<i>Streptococcus pyogenes</i>	13 (4)	14 (4)	14 (4)	17 (5)	27 (4)	31 (5)
<i>Streptococcus agalactiae</i>	11 (4)	7 (2)	11 (3)	14 (4)	22 (3)	21 (3)
<i>Streptococcus anginosus</i>	7 (2)	3 (<1)	5 (1)	4 (1)	12 (2)	7 (1)
<i>Streptococcus constellatus</i>	2 (<1)	3 (<1)	4 (1)	4 (1)	6 (<1)	7 (1)
<i>Streptococcus intermedius</i>	2 (<1)	1 (<1)	1 (<1)	2 (<1)	3 (<1)	3 (<1)
Gram-Positive Pathogens Only	244 (81)	274 (85)	289 (85)	302 (83)	533 (83)	576 (84)
Gram-Negative Pathogens Only	22 (7)	15 (5)	11 (3)	17 (5)	33 (5)	32 (5)
Mixed Gram-Positive/Gram-Negative Infection	35 (12)	32 (10)	42 (12)	45 (12)	77 (12)	77 (11)

Figure 7 displays the telavancin MIC distribution for isolates of MSSA and MRSA recovered from patients in studies 0017 and 0018. These susceptibility data are consistent with the results from contemporary surveillance studies, and demonstrate the potency of telavancin against these pathogens. Figure 8 displays the data for vancomycin.

Figure 7: Telavancin MIC Distributions for MSSA and MRSA from Studies 0017 and 0018, MAT Population Excluding Study Sites 37004, 38020, and 38091

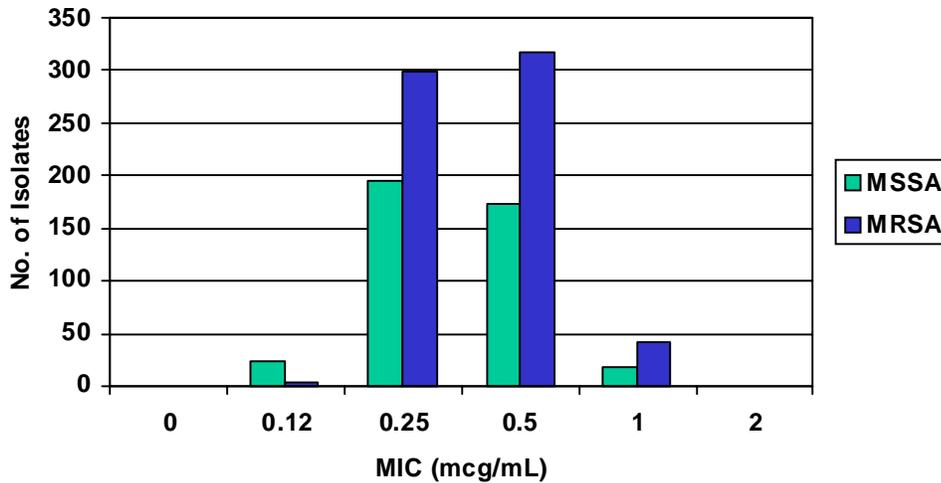
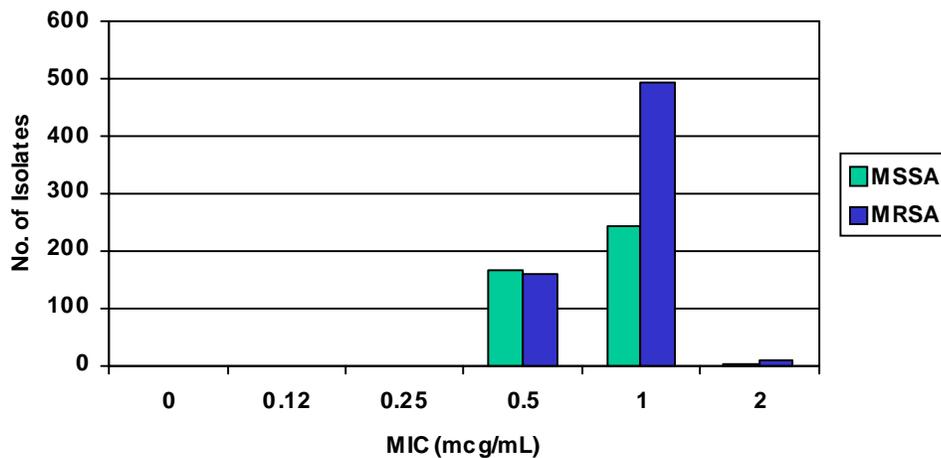


Figure 8: Vancomycin MIC Distributions for MSSA and MRSA from Studies 0017 and 0018, MAT Population Excluding Study Sites 37004, 38020, and 38091



Isolates of *S. aureus* were submitted to a reference laboratory (V. Fowler, Duke University) and analyzed for the presence of the gene encoding the Pantone-Valentine leukocidin (PVL). Table 13 displays susceptibility data for these isolates of *S. aureus* from any study visit by their PVL positivity and by methicillin resistance phenotype. Of the 650 strains of MRSA that were tested, 548 (84%) were PVL-positive, while 280 of 403 (69%) MSSA strains were PVL-negative. There did not appear to be any evident differences in susceptibility of these strains to telavancin or vancomycin based upon their PVL status.

Table 13: Susceptibility of *Staphylococcus aureus* by Presence of PVL Gene – Studies 0017 and 0018, Excluding Study Sites 37004, 38020, and 38091

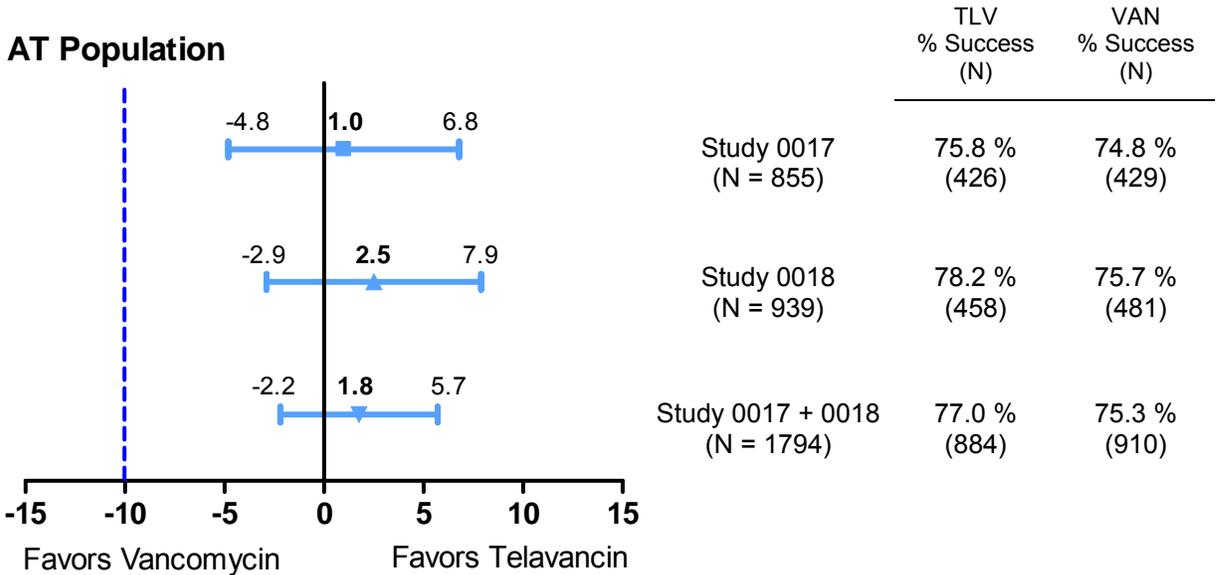
	MIC50 (90)	Range	MIC50 (90)	Range	MIC50 (90)	Range
PVL Positive	<i>S. aureus</i> N=671		MRSA N=548		MSSA N=123	
Telavancin	0.5 (0.5)	0.12 to 1	0.5 (0.5)	0.12 to 1	0.25 (0.5)	0.12 to 1
Vancomycin	1 (1)	0.5 to 2	1 (1)	0.5 to 2	1 (1)	0.5 to 2
PVL Negative	<i>S. aureus</i> N=382		MRSA N=102		MSSA N=280	
Telavancin	0.25 (0.5)	0.12 to 1	0.5 (0.5)	0.12 to 1	0.25 (0.5)	0.12 to 1
Vancomycin	1 (1)	0.5 to 2	1 (1)	0.5 to 2	1 (1)	0.5 to 2

MIC - Minimum Inhibitory Concentration (µg/mL)

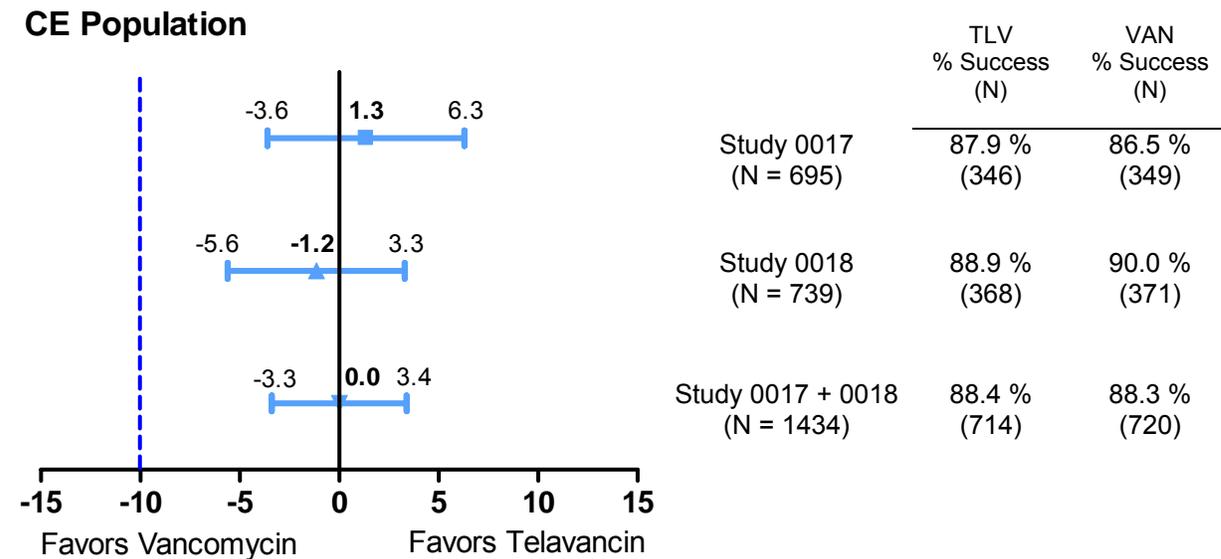
7.5 Clinical Response at Test of Cure – The Primary Efficacy Variable

Figure 9 displays the difference (telavancin – vancomycin) in cure (also referred to as “success”) rates between telavancin and vancomycin for the AT and CE populations in Studies 0017 and 0018 individually and combined. On this, the primary endpoint, the studies demonstrated that telavancin was effective in the treatment of cSSSI as the results demonstrated noninferiority to vancomycin in both the AT and CE populations. This was evidenced by the lower bound of the 95% CI around the difference (telavancin - vancomycin) in cure rates being well above -10% when these studies were considered individually and when they were combined.

Figure 9: Difference (Telavancin vs. Vancomycin) and 95% CIs in Cure Rates at Test-of-Cure – Studies 0017 and 0018, AT and CE Populations Excluding Study Sites 37004, 38020, and 38091



**Difference in Success Rates
 (TLV - VAN, %) with 95% Confidence Interval**



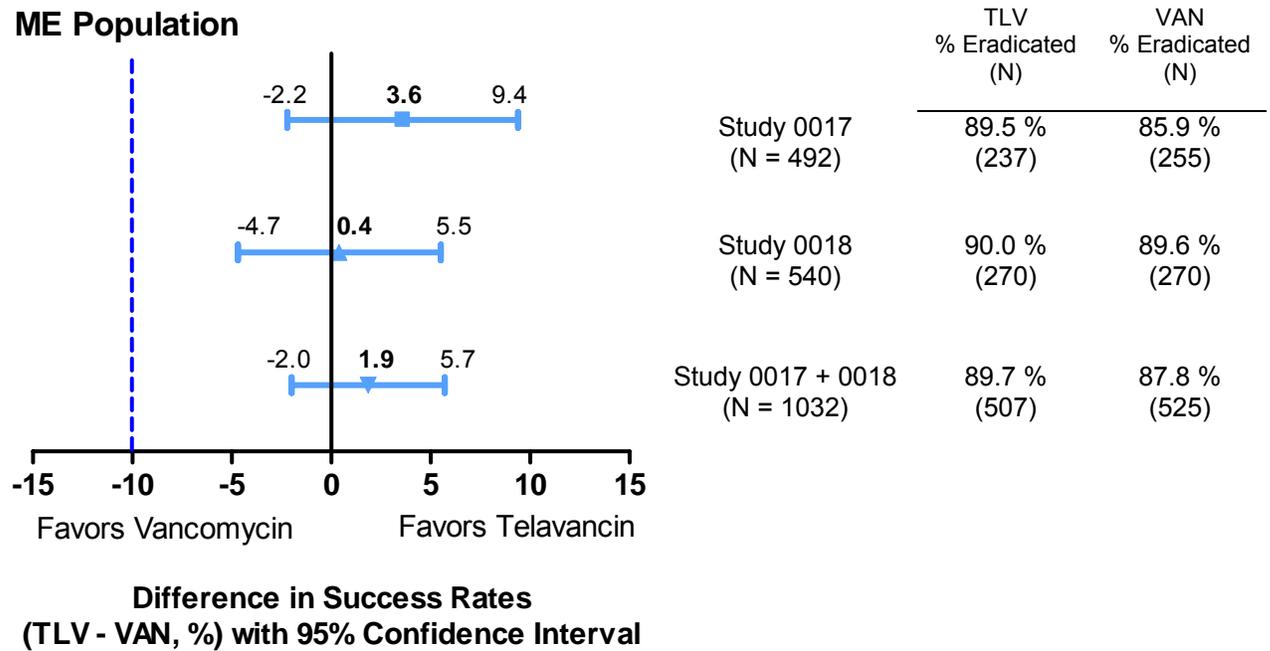
**Difference in Success Rates
 (TLV - VAN, %) with 95% Confidence Interval**

Fourteen patients treated in Studies 0017 and 0018, (0.7%; 8 telavancin, 6 vancomycin) from 11 different sites were judged by the investigators to have an Indeterminate outcome at the EOT visit, were given non-study antibiotics for their cSSSI, and judged to be Cured at the TOC visit. In the efficacy analyses these patients were excluded from the CE population because they received non-study antibiotics. However, the investigators' assessments should have been questioned, as the requirement for additional antibiotic treatment may be evidence that these patients were not cured at EOT. In Theravance's analysis, patients who were judged Not Cured at EOT were automatically rendered Not Cured at TOC. After changing the clinical response of these 14 patients from Cured at TOC and Not CE to Not Cured and CE, the clinical response at TOC for the CE populations in the individual studies and the combined population were reanalyzed. Given the small numbers of patients affected by this reanalysis, the clinical response rates were largely unchanged and continued to demonstrate noninferiority of telavancin vs. vancomycin. In the AT Population, 76.1% of the telavancin group and 74.6% of the vancomycin group were Cured (difference, 95% CI: 1.5, -2.5 to 5.5). In the CE Population, 87.4% of the telavancin group and 87.6% of the vancomycin group were Cured (difference, 95% CI: 0.2, -3.6 to 3.2).

7.6 Microbiologic Response at Test of Cure

Consistent with the results for clinical response, noninferiority of telavancin to vancomycin was shown for the Microbiological Eradication rate in each study and for the two studies combined. Results for the ME population are shown in Figure 10; and results for the MAT population were similar.

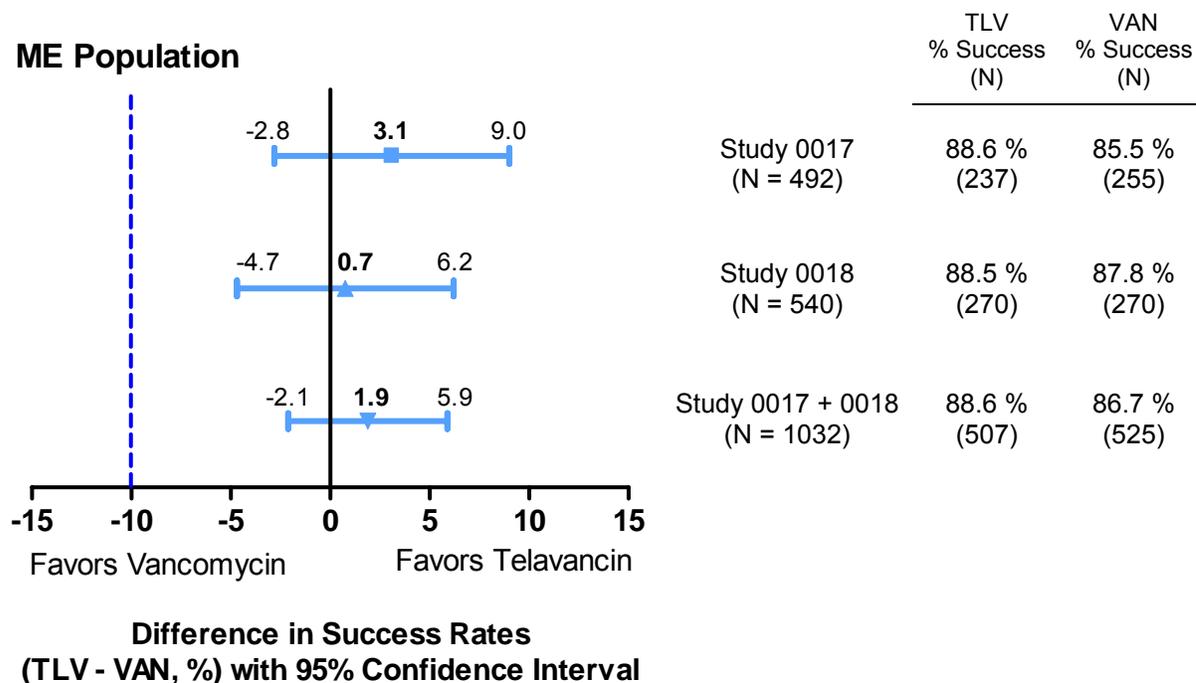
Figure 10: Difference (Telavancin vs. Vancomycin) and 95% CIs in Microbiological Eradication Rates at Test of Cure – Studies 0017 and 0018, ME Population Excluding Study Sites 37004, 38020, and 38091



7.7 Overall Therapeutic Response at Test of Cure

The overall therapeutic response, an endpoint requiring clinical cure plus microbiologic eradication, also demonstrated noninferiority of telavancin 10 mg/kg to vancomycin in each study and for the two studies combined. Results for the ME population are shown in Figure 11; and results for the MAT population were similar to the results for the ME population.

Figure 11: Difference (Telavancin vs. Vancomycin) and 95% CIs in Overall Therapeutic Response at Test of Cure – Studies 0017 and 0018, ME Population Excluding Study Sites 37004, 38020, and 38091



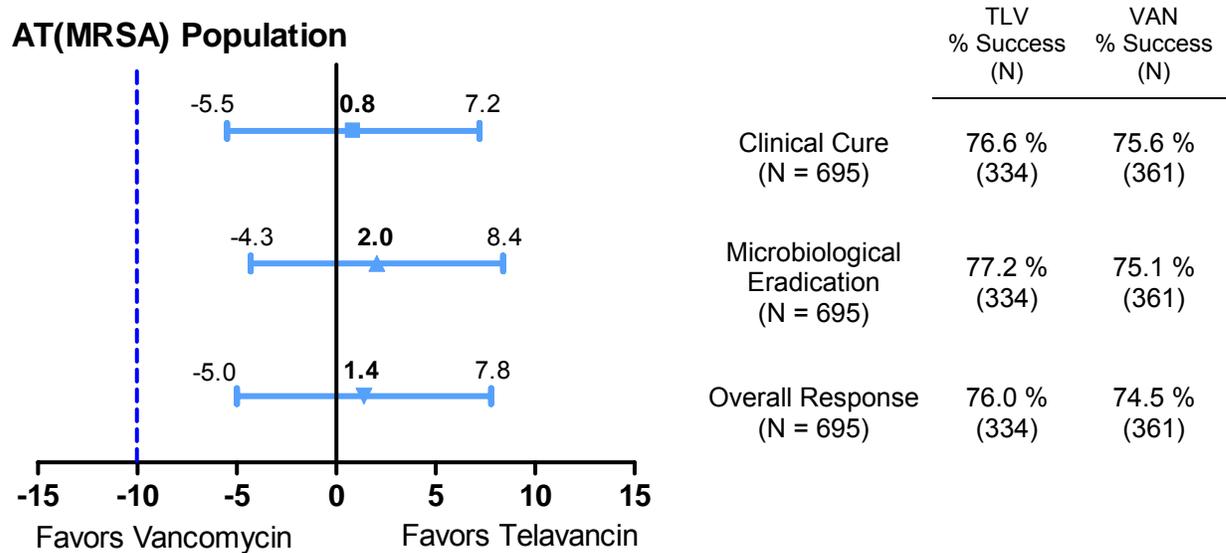
7.8 Efficacy Results in Patients with MRSA cSSSI

A prespecified objective of the cSSSI program was to pool the data from Studies 0017 and 0018 to test whether telavancin 10 mg/kg is superior to vancomycin in the treatment of cSSSI due to MRSA. Figure 12 summarizes the clinical response rates, microbiologic eradication rates and overall therapeutic response rates for patients in the AT(MRSA)⁴ and CE(MRSA)⁵ populations of Studies 0017 and 0018 combined. Results of this analysis demonstrated that while statistical superiority of telavancin over vancomycin was not found, the clinical, microbiologic, and overall therapeutic response rates were consistently numerically higher in the telavancin group in both analysis populations.

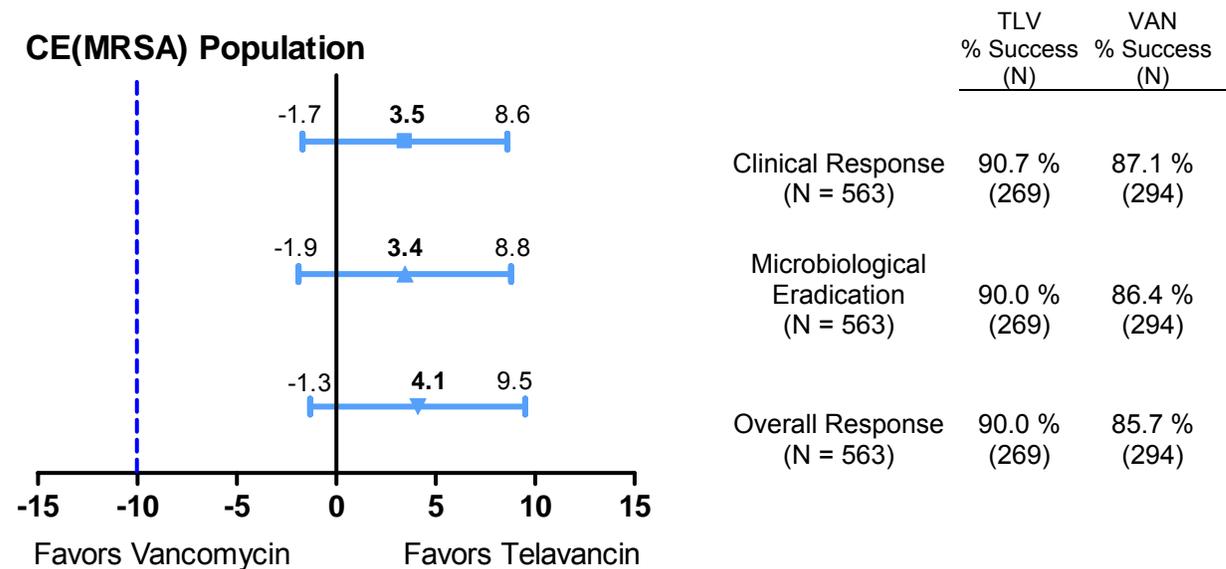
⁴ AT(MRSA) = AT patients with MRSA at baseline, which by definition is also MAT patients with MRSA at baseline

⁵ CE(MRSA) = CE patients with MRSA at baseline, which by definition is also ME patients with MRSA at baseline

Figure 12: Summary of Efficacy for Patients with MRSA at Baseline - Studies 0017 and 0018, AT(MRSA) and CE(MRSA) Populations Excluding Study Sites 37004, 38020, and 38091



**Difference in Success Rates
(TLV - VAN, %) with 95% Confidence Interval**



**Difference in Success Rates
(TLV - VAN, %) with 95% Confidence Interval**

7.9 Clinical Response in Patients with Gram-positive Pathogens Other than MRSA

Clinical response rates in patients with other commonly isolated Gram-positive cSSSI pathogens are shown in Table 14. Similar clinical responses were seen for the two treatment groups demonstrating the efficacy of telavancin in infections due to a range of Gram-positive pathogens.

Table 14: Clinical Cure Rates in Patients with Common Gram-positive Pathogens – Studies 0017 and 0018, ME Population Excluding Study Sites 37004, 38020, and 38091

	TLV 10 mg/kg (N=507)	VAN (N=525)
Gram-Positive Pathogens		
<i>S. aureus</i> (All)	396 / 441 (89.8)	406 / 465 (87.3)
<i>S. aureus</i> (MSSA)	154 / 175 (88.0)	153 / 175 (87.4)
<i>Enterococcus faecalis</i>	23 / 25 (92.0)	28 / 34 (82.4)
<i>Streptococcus agalactiae</i>	15 / 19 (78.9)	16 / 18 (88.9)
<i>Streptococcus anginosus</i>	10 / 10 (100.0)	7 / 7 (100.0)
<i>Streptococcus pyogenes</i>	21 / 23 (91.3)	22 / 24 (91.7)

7.10 Clinical Response by Baseline Pathogen Susceptibility (MIC)

Table 15 displays the clinical response rates by MIC for the patients in the telavancin and vancomycin treatment groups who had MSSA or MRSA as baseline pathogens. For each treatment group, the cure rates are displayed for the MIC of the study medication (telavancin or vancomycin). There are no evident trends to lower responses with increasing MIC, although the numbers of patients in the groups with the highest MIC are very small, and are significantly affected by a single cure or failure.

Table 15: Clinical Response by MIC for Baseline Pathogens in Patients with MSSA or MRSA - Studies 0017 and 0018, ME Population Excluding Study Sites 37004, 38020, and 38091

MIC (µg/mL)	Telavancin		Vancomycin	
	MRSA	MSSA	MRSA	MSSA
0.12	0 / 1 (0.0)	9 / 9 (100.0)	--	--
0.25	114 / 121 (94.2)	72 / 82 (87.8)	--	--
0.5	105 / 118 (89.0)	61 / 70 (87.1)	56 / 67 (83.6)	58 / 68 (85.3)
1	12 / 15 (80.0)	6 / 7 (85.7)	185 / 206 (89.8)	84 / 96 (87.5)
2	--	--	4 / 6 (66.7)	1 / 1 (100.0)

In addition, clinical response in the telavancin group was assessed for patients infected with *S. aureus* by the vancomycin MIC of the baseline pathogens. The proportion of patients with a clinical response of cure was not diminished in patients treated with telavancin whose baseline pathogens had vancomycin MIC of 1 - 2 µg/mL (Table 16).

Table 16: Clinical Response of Cure by Baseline Vancomycin MIC in Telavancin Patients with *Staphylococcus aureus* as Baseline Pathogen – Studies 0017 and 0018, ME Population Excluding Study Sites 37004, 38020, and 38091

Vancomycin MIC (µg/mL)	Telavancin		
	<i>S. aureus</i> (All)	MRSA	MSSA
0.5	115 / 130 (88.5)	52 / 59 (88.1)	63 / 71 (88.7)
1	261 / 290 (90.0)	177 / 194 (91.2)	84 / 96 (87.5)
2	3 / 3 (100.0)	2 / 2 (100.0)	1 / 1 (100.0)

7.11 Clinical Response by Renal Function

The results of Studies 0017 and 0018 were consistent in demonstrating that telavancin is noninferior to vancomycin in patients with cSSSI. To evaluate the consistency of results, multiple exploratory subgroup analyses were performed. These included intrinsic factors such as demographics (age, sex, race, ethnicity, and body mass index), diabetic status and renal status (normal, mild, moderate or severe renal deficiency). Extrinsic factors examined included geographic region (US vs. non-US and prespecified country grouping), surgical intervention, infection type (major abscess, wound infection, deep/extensive cellulitis, infected ulcer, infected burn), prior antimicrobial therapy, and presence or absence of bacteremia. Across nearly all subgroups, findings were generally consistent with the overall

demonstration of noninferiority. For the subgroup of patients who entered the study with decreased creatinine clearance, lower clinical cure rates for telavancin relative to vancomycin were identified (Table 17).

Table 17: Clinical Cure Rates by Baseline Renal Function - Studies 0017 and 0018, CE Population, Excluding Sites 37004, 38020, and 38091

	TLV 10 mg/kg (N= 714) % (s/n [1])	VAN (N= 720) % (s/n [1])	Difference TLV - VAN Difference (95% CI) [2]
Creatinine Clearance			
Normal	92.6 (415 /448)	89.2 (406 /455)	3.4 (-0.3 , 7.1)
Mild Deficiency	86.6 (136 /157)	88.0 (146 /166)	-1.3 (-8.6 , 5.9)
Moderate Deficiency	75.8 (47 /62)	83.3 (55 /66)	-7.5 (-21.5 , 6.4)
Severe Deficiency	69.2 (18 /26)	89.5 (17 /19)	-20.2 (-40.7 [^] , 5.0) [^]

[1] s/n = Number of cured patients / Number of patients in subgroup.

[2] Difference in cure rates (telavancin - vancomycin); two-sided 95% CI.

[^] = Confidence interval uses Agresti-Caffo adjustment.

In the renal status (i.e., creatinine clearance) categories used in the subgroup analyses displayed in Table 17, the overall treatment-by-renal status subgroup interaction p-value was 0.086. The largest group of patients (63%) were in the Normal creatinine clearance category where the cure rate in the telavancin group exceeded the cure rate in the vancomycin group by 3.4% (95% CI: (-0.3, 7.1). Vancomycin cure rates were higher than telavancin in the abnormal creatinine clearance categories. Confidence intervals for treatment differences overlapped among all of the subgroups. The possibility was assessed that inadequate upwards dosage adjustment in patients with moderate or severe baseline renal function whose renal function improved during the study could have led to the lower cure rates in the telavancin group. Table 18 reveals that cure rate in patients with improving renal function whose doses were not adjusted was 100% vs. approximately 77% in patients whose dose was adjusted. It should be noted, however, that renal function improved during telavancin treatment in approximately 36% (40/111, Table 9) of the patients with moderate or severe impairment at Baseline.

Table 18: Clinical Response by Dose Adjustment in Patients With Improving Renal Function – Studies 0017 and 0018, AT Population Excluding Sites 37004, 38020, and 38091

	N (%) Patients Treated with Telavancin (N = 885)	Clinical Cures N (%)	
		Dose Adjusted	Dose Not Adjusted
Improving Renal Function			
Severe ==> Moderate	10 (1.1 %)	5 /9 (55.6%)	1 /1 (100.0%)
Severe ==> Normal/Mild	3 (0.3 %)	2 /2 (100.0%)	1 /1 (100.0%)
Moderate ==> Normal/Mild	27 (3.1 %)	19 /23 (82.6%)	4 /4 (100.0%)
Total	40 (4.5%)	26 /34 (76.5%)	6 /6 (100%)

Because MRSA was a predefined subgroup and associated efficacy rates are potentially confounded by creatinine clearance it is of interest to describe the MRSA subset for the Normal and Mild renal function groups. This analysis should be viewed with caution but is reported for completeness and provided for full documentation of this exploratory analysis of renal function on outcome. Table 19 displays MRSA cure rates for the AT and CE populations. The pooled estimate of the difference between telavancin and vancomycin was 5.6% with 95% confidence interval of (0.5, 10.7) indicating a statistical benefit. The magnitude of this benefit was not observed in the AT analysis set, which is a noisier group than the CE analysis set, which offers a more specific assessment.

Table 19: Clinical Response at Test-of-cure in Patients with MRSA Isolated at Baseline – Studies 0017, 0018, and 0017/0018 Combined, AT (MRSA) and CE (MRSA) Populations, Post Amendment Patients with Normal or Mildly Impaired Baseline Renal Function (> 50mL/min), Excluding Study Sites 37004, 38020, and 38091

	Study 0017		Study 0018		Total	
	TLV 10 mg/kg N (%)	VAN N (%)	TLV 10 mg/kg N (%)	VAN N (%)	TLV 10 mg/kg N (%)	VAN N (%)
AT(MRSA)						
Cure	95 (73.1)	111 (73.5)	137 (82.0)	134 (77.9)	232 (78.1)	245 (75.9)
Not Cured	13 (10.0)	21 (13.9)	12 (7.2)	20 (11.6)	25 (8.4)	41 (12.7)
Indeterminate	7 (5.4)	1 (0.7)	7 (4.2)	6 (3.5)	14 (4.7)	7 (2.2)
Missing	15 (11.5)	18 (11.9)	11 (6.6)	12 (7.0)	26 (8.8)	30 (9.3)
- Total -	130 (100.0)	151 (100.0)	167 (100.0)	172 (100.0)	297 (100.0)	323 (100.0)
Difference (95% CI)[1]	-0.4 (-10.8 , 9.9)		4.1 (-4.4 , 12.6)		2.1 (-4.6 , 8.7)	
p value [2]	0.271					
CE(MRSA)						
Cure	92 (90.2)	108 (86.4)	132 (95.7)	125 (88.7)	224 (93.3)	233 (87.6)
Not Cured	10 (9.8)	17 (13.6)	6 (4.3)	16 (11.3)	16 (6.7)	33 (12.4)
- Total -	102 (100.0)	125 (100.0)	138 (100.0)	141 (100.0)	240 (100.0)	266 (100.0)
Difference (95% CI)[1]	3.8 (-4.5 , 12.1)		7.0 (0.5 , 13.3)^		5.6 (0.5 , 10.7)	
p value [2]	0.016					

[1] Difference in Cure rates (telavancin – vancomycin); two-sided 95% CI. For pooled-study presentation (0017 + 0018), the analysis was stratified by study.

[2] One-sided p value for test of superiority TLV vs VAN at 0.025 level. The test is stratified by study.

Note: Baseline Renal Function based on baseline creatinine clearance value from central labs.

In contrast to the MRSA subgroup analyses summarized in Section 7.8, which were prespecified and subjected to statistical testing through a gatekeeper approach, none of the subgroup analyses summarized in this section were prespecified and subjected to such rigor. Accordingly, all the subgroup analyses summarized in this section, including the subgroup analyses by renal status, should be considered exploratory.

7.12 Compassionate Use Protocol

Telavancin has been made available for compassionate use (emergency IND) in clinical situations where other available therapies are inactive in vitro, have failed clinically or the patient cannot tolerate them. To date, three patients have received telavancin under this program. Brief summaries are available for two patients who have completed therapy with telavancin. Minimal information is available for the third patient. This is a female with complicated chronic sinusitis due to MRSA that had been unresponsive to several courses of different antibiotics. She was given telavancin for a period of approximately 2 weeks prior to a surgical procedure to drain and debride the sinuses. Following surgery, she received several more weeks of telavancin and has done well with resolution of the infection.

The first patient was a 25-year-old female with persistent MRSA septicemia and bacteremia following perineal soft tissue infection. She remained ill despite therapy with vancomycin, linezolid, and intravenous clindamycin. Additionally, she had decreased hearing unilaterally beginning after the first dose of vancomycin. Multiple septic pulmonary emboli and pulmonary infiltrates precluded the use of daptomycin. She received telavancin under an emergency IND and had a rapid clinical and microbiologic cure. She completed a 28-day course of therapy and tolerated the therapy well with the only adverse events reported being foamy urine and taste disturbance. She became pregnant shortly after treatment with telavancin was discontinued, and delivered a healthy baby. She has remained well.

The second patient was a 51-year-old female with end-stage renal disease on hemodialysis who was admitted on 11 January 2008 with MRSA sepsis due to an infected implantable cardioverter defibrillator (ICD). The ICD was removed on 12 January 2008. She developed back pain and an MRI on 25 January 2008 showed discitis with vertebral osteomyelitis of L4-5. Her blood cultures remained positive through 07 February 2008. MICs for the MRSA in her blood were determined—daptomycin 3 mcg/mL, tigecycline 0.19 mcg/mL, vancomycin

4 mcg/mL, linezolid 2 mcg/mL. Believing that this was an endovascular infection due to a VISA strain of *S. aureus*, treatment was switched to telavancin. Her blood cultures became sterile on 10 February 2008. Telavancin was initiated on 11 February 2008 and continued until approximately 18 February 2008, at which time she developed a new fever. She experienced no adverse effects related to the use of telavancin. The fever was likely due to peritonitis with necrosis of the rectosigmoid colon with *Klebsiella* in the blood on 26 February 2008. She underwent a sigmoid colectomy and proctectomy but failed to improve and expired on 15 April 2008.

8 SAFETY

This summary of safety is focused on patients enrolled in the cSSSI efficacy and safety studies. Where relevant, safety results from the HAP studies, which have been submitted to the FDA, have been referenced to provide information on an additional population of patients treated with telavancin. The number of patients exposed to study medication in the Phase 2 and 3 studies for both cSSSI and HAP is shown in Table 20. The Safety Population includes all patients treated in studies evaluating telavancin 10 mg/kg once daily. The only data excluded are ECG data from two sites, as noted previously.

Table 20: Patients Treated – Studies 0017, 0018, 202b, 0015, and 0019, Safety Population

	TLV 10 mg/kg	VAN [1]
cSSSI Studies (Studies 202b, 0017 and 0018)	1029	1033
HAP Studies (Studies 0015 and 0019)	751	752
Total	1780	1785

[1] Includes subjects who received an antistaphylococcal penicillin instead of vancomycin (20 subjects in 0015 and 0019, 7 subjects in 202b).

In nonclinical, Phase 1 and Phase 2 testing of telavancin, signals for potential renal impairment and effects on QTc prolongation were detected. The Phase 3 programs were designed to further assess the importance of these effects by including at-risk patients (individuals with underlying significant renal impairment and patients taking medications that are known to affect the QTc interval). The Phase 3 studies confirmed the potential for renal impairment with telavancin, while not revealing any new safety signals.

8.1 Summary of Adverse Events

Telavancin was well-tolerated, with the majority of adverse events being mild to moderate and reversible. Table 21 displays an overview of adverse events in the cSSSI studies.

Table 21: Overview of Treatment-emergent Adverse Events – Studies 0017, 0018, and 202b, Safety Population

	TLV 10 mg/kg (N=1029)	VAN [1] (N=1033)
	Number (%) of Patients	
Patients with at Least One Adverse Event	791 (77%)	730 (71%)
Deaths	8 (<1%)	9 (<1%)
Patients with Any Serious Adverse Event	76 (7%)	45 (4%)
Patients Who Discontinued Study Medication Due to Adverse Event	79 (8%)	56 (5%)

[1] Includes 7 patients who received an antistaphylococcal penicillin instead of vancomycin in Study 202b.

8.1.1 Common Adverse Events

The overall incidence of adverse events was 77% in the telavancin group and 71% in the vancomycin group (Table 21). Table 22 lists events that occurred in > 2% of patients in either treatment group.

- Nausea, vomiting and headache were the most frequently reported (> 10%) events in telavancin-treated patients, but rarely led to treatment discontinuation. Taste disturbance (coded as dysgeusia) and foamy urine (coded as urine abnormality) were commonly reported side effects in telavancin-treated patients.
- Nausea, pruritus, and headache were the most frequently reported (> 10%) events in vancomycin-treated patients, and again rarely led to treatment discontinuation.
- Less than 10% of patients in either treatment group experienced an event that was classified as severe. Less than 0.4% of telavancin- or vancomycin-treated patients experienced severe nausea or vomiting.

- Table 23 lists the events that occurred in $\geq 10\%$ of patients by greatest severity. No individual severe event occurred in $\geq 1\%$ of patients.

Table 22: Adverse Events Occurring in > 2% of Patients Treated with Telavancin or Vancomycin - cSSSI Studies, Safety Population

	Telavancin 10 mg/kg (N=1029)	Vancomycin (N=1033)
Any Event in Full Safety Population	791 (77%)	730 (71%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anaemia	26 (3%)	22 (2%)
GASTROINTESTINAL DISORDERS		
Abdominal Pain	17 (2%)	26 (3%)
Constipation	101 (10%)	68 (7%)
Diarrhoea	73 (7%)	81 (8%)
Nausea	265 (26%)	148 (14%)
Vomiting	135 (13%)	75 (7%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue	42 (4%)	31 (3%)
Infusion Site Erythema	26 (3%)	27 (3%)
Infusion Site Pain	42 (4%)	40 (4%)
Rigors	47 (5%)	23 (2%)
METABOLISM AND NUTRITION DISORDERS		
Decreased Appetite	27 (3%)	19 (2%)
NERVOUS SYSTEM DISORDERS		
Dizziness	58 (6%)	55 (5%)
Dysgeusia	325 (32%)	62 (6%)
Headache	138 (13%)	124 (12%)
PSYCHIATRIC DISORDERS		
Anxiety	27 (3%)	22 (2%)
Insomnia	103 (10%)	89 (9%)
RENAL AND URINARY DISORDERS		
Foamy Urine ¹	125 (12%)	27 (3%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Pruritus	60 (6%)	128 (12%)
Pruritus Generalised	28 (3%)	60 (6%)
Rash	37 (4%)	43 (4%)

Note: Includes Studies 0017, 0018, and 202b.

[¹]Coded as urine abnormality

Table 23: Adverse Events Occurring in $\geq 10\%$ of Patients Treated with Telavancin or Vancomycin by Severity – cSSSI Studies, Safety Population

	Telavancin 10 mg/kg (N=1029)	VAN (N=1033)
Any Event in Full Safety Population	791 (77%)	730 (71%)
Mild	409 (40%)	395 (38%)
Moderate	305 (30%)	269 (26%)
Severe	77 (7%)	66 (6%)
Adverse Events in $\geq 10\%$ of Patients by Severity		
CONSTIPATION	101 (10%)	68 (7%)
Mild	80 (8%)	56 (5%)
Moderate	21 (2%)	11 (1%)
Severe	0	1 (<1%)
DYSGEUSIA	325 (32%)	62 (6%)
Mild	286 (28%)	58 (6%)
Moderate	37 (4%)	4 (<1%)
Severe	2 (<1%)	0
HEADACHE	138 (13%)	124 (12%)
Mild	108 (10%)	93 (9%)
Moderate	29 (3%)	28 (3%)
Severe	1 (<1%)	3 (<1%)
INSOMNIA	103 (10%)	89 (9%)
Mild	90 (9%)	78 (8%)
Moderate	13 (1%)	11 (1%)
NAUSEA	265 (26%)	148 (14%)
Mild	190 (18%)	114 (11%)
Moderate	71 (7%)	31 (3%)
Severe	4 (<1%)	3 (<1%)
PRURITUS	60 (6%)	128 (12%)
Mild	49 (5%)	99 (10%)
Moderate	10 (<1%)	28 (3%)
Severe	1 (<1%)	1 (<1%)
FOAMY URINE ¹	125 (12%)	27 (3%)
Mild	111 (11%)	24 (2%)
Moderate	14 (1%)	3 (<1%)
VOMITING	135 (13%)	75 (7%)
Mild	90 (9%)	56 (5%)
Moderate	41 (4%)	19 (2%)
Severe	4 (<1%)	0

[¹]Coded as urine abnormality

8.1.2 *Death and Serious Adverse Events*

Seventeen patients (0.8%) in the safety population died (8 patients in the telavancin group and 9 patients in the vancomycin group) (Table 21). One patient (0017-02008-0120) treated with telavancin 7.5 mg/kg also died during the pre-specified reporting period. An additional 7 patient deaths (5 telavancin and 2 vancomycin) occurred outside the reporting period and were reported spontaneously. Narratives for all patient deaths are contained in Appendix 2.

Serious adverse events occurred in 76 (7%) telavancin-treated patients and 45 (4%) vancomycin-treated patients (Table 21). SAEs assessed by the investigator as possibly related to study medication occurred in 2% of telavancin-treated patients and 1% of vancomycin-treated patients. All individual serious adverse events occurred at an incidence of < 1%. Anaemia, renal failure acute, and renal insufficiency (five patients each), and myocardial infarction and blood creatinine increased (four patients each) were the most frequently reported serious treatment-emergent adverse events in patients treated with telavancin. Cellulitis and respiratory failure (four patients each), and pneumonia, atrial fibrillation, and pulmonary embolism (three patients each) were the most frequently reported serious treatment-emergent adverse events in patients treated with vancomycin overall in these studies. Serious renal adverse events are discussed in Section 8.2.1.

8.1.3 *Discontinuation of Study Medication due to an Adverse Event*

Discontinuation of study medication due to an adverse event occurred in 79 (8%) telavancin-treated patients and 56 (5%) vancomycin-treated patients (Table 21).

Renal adverse events (1%), nausea, vomiting, and rash (each < 1%) were the most frequent events resulting in discontinuation of telavancin.

Pruritus, drug hypersensitivity, and rash (each < 1%) were the most frequent events resulting in discontinuation of vancomycin.

8.2 Adverse Events of Clinical Importance

The following sections provide detailed summaries of renal and cardiac safety, since these two organ systems were identified in preclinical studies as potentially of clinical importance.

8.2.1 Renal Safety

The incidence of renal adverse events in the cSSSI studies was higher in the telavancin group than in the vancomycin group (3.4% vs. 1.2%). Renal adverse events were defined as those that code to the following MedDRA preferred terms: renal failure acute, renal failure chronic, renal insufficiency, renal impairment, and blood creatinine increased. One patient who experienced “Renal insufficiency” also experienced the adverse event of “renal tubular necrosis”, but is only counted once in the analysis. Renal events were primarily associated with comorbidities that independently increase the risk for renal impairment and, with sufficient follow-up, were shown to be reversible. In patients without comorbidities, there was essentially no difference between the two treatment groups in the incidence of renal adverse events. Renal function monitoring is recommended for all patients receiving telavancin. In patients with comorbidities predisposing to renal dysfunction, the potential benefit of treatment with telavancin should be weighed against the possible risk.

Overall Rate of Renal Adverse Events

Table 24 displays the overall rate of renal adverse events in the cSSSI studies. The incidences of renal AEs, SAEs, and discontinuations due to a renal AE were low but more frequent in the telavancin group. Among the renal AE's, the most common were elevations in serum creatinine: 14 telavancin patients and 6 vancomycin patients, renal insufficiency: 10 telavancin patients and 2 vancomycin patients, and renal failure: nine telavancin patients and two vancomycin patients, including one vancomycin patient who experienced worsening of chronic renal failure. Some patients were listed as having both elevations in creatinine and another adverse renal event such as renal failure or renal insufficiency.

Table 24: Renal Adverse Events – cSSSI Studies, Safety Population

	TLV 10 mg/kg (N=1029)	VAN [1] (N=1033)
	Number (%) of Patients	
Any Renal AE	35 (3.4%)	12 (1.2%)
At Least One Renal SAE	12 (1.2%)	4 (0.4%)
Renal AE Leading to Discontinuation	14 (1.4%)	3 (0.3%)
Patient Died	1 (<0.1%)	1 (<0.1%)

Note: Includes Studies 0017, 0018, and 202b.

[1] Includes 7 patients who received an antistaphylococcal penicillin instead of vancomycin in Study 202b.

Renal AEs include renal impairment, renal insufficiency, renal failure acute, renal failure chronic and blood creatinine increased.

In light of the higher incidence of renal adverse events with telavancin, a more detailed review of renal safety in telavancin-treated patients in both the cSSSI and HAP studies was conducted.

Relationship of Renal AEs with Baseline Comorbidities

Renal AEs occurred in the cSSSI studies in 3.4% (35/1029) of telavancin-treated patients compared with 1.2% (12/1033) of vancomycin-treated patients. The majority of these events (33/35 for telavancin and 9/12 for vancomycin) occurred in patients with baseline comorbidities that increase the risk for renal impairment (Table 25). These baseline comorbidities, which were present in approximately 50% of patients in the AT Population in both treatment groups, included atheroembolic disease, hypertension, hypotension, blood pressure abnormality, cutaneous and systemic lupus erythematosus, diabetes, heart failure, HIV infection, liver disease, prostate disease, kidney disease, and sepsis. In patients without these baseline comorbidities, renal AEs occurred in two telavancin-treated patients (0.4%) and three vancomycin-treated patients (0.6%).

Table 25: Renal Adverse Events by Baseline Comorbidities Associated with Increased Risk for Renal Impairment - Studies 0017, 0018, and 202b, Safety Population

	TLV 10 mg/kg (N=1029)	VAN[1] (N=1033)
	Number (%) of Patients	
Any Renal AE[2]	35 /1029 (3.4%)	12 /1033 (1.2%)
No Baseline Renal Risk Factors	2 /518 (0.4%)	3 /532 (0.6%)
Any Baseline Renal Risk Factor	33 /511 (6.5%)	9 /501 (1.8%)

[1] Includes 7 patients who received an antistaphylococcal penicillin instead of vancomycin in Study 202b.

[2] Includes the following preferred terms: renal failure acute, renal failure chronic, renal insufficiency, renal impairment, blood creatinine increased.

[3] Includes the following comorbidities: Atheroembolic Disease, Blood Pressure Abnormalities, Cutaneous Lupus Erythematosus, Systemic Lupus Erythematosus, Diabetes, Heart Failure, HIV, Liver Disease, Potential Obstruction, Prostate Disease, Renal Disease, Sepsis.

Similarly, renal SAEs were uncommon (one patient [0.2%] in each treatment group) in patients without baseline comorbidities that are associated with increased risk for the development of renal impairment (Table 26).

Table 26: Serious Renal Adverse Events by Baseline Comorbidities Associated with Increased Risk for Renal Impairment - Studies 0017, 0018, and 202b, Safety Population

	TLV 10 mg/kg (N=1029)	VAN[1] (N=1033)
	Number (%) of Patients	
At Least One Renal SAE[2]	12 /1029 (1.2%)	4 /1033 (0.4%)
No Baseline Renal Risk Factors	1 /518 (0.2%)	1 /532 (0.2%)
Any Baseline Renal Risk Factor	11 /511 (2.2%)	3 /501 (0.6%)

[1] Includes 7 patients who received an antistaphylococcal penicillin instead of vancomycin in Study 202b.

[2] Includes the following preferred terms: renal failure acute, renal failure chronic, renal insufficiency, renal impairment, blood creatinine increased.

[3] Includes the following comorbidities: Atheroembolic Disease, Blood Pressure Abnormalities, Cutaneous Lupus Erythematosus, Diabetes, Heart Failure, Liver Disease, Potential Obstruction, Prostate Disease, Renal Disease, Sepsis.

Evaluation of Renal SAEs

Three independent nephrologists (J. Lewis M.D., E. Siew M.D., Vanderbilt University; S. Korbet, Rush University) with expertise in drug-induced nephrotoxicity reviewed, in a blinded fashion, the 19 renal SAE cases in the cSSSI studies. The nephrologists independently approached each case as they would an in-hospital renal consult and made a recommendation on the need for discontinuation of treatment. The categories developed by the nephrologists for attribution of the renal event to study drug were as follows:

Highly Unlikely: Patients with an increasing serum creatinine at enrollment or were receiving dialysis at the time of enrollment. While a contribution of further injury from medication cannot entirely be ruled out, it would be extremely difficult to ascertain this in the setting of a clear injury beginning before enrollment and evolving through the time of enrollment. Nephrology consultation in these cases would be highly unlikely to recommend switching study medication treatment drug before addressing the cause of the earlier injury.

Very Unlikely: Patients who had well-recognized, and often, multiple major ongoing risk factors for AKI including but not limited to ongoing shock (distributive, hypovolemic, or cardiogenic), sepsis, known potent nephrotoxins (e.g., NSAIDs, aminoglycosides, IV contrast, amphotericin B), and/or pressor use responsible for the primary clinical picture. Nephrology consultation in these cases would be highly unlikely to recommend switching study medication treatment before addressing the above risk factors (clinical suspicion low).

Unlikely: Patients who may have at least one major risk factor for AKI that seemed mild-moderate in severity or well-compensated (clinical suspicion moderate).

Possibly: Patients without other overt risk factors for ongoing acute kidney injury (AKI) as could be discerned from case report forms, in whom suspicion for possible drug contribution would otherwise be high (clinical suspicion high).

In all cases, the independent assessments were concordant. Table 27 displays the results of their blinded review. Table 28 contains a complete listing of the cases with treatment

group, site investigator relatedness, and nephrologist attribution. One case in the telavancin 10 mg/kg treatment group was assessed as possibly attributable to study treatment by the reviewers (0018-38260-2099). Narratives for all patients with renal SAEs can be found in Appendix 3.

- Patient 0018-38260-2099 was a 50-year-old female who had a history of cutaneous lupus erythematosus. Concomitant medications included: hydrochlorothiazide and naproxen. Baseline creatinine was 0.9 mg/dL. At EOT (Study Day 5), her creatinine was 4.6 mg/dL and study drug was discontinued. The patient was given IV fluids and discharged home 6 days after EOT with a follow-up serum creatinine taken 3 weeks later at 1.5 mg/dL. The event of increased creatinine was considered possibly/probably related to study medication by the investigator.

In the remaining 15 cases, study medication was deemed an unlikely, very unlikely, or highly unlikely contributor to the renal event (11 in the telavancin 10 mg/kg group and 4 in the vancomycin group).

Table 27: Nephrologist Blinded Review of Serious Renal Adverse Events – Studies 0017, 0018, and 202b (Post-amendment)

	TLV 10 mg/kg N = 1029		VAN N = 1033	
	Number (%) of Patients			
Any Renal SAE	12	(1.2)	4	(0.4)
Attribution				
Possible	1	(0.1)	0	(0.0)
Unlikely	4	(0.4)	1	(0.1)
Very Unlikely	5	(0.5)	2	(0.2)
Highly Unlikely	2	(0.2)	1	(0.1)

In addition to the cases discussed above, three telavancin patients enrolled prior to Amendment 1 in the Phase 2/3 cSSSI studies and treated with 7.5 mg/kg telavancin experienced a renal SAE. The attribution for these patients was one possible (202b-101-7008) and two very unlikely.

- Patient 202b-101-7008, a 76-year-old woman, had a history of non-insulin-dependent diabetes with an amputation of the second phalange. Baseline creatinine was 0.9 mg/dL and the patient received telavancin 7.5 mg/kg daily for 9 days. On Study Day 9, creatinine was noted to be elevated at 3.1 mg/dL and study drug was discontinued. A nephrologist evaluated the patient and felt that the acute renal insufficiency could be multifactorial with possible causes including prerenal azotemia, medications including study drug as well as benazepril and NSAIDs or renal artery stenosis. Ten days after study drug was discontinued, serum creatinine declined to 1.2 mg/dL and the event was considered resolved by the investigator. The investigator assessed the event of acute renal insufficiency as possibly/probably related to study drug.

Table 28: Serious Renal Adverse Events – Studies 0017, 0018, and 202b, Safety Population

Patient ID	Age / Sex	Comorbid Condition	Concom Meds	Renal SAE	Increase Cr on Study Med	BL Cr	Max Cr	Last Cr	Investigator Relatedness	Nephrologists Assessment	Nephrologists Reasons for Event
Telavancin 10 mg/kg											
0017-38117-0240	51 / F	Yes	Yes	Acute renal failure	Yes	1.0 mg/dL	3.1 mg/dL	1.1 mg/dL	No	Very Unlikely	1) Volume Depletion on ACE-I 2) Dye 3) Other Drugs
0017-38271-0953	93 / M	Yes	Yes	Renal impairment (worsening of)	Yes	1.4 mg/dL	2.3 mg/dL	1.8 mg/dL	No	Unlikely	1) Diuretics and ACE-I with decreased intravascular volume 2) Atrial Fibrillation leading to decreased cardiac output
0017-38002-0428	70 / M	Yes	Yes	Renal insufficiency (death – refused dialysis)	Yes	1.0 mg/dL	2.7 mg/dL	N/A	Yes	Unlikely	1) CHF, poor renal perfusion 2) other drugs
0017-18001-0721	46 / M	Yes	Yes	Renal impairment (hemodialysis initiated)	Increasing prior to study	5.5 mg/dL	10.8 mg/dL	7.3 mg/dL	Yes	Highly Unlikely	1) Acute renal failure before study drug
0018-06003-2353	84 / F	Yes	Yes	Acute renal failure	Yes	1.7 mg/dL	3.0 mg/dL	1.2 mg/dL	No (changed)	Very Unlikely	1) Decreased intravascular volume 2) Bactrim 3) use of pressors indicating low blood pressure
0018-06003-2721	56 / F	Yes	Yes	Acute renal failure	?*	0.9 mg/dL	1.7 mg/dL	0.7 mg/dL	Yes	Very Unlikely	Dehydration due to diarrhea from C. diff colitis
0018-38160-3068	95 / M	Yes	Yes	Acute renal failure (death – refused dialysis)	Yes	4.1 mg/dL	10.3 mg/dL	N/A	Yes	Highly Unlikely	Acute renal failure before study drug
0018-38148-2498	47 / F	Yes	Yes	Elevated blood creatinine Elevated blood urea	Yes	0.7 mg/dL	2.7 mg/dL	1.2 mg/dL	Yes	Very Unlikely	1) Acute deterioration 2) Indocin/ ACE-I

Telavancin

Patient ID	Age / Sex	Comorbid Condition	Concom Meds	Renal SAE	Increase Cr on Study Med	BL Cr	Max Cr	Last Cr	Investigator Relatedness	Nephrologists Assessment	Nephrologists Reasons for Event
0018-38260-2099	50 / F	Yes	Yes	Renal insufficiency (interstitial nephritis)	Yes	0.9 mg/dL	6.0 mg/dL	2.0 mg/dL	Yes	Possible	Intermittent NSAID use
0018-38148-2359	57 / F	Yes	Yes	Elevated creatinine	Yes	0.9 mg/dL	2.1 mg/dL	1.0 mg/dL	Yes	Very Unlikely	1) Volume depletion 2) NSAIDs 3) levofloxacin
0018-38322-2757	66 / F	Yes	Yes	Acute renal failure	Yes	0.6 mg/dL	3.7 mg/dL	0.9 mg/dL	Yes	Unlikely	Nausea and vomiting leading to volume depletion
202b-00910-9058	28 / M	No	Yes	Acute renal failure	Yes	1.0 mg/dL	3.5 mg/dL	1.1 mg/dL	Yes	Unlikely	1) NSAIDS
Telavancin 7.5 mg/kg											
0017-02008-0120	82 / F	Yes	Yes	Renal insufficiency (death)	Yes	1.0 mg/dL	3.2 mg/dL	3.2 mg/dL	Yes	Very Unlikely	1) Decreased blood pressure 2) Sepsis 3) Aztreonam
0018-38160-2007	51 / M	No	Yes	ATN (resolution)	Yes	0.7 mg/dL	3.4 mg/dL	1.9 Mg/dL	No	Very Unlikely	1) ATN/sepsis 2) Liver disease/paracentesis 3) Diuretics
202b-00101-7008	76 / F	Yes	Yes	Acute renal insufficiency Prerenal azotemia Elevated BUN Elevated Cr	Yes	0.9 mg/dL	3.4 mg/dL	1.2 mg/dL	Yes	Possible	1) NSAID 2) Aztreonam
Vancomycin											
0017-38005-0180	77 / F	Yes	Yes	Increased Cr	Yes	1.4 mg/dL	3.4 mg/dL	1.0 mg/dL	Yes	Very Unlikely	1) Contrast 2) Cholesterol emboli 3) Nafcillin 4) Other drugs/antibiotics
0017-38024-0697	62 / M	Yes	Yes	Increased Cr	Yes	0.7 mg/dL	3.0 mg/dL	1.0 mg/dL	Yes	Very Unlikely	1) Volume Depletion 2) Drugs 3) Possible Obstruction 4) NSAIDS
0018-38260-2555	53 / M	Yes	Yes	Renal failure chronic	Yes (?)	HD	HD	HD	No	Highly Unlikely	ESRD

Telavancin

Patient ID	Age / Sex	Comorbid Condition	Concom Meds	Renal SAE	Increase Cr on Study Med	BL Cr	Max Cr	Last Cr	Investigator Relatedness	Nephrologists Assessment	Nephrologists Reasons for Event
202b-00903-9037	41 / F	No	?	Renal failure acute	Yes	0.6 mg/dL	2.3 mg/dL (?)	(?)	No	Unlikely	1) Multi-organ failure 2) Aztreonam 3) NSAIDs

In summary, a review of patients with renal SAEs indicates that nearly all of them had multiple reasons for developing renal impairment that are deemed more likely than the use of study drug. Furthermore, in most of these patients, the reviewing nephrologists indicated that they would not recommend discontinuation of study drug therapy since other underlying conditions and the infection would take precedence. It should be noted that renal function improved during telavancin treatment in approximately 36% (40/111) of the patients with moderate or severe impairment at Baseline.

Renal Event Follow-up

Forty-seven patients had renal AEs or SAEs during the study (35 in the telavancin group and 12 in the vancomycin group). Of these 47 patients, 28 continued study drug therapy despite the event and 19 discontinued study drug due to an AE. As shown in Table 29, 16 of 35 patients in the telavancin group and 5 of 12 patients in the vancomycin group had completely resolved the renal event by the end of the study.

Table 29: Outcome of Renal Adverse Events by Discontinuation of Study Medication – Studies 0017, 0018, and 202b, Safety Population

	TLV 10 mg/kg (N=1029)	VAN [1] (N=1033)
	Number (%) of Patients	
Renal AE and Discontinued for Any AE [2],[3]	16 (2%)	3 (<1%)
Patient Died of Renal Event	1 (6%)	1 (33%)
Patient Died of Other Cause	0	0
Condition Still Present and Unchanged	1 (6%)	0
Condition Improving	3 (19%)	1 (33%)
Recovered with Sequelae	1 (6%)	0
Completely Recovered	10 (63%)	1 (33%)
Renal AE and Continued Study Drug [2],[3]	19 (2%)	9 (<1%)
Patient Died of Renal Event	0	0
Patient Died of Other Cause	3	3
Condition Still Present and Unchanged	8 (42%)	1 (11%)
Condition Improving	2 (11%)	1 (11%)
Recovered with Sequelae	0	0
Completely Recovered	6 (32%)	4 (44%)

[1] Includes 7 patients who received an antistaphylococcal penicillin instead of vancomycin in Study 202b.

[2] Event percentages based on total number of patients in treatment group. Outcome category percents based on number of patients with the event.

[3] For each patient, the worst outcome of any listed adverse event is tabulated.

Note: 'Renal AE' includes the following preferred terms: renal failure acute, renal failure chronic, renal insufficiency, renal impairment, blood creatinine increased.

To determine what happened to the patients who had not completely resolved, i.e., patients with an outcome of improving, recovered with sequelae, or condition present and unchanged, study sites were asked to provide further creatinine values and to determine if the outcome had changed. Further follow-up was requested for 14 patients in the telavancin group and 2 patients in the vancomycin group. The results of this analysis for the telavancin patients are listed in in Table 30.

Table 30: Follow-up Outcomes of Renal Adverse Events in Telavancin-treated Patients – Studies 0017, 0018, and 202b, Safety Population

Patient ID	End-of-Study Outcome	Relevant Medical History	Last Creatinine Concentration (mg/dL)/ Follow-up Outcome
0018-38110-2568	Condition Still Present and Unchanged	Chronic renal insufficiency, diabetes, hypertension and pulmonary embolus	Day 22 Creatinine 7.6 / Recovered with sequelae
0018-38260-2099	Condition Improving		Day 29 Creatinine 1.5 / Completely recovered
0018-38304-2233	Condition improving		No new information available
202b-00107-6002	Condition Improving		Day 39 Creatinine 1.3 / Completely recovered
0018-38304-2670	Recovered with sequelae		Day 23 Creatinine 2.3 / Completely recovered
0018-18001-0721	Condition still present and unchanged	Chronic renal failure, diabetes, diabetic nephropathy, acute renal failure prior to study entry	Day 90 4.2, patient still on hemodialysis / Condition still present and unchanged
0017-3811-0380	Condition still present and unchanged		Day 31 2.6 / Improving
0017-38271-0429	Condition Still Present and Unchanged	Pretreatment creatinine 3.2 mg/dL	Day 16 2.5 / Improving
0017-38271-0978	Condition Still Present and Unchanged		Withdrew from study on Day 8, no new information available
0018-38112-2996	Condition Still Present and Unchanged		Day 90 1.2 / Completely recovered

Patient ID	End-of-Study Outcome	Relevant Medical History	Last Creatinine Concentration (mg/dL)/ Follow-up Outcome
0018-38322-2428	Condition Still Present and Unchanged	Creatinine returned to baseline (1.3 mg/dL) on last day of therapy after peaking at 2.2 mg/dL but then rose 8 days after last dose	No new information available
202b-00101-7128	Condition Still Present and Unchanged	Baseline creatinine of 0.5 mg/dL with peak of 0.7 mg/dL	Site investigator noted that adverse event entered in error
202b-00911-9053	Condition Still Present and Unchanged		Day 22 1.3 / Completely recovered
0018-31007-2513	Condition Improving		Day 60 1.2 / Completely recovered

All patients who had a renal AE and discontinued study drug were resolving or had resolved by last patient contact. In the patients with a renal AE who continued study drug, 3 telavancin-treated patients and 1 vancomycin-treated patients the event was still present and unchanged at last patient contact. Each of these patients had baseline comorbidities that put them at risk for renal events.

Two of the three telavancin-treated patients whose event was still present and unchanged did not have any follow-up past the TOC visit. One patient's increased creatinine resolved while still on telavancin treatment (0018-38322-2428). The other patient had a maximum creatinine value of 2.6 mg/dL at TOC from a baseline value of 0.5 mg/dL(0017-38271-0978). Patient 0017-18001-0721, the third telavancin-treated patient, had underlying chronic renal failure and experienced acute renal failure before enrollment in the study. The patient's baseline creatinine value was 5.5 mg/dL. He had hemodialysis during the study with the last reported value at 4.2 mg/dL while still on hemodialysis 3 months after study conclusion.

These results are consistent with published studies in other anti-infectives (Leehey DJ, et al. J Am Soc Nephrol. 1993;4:81-90; Ditlove J, et al. Medicine. 1977;56:483-491), which indicate that the vast majority of antibiotic-induced renal events are reversible.

Decreases in Creatinine Clearance

Table 31 displays potentially clinically significant (PCS) decreases in CrCl (at least 50% reduction in CrCl from baseline) for patients with normal renal function at baseline in Studies 0017 and 0018. The incidences of PCS decreases in CrCl were low in both groups (3% vs.3%, respectively).

Table 31: Incidence of Potentially Clinically Significant Decrease in Creatinine Clearance in Patients with Normal Baseline (>80 mL/min) – Studies 0017 and 0018, Safety Population

	TLV 10 mg/kg		VAN	
	N [1]	Pts with Abnormal Values [2]	N [1]	Pts with Abnormal Values [2]
CrCl - Lowest Post-baseline result				
≤ 50% of baseline value	579	20 (3.4%)	592	15 (2.5%)

[1] 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 up time and (2) for whom baseline value was normal.

[2] Patients who had at least one abnormal value who met the criteria in number 1.

Note: Unless otherwise specified, all laboratory assessments after initiation of study medication, including post-medication Follow-up were considered.

Increases in Serum Creatinine

Table 32 displays potentially clinically significant (PCS) abnormalities in serum creatinine (maximum value ≥ 1.5 mg/dL and at least 50% greater than baseline) for patients with normal serum creatinine at baseline in Studies 0017 and 0018. Twenty-four of 48 telavancin-treated patients (50%) who developed abnormal serum creatinine during the study had maximum values of 1.5 to < 2.0 mg/dL. An additional 17 (35%) telavancin-treated patients had maximum values of 2.0 to < 3.0 mg/dL.

Table 32: Incidence of Potentially Clinically Significant Increase in Creatinine in Patients with Normal Baseline Renal Function - Studies 0017 and 0018, Safety Population

	TLV 10 mg/kg		VAN	
	N [1]	Pts with Abnormal Values [2]	N [1]	Pts with Abnormal Values [2]
	Number (%) of Patients			
Any post-BL Creatinine \geq 1.5 mg/dL and at least 50% > baseline	822	48 (6%)	856	17 (2%)
Highest Post-baseline Result				
1.5 mg/dL -< 2.0 mg/dL and at least 50% > baseline	822	24 (3%)	856	13 (2%)
2.0 mg/dL -< 3.0 mg/dL and at least 50% > baseline	822	17 (2%)	856	2 (<1%)
3.0 mg/dL -< 5.0 mg/dL and at least 50% > baseline	822	5 (<1%)	856	2 (<1%)
\geq 5.0 mg/dL and at least 50% > baseline	822	2 (<1%)	856	0
BUN Post-baseline Result				
> 11 mmol/L	811	47 (6%)	827	24 (3%)

[1] 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 up time and (2) for whom baseline value was normal.

[2] Patients who had at least one abnormal value who met the criteria in number 1.

Note: Unless otherwise specified, all laboratory assessments after initiation of study medication, including post-medication Follow-up were considered.

Renal Safety in Hospital-acquired Pneumonia Studies

In the recently unblinded Phase 3 studies of telavancin in HAP, the treatment population included more seriously ill patients with numerous comorbid conditions and greater baseline renal impairment compared with the patients in the cSSSI studies. In the HAP studies, the rate of adverse renal events was higher than observed in the cSSSI trials (Table 33). The relative difference between the treatment groups in the HAP patients was less than that in the cSSSI studies (9.9% vs. 7.6% for HAP compared with 3.4% vs. 1.2% for cSSSI).

Table 33: Incidence of Renal Adverse Events– HAP and cSSSI Studies, Safety Population

	HAP Studies 0015, 0019		cSSSI Studies 0017,0018,202b		HAP and cSSSI Studies	
	TLV 10 mg/kg (N=751)	VAN (N=752)	TLV 10 mg/kg (N=1029)	Vanc[1] (N=1033)	TLV 10 mg/kg (N=1780)	VAN[1] (N=1785)
	Number (%) of Patients					
Renal Adverse Event	74 (9.9%)	57 (7.6%)	35 (3.4%)	12 (1.2%)	109 (6.1%)	69 (3.9%)
Renal Serious Adverse Event	26 (3.5%)	16 (2.1%)	12 (1.2%)	4 (0.4%)	38 (2.1%)	20 (1.1%)

[1] Includes subjects who received an antistaphylococcal penicillin instead of vancomycin (20 subjects in 0015 and 0019, 7 subjects in 202b).

Summary of Renal Safety

In the cSSSI studies, renal AEs were reported in 3.4% of telavancin-treated patients compared with 1.2% of vancomycin-treated patients.

Most of the renal AEs in both treatment groups occurred in patients with baseline comorbidities that are associated with increased risk for renal impairment. Where no such baseline comorbidity was present, the incidence of renal AEs was similar for both treatment groups (0.4% telavancin and 0.6% vancomycin).

No difference in the incidence of clinically meaningful decreases in creatinine clearance was observed between the two treatment groups.

For those patients who did experience renal AEs, the majority of these events in both treatment groups resolved or were resolving at the last patient contact. In all cases of a renal SAE, except for one patient who refused hemodialysis, the patient’s renal impairment had resolved or was resolving at the last patient contact.

The recently unblinded Phase 3 studies in HAP provide additional information on the renal safety of telavancin relative to vancomycin. The patients that were enrolled in the HAP

studies had a greater tendency to have baseline renal risk factors and to exhibit worse renal function at study enrollment than patients enrolled in the cSSSI studies. Assessment of renal outcomes in the HAP studies indicate that the incidence of renal SAEs and renal AEs were similar between telavancin and vancomycin.

Dose adjustment of telavancin is indicated for patients with evidence of moderate to severe renal impairment. Serum creatinine monitoring is recommended for all patients receiving telavancin. In considering the use of telavancin in patients with underlying renal dysfunction and in patients with underlying conditions that would predispose to renal dysfunction, the potential benefit of telavancin should be weighed against the possible risk.

Conclusions Regarding Renal Safety

In conclusion, renal AEs were uncommon in the cSSSI studies, although occurring more frequently in telavancin-treated patients, and these events were readily detectable and manageable. The majority of renal adverse events occurred in patients with underlying comorbidities that increase the risk of renal impairment. Where no underlying comorbidity was present, the risk of renal adverse events was very low and not different from the risk with vancomycin therapy.

Theravance proposes that appropriate information be included in the label informing prescribers about the renal effects of telavancin and the importance of risk factors for renal dysfunction, as well as appropriate dosage modifications. In all patients, monitoring of renal function should be performed. In considering the use of telavancin in patients with underlying renal dysfunction and in patients with underlying conditions that would predispose to renal dysfunction, the potential benefit of telavancin should be weighed against the possible risk.

8.2.2 Cardiac Safety and QTc Prolongation Effects

Thorough QT/QTc Study (Study 104a)

The effect of telavancin on cardiac repolarization was assessed in a randomized, double-blind, multiple-dose, positive-controlled and placebo-controlled, parallel study

(n=160) (Table 34). Healthy subjects received telavancin 7.5 mg/kg, telavancin 15 mg/kg, moxifloxacin 400 mg IV, or placebo infused over 60 minutes once daily for 3 days to achieve steady state. The positive control, moxifloxacin 400 mg IV, served as a measure of assay sensitivity.

Table 34: Day 3 Mean and Maximum QTcF Changes from Baseline Relative to Placebo – Study 104a

Drug/Dose	Mean Change from Baseline (Upper 90% Confidence Limit) msec	Maximum Change from Baseline (Upper 90% Confidence Limit) msec
	Number (%) of Patients	
Telavancin 7.5 mg/kg	4.1 (7)	11.6 (16)
Telavancin 15 mg/kg	4.6 (8)	15.1 (20)
Moxifloxacin 400 mg	9.5 (13)	21.6 (26)

Fridericia corrected

Upper CL from a two-sided 90% CI on difference from placebo (msec)

In the immediate post-infusion period, no subject demonstrated QTcF prolongation greater than 60 msec and no subject demonstrated a QTcF value greater than 500 msec. One subject treated with telavancin 15 mg/kg had an increase of 63 msec at 17 hours post-dose. This finding was attributed by Theravance to the fact that this subject's pre-dose QTc interval was short (369 msec). His plasma drug concentration at the time of the notable prolongation was 27 µg/mL. There was no evidence of a gender effect with telavancin, and no correlation was found between telavancin pharmacokinetic parameters and the extent of QTc prolongation.

In summary, Study 104a demonstrated that telavancin 7.5 and 15 mg/kg had an effect on QTc duration. The magnitude of this effect, a mean change of < 5.0 msec, was about half that of the positive control, moxifloxacin 400 mg IV (the standard dose) with no evident dose-response relationship.

QT Evaluation in Phase 2 and 3 Efficacy and Safety Studies with Telavancin

In the Phase 2 and 3 cSSSI studies, 12-lead ECGs were obtained in triplicate at pretreatment, Study Day 4, and EOT. ECGs were transmitted to the central ECG lab for analysis of ECG intervals and morphology, including determination of the QT/QTc interval.

QT, QTc Bazett-corrected (QTcB), and QTc Fridericia-corrected (QTcF) were each reported. QTcF data were prospectively analyzed since assessment of cardiac repolarization is best made with QTcF.

Patients receiving medications known to prolong the QT interval were not excluded from participation in the telavancin cSSSI studies. In these studies, 232 of 1029 (23%) telavancin patients and 184 of 1033 (18%) vancomycin patients received concomitant medications that are known to prolong the QTc interval and are associated with definite or possible risk of torsades de pointes (see <http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm>).

Table 35: Patients Taking Concomitant Medications with a Risk of Torsades - Studies 0017, 0018, and 202b, Safety Population Excluding Study Site 38016 and 38163

	TLV 10 mg/kg (N=1029)	VAN [1] (N=1033)
	Number (%) of Patients	
Took any meds with any level of risk of Torsades	232 (22.5%)	184 (17.8%)
Definite risk of Torsades	111 (10.8%)	94 (9.1%)
Possible risk of Torsades	147 (14.3%)	106 (10.3%)

Note: Patients who received both meds with definite risk and meds with possible risk are shown in both categories.

[1] Includes 7 patients who received an antistaphylococcal penicillin instead of vancomycin in Study 202b.

In the cSSSI studies, the mean and mean maximum changes in QTcF from baseline were approximately 7 to 8 msec greater in the telavancin group compared with the vancomycin group. The incidence of QTc prolongation > 60 msec from baseline or QTc value > 500 msec was 1.5% (15 patients) in the telavancin group and 0.7% (6 patients) in the vancomycin group (Table 36). One vancomycin-treated patient had both QTc prolongation > 60 msec from baseline and a QTc value > 500 msec. Nine of the 15 telavancin patients received concomitant medications that are known to prolong the QTc interval and definitely or possibly associated with a risk of torsades de pointes, compared with one of the six patients who received vancomycin. Therefore, although there were more patients in the telavancin group who were at risk for QTc prolongation, a similar number of patients in each group who did not receive a concomitant medication known to prolong the QTc interval experienced a prolongation > 60 msec from baseline. In a separate analysis, one patient in

the telavancin group and two patients in the vancomycin group experienced QTc > 500 msec. No cardiac adverse events were noted in these patients with extreme changes or values.

In the Phase 3 studies of telavancin in HAP, the effects of study medication on QTc prolongation were assessed. The results were consistent with those seen in the cSSSI studies. Table 36 displays the data for the studies in HAP as well as the cSSSI studies. In the HAP studies, the mean and mean maximum changes in QTcF from baseline were approximately 4 msec greater in the telavancin group compared with the vancomycin group. As patients with HAP were older, more seriously ill, and had substantial comorbid conditions, it was possible that the QTc prolonging effect of telavancin could have been exacerbated. However, there was little difference in the number of outliers (QTcF > 500 msec or > 60 msec increase from baseline) between telavancin- and vancomycin-treated patients.

Table 36: Changes from Baseline in QTcF Interval - Studies 0017, 0018, 202b, 0015, and 0019, Excluding Study Sites 38016 and 38163, Safety Population

	Studies 0015, 0019 (HAP)		Studies 0017, 0018, 202b (cSSSI)		Total	
	TLV 10 mg/kg (N=751)	VAN [1] (N=752)	TLV 10 mg/kg (N=1004)	VAN [1] (N=992)	TLV 10 mg/kg (N=1755)	VAN [1] (N=1744)
Post-Medication Average [2] Change (msec)						
N	631	640	947	940	1578	1580
Mean	6.0	2.1	9.6	2.7	8.2	2.5
Standard Deviation	24.6	26.9	17.3	16.0	20.6	21.1
Minimum	-88.3	-93.7	-98.8	-52.5	-98.8	-93.7
Median	5.2	2.6	9.0	2.7	7.8	2.7
Maximum	143.9	104.3	93.5	66.3	143.9	104.3
Post-Medication Maximum [3] Change (msec)						
N	631	640	947	940	1578	1580
Mean	19.1	15.1	16.2	8.4	17.3	11.1
Standard Deviation	29.7	30.2	18.6	16.8	23.7	23.4
Minimum	-75.3	-93.7	-89.0	-49.7	-89.0	-93.7
Median	16.3	13.0	15.3	8.0	15.7	9.3
Maximum	246.7	173.0	103.7	94.7	246.7	173.0
Maximum Post-Medication Value (number (%) by category)						
≤ 450 msec	558 (84%)	579 (84%)	852 (88%)	897 (95%)	1410 (86%)	1476 (90%)
> 450 - 480 msec	86 (13%)	83 (12%)	103 (11%)	39 (4%)	189 (12%)	122 (7%)
> 480 - 500 msec	12 (2%)	15 (2%)	8 (<1%)	9 (<1%)	20 (1%)	24 (1%)
> 500 msec	12 (2%)	12 (2%)	1 (<1%)	2 (<1%)	13 (<1%)	14 (<1%)
- Total -	668 (100%)	689 (100%)	964 (100%)	947 (100%)	1632 (100%)	1636 (100%)
Maximum Post-Medication Change (number (%) by category)						
≤ 30 msec	439 (70%)	478 (75%)	766 (81%)	848 (90%)	1205 (76%)	1326 (84%)
> 30 - 60 msec	144 (23%)	118 (18%)	167 (18%)	87 (9%)	311 (20%)	205 (13%)
> 60 msec	48 (8%)	44 (7%)	14 (1%)	5 (<1%)	62 (4%)	49 (3%)
- Total -	631 (100%)	640 (100%)	947 (100%)	940 (100%)	1578 (100%)	1580 (100%)

[1] Includes subjects who received an antistaphylococcal penicillin instead of vancomycin (20 subjects in 0015 and 0019, 7 subjects in 202b).

[2] Based on all QT measurements from patients with at least one post-baseline value and a baseline value.

[3] Based on maximum value of all QT measurements (triplicate averages) from patients with at least one post-baseline value and a baseline value.

Note: Three ECGs were obtained at each assessment time. Triplicate readings were reduced to a single value at each assessment time by averaging within the triplicate. In 202b, 0015 and 0019 post-medication ECGs were obtained on every third day of Study Medication and at the end-of-therapy evaluation. In 0017 and 0018, post-medication ECGs were obtained once on Day 3, 4, and 5 and at the End-of-therapy evaluation.

Cardiac Adverse Events

Table 37 displays the overall incidence of cardiac AEs in the Phase 2 and 3 cSSSI studies.

The incidence of cardiac AEs was 5% for the telavancin group compared with 4% for the

vancomycin group. All distinct cardiac AEs occurred in < 1% of patients. The most common cardiac AEs ($\geq 0.5\%$) in the telavancin group were palpitations (0.9%), angina pectoris (0.9%), and congestive cardiac failure (0.8%). In the vancomycin group, the most common cardiac AEs ($\geq 0.5\%$) were palpitation (0.6%) and bradycardia (0.5%).

Table 37: Cardiac Adverse Events - Studies 0017, 0018, and 202b, Safety Population

	TLV 10 mg/kg (N=1029)	VAN [1] (N=1033)
	Number (%) of Patients	
Cardiac AE	50 (4.9%)	37 (3.6%)
Cardiac SAE	11 (1.1%)	11 (1.1%)
Non-fatal Cardiac SAE Leading to Withdrawal [2]	0 (0.0%)	2 (0.2%)
Cardiac SAE with Death	4 (0.4%)	6 (0.6%)

[1] Includes 7 patients who received an antistaphylococcal penicillin instead of vancomycin in Study 202b.

[2] Excludes the patients who died.

Ten patients (four telavancin-treated and six vancomycin-treated) died after experiencing a cardiac adverse even. A summary of the clinical aspects of these 10 deaths is provided in Table 38. Investigators assessment of the association with study drug was “possibly/probably-related” in three patients (0018-38260-2555, 0018-01002-2474, and 0017-02010-0546). The causes of death in these cases were stated as cardiac failure, cardiac arrest, ventricular arrhythmia; respectively. Six of the seven deaths judged “not related” had similar causes of death (cardiac failure, cardiac arrest, cardiac insufficiency). All 10 case summaries are notable for the lack of documentation of any ventricular arrhythmia.

An independent cardiologist (C. Pratt, M.D., Cornell Medical College [New York] and The Methodist Hospital [Houston]) examined the information available for each of these cases and provided an assessment of association with study drug (Table 38). He noted that the patients had significant cardiac and noncardiac comorbidities and that the deaths occurred in the setting of multi-organ failure (renal and/or hepatic) and serious infections, including sepsis (0018-30907-2323). In his opinion, many of these deaths should have been classified as “noncardiac.”

In looking for an imbalance in cardiac toxicity, cardiac serious adverse events, serious adverse events requiring discontinuation and electrocardiographic information should be assessed. The most objective finding regarding the deaths in this study is the actual number of deaths (6 vancomycin vs. 4 telavancin).

Table 38: Deaths Associated With Cardiac Adverse Events – Studies 0017 and 0018

Patient Identification Dates in Study No. of Days on Study Drug Treatment Assignment	Cardiovascular Comorbidities	Noncardiac Comorbidities	Additional Clinical Data Relationship of Death to Study Drug Cause of Death*
0018-38260-2555 11/23/05 – 12/1/05 1 Day VAN	<ul style="list-style-type: none"> Congestive heart failure Atrial fibrillation / on amiodarone Hypertension 	<ul style="list-style-type: none"> Cirrhosis with ascites ESRD on Hemodialysis Placement of vascular shunt 	<ul style="list-style-type: none"> Hospitalization for leg cellulitis abscesses No VT mentioned <p>PI “possibly / probably related to study drug” COD “Cardiac failure”</p>
0018-01002-2474 11/08/05 – 11/15/05 6 Days TLV	<ul style="list-style-type: none"> Peripheral vascular disease 	<ul style="list-style-type: none"> Renal failure Fell in hospital 	<ul style="list-style-type: none"> Cellulitis of hand Abscess of hand “Morphine OD” Non-witnessed death (“cardiac arrest”) No VT mentioned <p>PI “possibly / probably related” COD “Cardiac arrest”</p>
0018-22000-2742 1/13/06 – 1/15/06 2 Days VAN	<ul style="list-style-type: none"> Atrial fibrillation Cardiac insufficiency 	<ul style="list-style-type: none"> Acute renal failure, anuria, anemia Dermal T-cell lymphoma. Chemo X 3 courses 	<ul style="list-style-type: none"> Cellulitis / skin ulcers No VT mentioned <p>PI “not related” COD “Cardiac insufficiency – ARF”</p>
0018-19006-2894 3/1/06 – 3/9/06 9 Days TLV	<ul style="list-style-type: none"> Hypotension (Rx hydrocortisone) History of ↑ BP New atrial fibrillation Peripheral vascular disease 	<ul style="list-style-type: none"> Insulin dependent diabetes mellitus Rheumatoid arthritis Hepatic carcinoma ↑ LFTS / OT, PT, ALK Phos 	<ul style="list-style-type: none"> No VT mentioned <p>PI “not related” COD “Cardio respiratory arrest”</p>
0018-38160-2501 11/16/06 – 11/20/06 6 Day TLV	<ul style="list-style-type: none"> Supraventricular tachycardia Congestive heart failure Angina Myocardial infarction (positive Troponin) 	<ul style="list-style-type: none"> Pulmonary fibrosis Pneumonia Silicosis 	<ul style="list-style-type: none"> Made DNR by family – refused ventilator No VT mentioned <p>PI “not related” COD “MI / Acute respiratory failure”</p>

Patient Identification Dates in Study No. of Days on Study Drug Treatment Assignment	Cardiovascular Comorbidities	Noncardiac Comorbidities	Additional Clinical Data Relationship of Death to Study Drug Cause of Death*
0018-30907-2323 9/29/08 – 10/1/08 2 Days VAN	<ul style="list-style-type: none"> • Cardiac vs. septic shock • Supraventricular tachycardia • Pulmonary edema 	<ul style="list-style-type: none"> • Acute plus chronic renal failure • Septic shock 	<ul style="list-style-type: none"> • Admitted for cellulitis of right arm • No VT mentioned PI “not related” COD “Septic / cardiac shock”
0017-3806-0824 2/22/06 – 2/23/06 2 Days VAN	<ul style="list-style-type: none"> • Hypotension • “Witnessed sudden death” 	<ul style="list-style-type: none"> • Morbid obesity (366 lbs / 5’7”) • Diabetes 	<ul style="list-style-type: none"> • Admitted for abdominal abscess • No VT mentioned PI “not related” COD “Pulmonary embolism / cardio-pulmonary arrest” PE confirmed by autopsy
0017-38024-0695 12/20/05 – 1/2/06 14 Day VAN	<ul style="list-style-type: none"> • Congestive heart failure • Pleural effusions 	<ul style="list-style-type: none"> • Chronic renal failure (Cr Cl = 32 mL / min) 	<ul style="list-style-type: none"> • Admitted for non-healing leg ulcers • No VT mentioned PI “not related” COD “CHF / cardio respiratory failure”
0017-02010-0546 10/13/05 1 Day TLV	<ul style="list-style-type: none"> • Coronary artery disease • Hypoxia • Cor pulmonale 	<ul style="list-style-type: none"> • Epilepsy • Diabetes 	<ul style="list-style-type: none"> • Death unwitnessed, in-hospital, no telemetry. • ECG pre-dose – normal QT • No VT mentioned PI “possibly / probably related” COD “Ventricular arrhythmia”
0017-38271-0659 11/25/05 – 11/30/05 6 Days VAN	<ul style="list-style-type: none"> • Hypertension 	<ul style="list-style-type: none"> • Hepatitis C • Cirrhosis • ETOH abuse • Ascites / encephalopathy / coagulopathy • Respiratory failure • Hepatic coma 	<ul style="list-style-type: none"> • Admitted for cellulitis – leg • No VT mentioned PI “not related” COD “Hepatic coma / respiratory failure”

PI = Principal Investigator; COD = Cause of Death; VT = ventricular tachycardia.

*Principal Investigator (PI) determined cause of death (COD).

Eleven patients in each treatment group experienced a serious cardiac AE. Not counting the 10 patients who died following a cardiac SAE, a further 2 patients in the vancomycin group discontinued study medication after experiencing a cardiac SAE, compared with no telavancin-treated patients.

Cardiac Adverse Events in Patients with QTc Prolongation

In the cSSSI studies, in one telavancin-treated and two vancomycin-treated patients who experienced a maximum QTcF value > 500 msec, no cardiac adverse events were observed. In the 14 telavancin-treated patients who had a change in QTcF from baseline \geq 60 msec, 2 experienced a cardiac AE. One of these two patients had an SAE of myocardial infarction. This was a 78-year-old male with a history of coronary artery bypass graft surgery, bilateral carotid endarterectomies, pacemaker placement, atrial fibrillation, peripheral vascular disease, arteriosclerotic heart disease, and mild left ventricular hypertrophy. The patient recovered fully from this event. The other patient with a change in QTcF from baseline > 60 msec and experiencing a cardiac AE was a 57-year-old female who developed cardiac failure in association with septic shock, due to a Gram-negative pyelonephritis, which led to discontinuation of study medication. Thus, in telavancin-treated patients with a change in QTcF from baseline of > 60 msec or who had a maximum QTcF value > 500 msec there were no cardiac adverse events attributed to QTc prolongation.

Summary of Cardiac Safety and QTc Prolongation Effects

- Based on a well-conducted thorough QT study, telavancin has less effect on prolonging the QTcF interval than moxifloxacin.
- The thorough QT study shows a flat dose-concentration QT curve for telavancin, a mean QTcF increase of only 0.5 msec for a doubling of the telavancin dose from 7.5 to 15 mg/kg. This implies a low risk of QT prolongation based on drug accumulation.
- QTc outliers for telavancin in the in healthy volunteers (thorough QT study) and in patients (HAP, cSSSI) were similar to moxifloxacin and vancomycin, respectively; especially for serious outliers with QTc > 500 msec.

- In the Phase 2 and Phase 3 studies, the number of deaths, cardiac SAEs, and SAEs requiring discontinuation were very similar for telavancin and vancomycin.

8.2.3 Safety in Pregnancy

In nonclinical developmental studies there were minor fetal effects, including lower fetal weights in rats and a low incidence of limb defects. Because there are no adequate and well-controlled studies in pregnant women, telavancin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2.4 Risk Minimization and Management Plan

Overall Plan

The main components of the telavancin pharmacovigilance plan include the following:

- Product Label/Prescribing Information
- Risk Minimization Strategy for cardiac events associated with QTc prolongation, nephrotoxicity, and adverse fetal development effects (detailed below)
- Targeted data collection for events of interest
 - Targeted data collection forms will be developed to collect additional information regarding all adverse cardiac events associated with QTc prolongation and nephrotoxicity that are reported post-approval.
 - These events will be reported to the FDA every 3 months for the first 2 years post-launch via special reporting.

Proposed Risk Minimization Plan for Telavancin

Goals And Objectives

The goals of the telavancin Risk Minimization Strategy are as follows:

- To minimize the risk of nephrotoxicity in patients taking telavancin

- To prevent or minimize the risk of adverse cardiac events associated with QTc prolongation in patients taking telavancin
- To minimize exposure of pregnant women to telavancin due to the potential risk of adverse effects on fetal development

The specific objectives to be achieved by the telavancin Risk Minimization Plan are as follows:

- To educate prescribers about risk factors predisposing to nephrotoxicity, the need for renal function monitoring for patients while receiving telavancin, and the requirement for dose adjustment for patients with creatinine clearance ≤ 50 mL/min
- To educate prescribers about the potential for QTc prolongation in association with the use of telavancin
- To educate prescribers and patients about the potential risk of adverse effects on fetal development for women exposed to telavancin during pregnancy
- To ensure safe use of telavancin by recommending that telavancin is initiated in a controlled healthcare setting where the patient can be adequately monitored
- To ensure the safe transition to the outpatient setting in patients taking telavancin

Elements Of The Risk Minimization Strategy

Prescribing Information and Patient Package Insert

The Prescribing Information and Patient Package Insert for telavancin will fully elaborate the risks of QTc prolongation, renal toxicity and effect on fetal development. This information will be incorporated prominently in all product promotion.

When a patient is transitioned to outpatient telavancin therapy the patient will receive a telavancin Patient Package Insert as part of the information provided during discharge planning.

Communication Plan

The Sponsor will implement a communication plan to healthcare providers to support implementation of the telavancin Risk Minimization Strategy. The Sponsor will provide educational materials for distribution to healthcare professionals involved in the prescribing, dispensing, or administration of telavancin, including infectious disease specialists, hospitalists, intensive care specialists, emergency room physicians, surgeons, hospital pharmacists, and home health care agencies. Educational materials will also be provided to hospital Pharmacy and Therapeutics and Formulary Committees to underscore the risk management strategies for telavancin.

The educational materials supportive of each risk minimization goal include:

- Goal: To minimize the risk of nephrotoxicity in patients taking telavancin
 - Telavancin Package Insert (PI)
 - A letter to prescribers and hospital pharmacists describing the goals and elements of the Risk Minimization Strategy
 - An information sheet for prescribers and pharmacies describing the basis for concern about a risk of renal toxicity and advising that the potential for renal toxicity should be weighed against the potential benefits when considering the use of telavancin in patients with renal impairment or with underlying conditions predisposing to renal impairment. The information sheet will also include details regarding recommended renal function monitoring and dose adjustment.
- Goal: To prevent or minimize the risk of adverse cardiac events associated with QTc prolongation in patients taking telavancin
 - Telavancin Package Insert (PI)
 - A letter to prescribers and hospital pharmacists describing the goals and elements of the Risk Minimization Strategy

- An information sheet for prescribers and pharmacies describing the basis for concern about a risk of QT prolongation when considering the use of telavancin in patients at risk of QT prolongation
- Goal: To minimize exposure of pregnant women to telavancin due to the potential risk of adverse effects on fetal development
 - Telavancin Package Insert (PI)
 - A letter to prescribers and hospital pharmacists describing the goals and elements of the Risk Minimization Strategy
 - An information sheet to inform prescribers to avoid use of telavancin during pregnancy, unless the potential benefit to the patient outweighs the potential risk to the fetus

In addition to these educational materials, the following items will also be utilized:

- An information sheet for prescribers that provides guidelines for use of telavancin in the outpatient setting
- A Patient Package Insert to be provided to patients who are transitioned to telavancin therapy in the outpatient setting
- Specific information to be included in the Formulary Kit provided to hospital pharmacies and P and T Committees regarding the appropriate use of telavancin

At the time of telavancin availability, the Introductory HCP letter will be sent by mass mailing to targeted medical specialists and hospitals to announce the availability of telavancin and to educate them on proper patient selection and use of the drug. The mailing will also include all of the educational materials indicated above. In addition, the information packet will be directed to the hospital formulary committee for distribution to appropriate prescribers and other medical staff. Additional materials will be available via sales and/or clinical representatives, the product website and through the Sponsor's toll-free medical information line. Information packets will also be sent to the leadership of the Infectious Disease Society of America, the American Society for Microbiology, the American Society of Health System Pharmacists, and the National Association for Home Care and Hospice Care.

In order to ensure that healthcare professionals remain informed of the telavancin Risk Minimization Strategy, the information packet will be updated annually and sent to all the above-mentioned organizations.

Settings for Initiation of Use

The Sponsor recommends that telavancin be initiated in a controlled healthcare setting where the patient can be adequately monitored.

Targeted Distribution

Sponsor will distribute to wholesalers and distributors that primarily distribute to hospitals, inpatient hospital pharmacies, and to pharmacies that supply home health care agencies. Each shipment will include the information for HCPs that outlines the appropriate use of telavancin.

Assessment of Risk Minimization

To measure the success of the risk minimization strategies information will be collected, evaluated and submitted to the FDA.

- Evaluation of Physician Compliance

To evaluate physician adherence to patient selection and monitoring in hospital, hospital pharmacists will be asked to participate in a study of telavancin use in their institutions. Participating pharmacists will use a standard abstraction form to collect information regarding compliance rates with key safety considerations (pregnancy, concomitant medication, and renal function monitoring). A total of 10 hospital pharmacies will each contribute 10 patients and repeat this 100-patient sampling at 6-, 18-, and 30-months post-launch. To increase feasibility and to be able to track change over time, the 10 participating hospital pharmacies will be retained to participate over the entire 30-month period. The initial selection of the 10 hospital pharmacies will be based both on willingness to participate and for diversity of hospital setting (to include small, medium and large projected volume of telavancin use).

- Knowledge, Attitude, and Behavior Surveys of Physicians and Pharmacists

Beginning 12 months post-launch, the Sponsor will administer surveys of prescribers and hospital pharmacists who have agreed to be contacted, auditing the telavancin Risk Minimization Strategy processes.

- Monitoring of Distribution Data

The distribution data for telavancin will be evaluated, and this information will be provided in the regular assessment reports for the Risk Minimization Strategy.

- Monitoring and Registration of Pregnancy Cases

The use of telavancin in pregnant women is to be avoided unless the potential benefit to the patient outweighs the potential risk to the fetus. Sponsor will monitor the post-marketing environment for any pregnancies exposed to telavancin. There will be a toll-free number listed in the Prescribing Information and in the Patient Package Insert for patients and/or prescribers to call to report pregnancies. All prospective reports of pregnancies will be followed until the outcome. The outcome information will be collected on retrospective reports.

Timetable for Submission of Assessments

Risk Minimization Strategy Assessments will be submitted to the FDA at agreed-to timeframes.

9 STUDY CONDUCT – QUALITY ASSURANCE

Investigator compliance with Good Clinical Practice was assessed in parallel with the conduct of the trials. In addition, Theravance conducted a comprehensive audit following completion of the studies to confirm the adequacy of their quality assurance measures. Results from these activities were reported to the FDA upon completion.

The FDA also assessed the integrity of the data submitted in support of these studies. After review of all findings, the FDA requested that Theravance remove efficacy data for three investigative sites (73 patients) and ECG data for two sites (66 patients) from the analyses. The tabular summaries presented in this Briefing Document reflect these deletions. Removal of these data did not change the conclusions drawn regarding the noninferiority of telavancin relative to vancomycin or alter conclusions drawn regarding the cardiac safety of telavancin.

10 RISK/BENEFIT

The risks of telavancin are compatible with the treatment of serious Gram-positive infections and include the following:

The most common adverse events were mild to moderate nausea, vomiting, and dysgeusia.

Renal adverse events and elevations in serum creatinine were more common in telavancin-treated patients than vancomycin-treated patients.

- In both groups, events were primarily seen in patients with underlying comorbidities that increase the risk for renal impairment
- The risk for renal adverse events in patients without underlying conditions predisposing to renal dysfunction was low and similar in the two treatment groups.
- The decreases in renal function were comparably reversible in the two treatment groups.

Telavancin has a small effect on the QTc interval.

- The thorough QT/QTc study demonstrated that the QTc effect seen with telavancin was approximately half that seen with the active control, moxifloxacin.
- In the Phase 2 and Phase 3 cSSSI studies, the frequencies of a > 60 msec change in QTcF from Baseline were similar between the treatment groups. One telavancin-treated patient compared with two vancomycin-treated patients had a maximum QTcF value > 500 msec.

In nonclinical developmental studies there were minor fetal effects, including lower fetal weights in rats and a low incidence of limb defects. Because there are no adequate and well-controlled studies in pregnant women, telavancin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Examples might include a pregnant woman who has cSSSI due to pathogens with diminished susceptibility or resistance to vancomycin, or a pregnant woman with cSSSI due to one or more of the

claimed pathogens and in whom other antibiotics are unacceptable for efficacy or safety reasons.

Telavancin has important benefits that address the need for additional antibiotics with demonstrated effectiveness against MRSA.

The first of a new class of antibiotics, the lipoglycopeptides, telavancin, was specifically designed to address the growing prevalence of Gram-positive resistance; and to provide enhanced activity against MRSA.

- Telavancin has a multifunctional mechanism of action; inhibition of cell wall synthesis and disruption of bacterial membrane function.
 - The multifunctional mechanism of action may be responsible for a low propensity for the emergence of resistance
 - During clinical trials there was no evidence of resistance developing to telavancin
- Telavancin displays potent, inoculum-independent, bactericidal activity (both extracellular and intracellular) against Gram-positive pathogens, including isolates with diminished susceptibility or resistance to other antimicrobials (vancomycin, daptomycin, linezolid, beta-lactams, trimethoprim-sulfamethoxazole, fluoroquinolones, macrolides/lincosamides, and tetracyclines).
 - Telavancin has potent activity (MIC \leq 1 μ g/mL) against strains of *S. aureus* with reduced susceptibility to vancomycin and is usually 4-fold more potent against all strains. Given the evolving MIC creep seen with vancomycin, the poor pharmacodynamic target attainment with usual vancomycin doses, and the increased risk for nephrotoxicity from higher doses, a drug such as telavancin would offer significant potential benefit.
- In numerous experimental models of infection, telavancin, administered at human equivalent doses, was shown to be superior to comparator drugs (vancomycin, linezolid or daptomycin [for MRSA] and nafcillin [for MSSA]). Telavancin has also been shown to be highly effective and superior to vancomycin in experimental models of biofilm infection.
- Telavancin exhibits linear, predictable pharmacokinetics, with good penetration into skin and lung tissue. The potency, half-life, and postantibiotic effect of the

drug allow for once daily dosing. Dosage adjustment is recommended for patients with renal impairment (creatinine clearance \leq 50 mL/min).

- There is no known potential for drug:drug interactions that could modify the pharmacokinetics of telavancin or affect the disposition of other drugs.
- Telavancin is effective in the treatment of cSSSI. In Studies 0017 and 0018 (individually and combined) the primary endpoint of noninferiority was met in all prespecified analysis populations, including the subset of patients infected with MRSA.

Risk :Benefit Assessment

Quantification of benefit:risk is optimal for understanding and assessing the value of a therapeutic agent. The overall benefit of telavancin includes numerous characteristics as outlined above, but in terms of measuring the benefit, the clinical outcome in the total population treated is most relevant. In terms of risk, the potential for QT prolongation with telavancin is minimal, and was not shown to lead to adverse outcomes in the cSSSI studies. Similarly, in the cSSSI patient population, no risk of adverse outcome in pregnancy was observed. Therefore, the only quantifiable risk is the development of renal impairment.

Two recent papers are instructive in helping to construct a quantification of the benefit to risk ratio for telavancin, specifically examining the clinical and economic consequences of treatment failure in cSSSI and of acute renal failure (ARF). Edelsberg et al recently assessed the consequences of failure of initial antibiotic therapy for patients with complicated skin and skin-structure infections. They found that compared with patients for whom initial treatment was successful, patients who experienced treatment failure received intravenous antibiotic therapy for a mean of 5.7 additional days, were hospitalized for a mean of 5.4 additional days (Edelsberg J, et al. *Infect Control Hosp Epidemiol.* 2008;29:160–169). Additionally, treatment failure was also associated with a 3-fold increase in mortality.

Similarly, Fischer et al used a statewide health care database to characterize the costs and lengths of stay (LOSs) incurred by hospitalized patients with uncomplicated ARF. Uncomplicated ARF was defined as not being associated with other organ failures. They found that patients hospitalized with uncomplicated ARF incurred median hospital LOS of 5 days, and mortality of 8% (Fischer MJ, et al. *Am J Kidney Dis.* 2005;46:1049–1057).

While it is not possible to directly compare these results since they are derived from two different studies, it does suggest that treatment failure in cSSSI could result in more adverse clinical and economic outcomes than uncomplicated acute renal failure, but at least are similar.

Renal failure (nearly all cases uncomplicated) in the telavancin cSSSI studies occurred in nine telavancin patients and two vancomycin patients, a difference of ~0.7% in the total population treated (Section 8.2.1). Among all patients treated in the telavancin cSSSI studies, the treatment failure rate was 1.8% higher in the vancomycin group (Figure 9). This would suggest that in the studies presented herein, even if one considered the clinical and economic consequences of acute renal failure and treatment failure in cSSSI to be similar, that the benefit:risk assessment for telavancin would be positive since there fewer treatment failures to potentially offset the slightly higher rate of renal failure.

11 CONCLUSIONS

Telavancin is a bactericidal, lipoglycopeptide antibiotic with a unique multifunctional mechanism of action that includes inhibition of bacterial cell wall synthesis and disruption of the functional integrity of the bacterial membrane. Telavancin is active against Gram-positive bacteria, including strains resistant or not susceptible to other classes of antibiotics (e.g., beta-lactams, linezolid, daptomycin, fluoroquinolones, macrolides, lincosamides, tetracyclines, and trimethoprim/sulfamethoxazole). Telavancin retains good activity against strains of *S. aureus* with reduced susceptibility to vancomycin (hVISA, VISA), and has activity against the strains of *S. aureus* resistant to vancomycin (VRSA).

Telavancin is active against many other clinically relevant Gram-positive pathogens: streptococci (including multidrug-resistant pneumococci), enterococci (including many vancomycin-resistant strains), Gram-positive anaerobes such as clostridia (including *C. difficile*), and other less commonly encountered pathogens.

To date, neither in vitro passaging studies nor evaluation of clinical isolates from patients exposed to telavancin for as long as 21 days have revealed evidence of the development of resistance to telavancin. These data indicate that there is a low potential for the emergence of resistance to telavancin, possibly as a result of the multifunctional mechanism of action.

Although some vancomycin-resistant enterococci have reduced susceptibility to telavancin, there is no known cross-resistance between telavancin and other classes of antibiotics.

Telavancin exhibits linear, predictable pharmacokinetics, with good penetration into skin and lung tissue. The potency, half-life, and postantibiotic effect of the drug allow for once daily dosing. Telavancin is cleared primarily by the kidneys. Therefore, dosage adjustment is recommended for patients with renal impairment (creatinine clearance \leq 50 mL/min).

The cSSSI Phase 3 program consisted of two randomized, multinational, double-blind studies conducted under identical protocols. Combined, the studies enrolled a total of 1867 adult patients, 719 of whom were infected with MRSA. The design of these studies followed applicable regulatory guidance, meeting the requirements for a suitable control agent and for assuring that patients had cSSSI. The telavancin program included the largest subset of patients infected with MRSA to date.

The studies demonstrated that telavancin 10 mg/kg IV q 24 hours for 7 to 14 days is as effective as a current standard of care, vancomycin, in treating patients with cSSSI caused by susceptible strains of Gram-positive pathogens. In patients infected with MRSA, the clinical, microbiologic, and overall therapeutic response rates were consistently numerically higher in the telavancin group.

The adverse events most commonly reported for telavancin-treated patients with cSSSI included abnormal taste, nausea, vomiting and foamy urine, which were mild or moderate in severity.

Renal adverse events occurred in more patients receiving telavancin (3.4%) than vancomycin (1.2%) and were associated with the presence of baseline comorbidities that increase the risk for renal impairment. Renal events were comparably reversible in both groups, consistent with the published experience with other anti-infectives.

Telavancin causes a prolongation of the QT interval. No cardiac adverse events could be directly related to QTc prolongation.

In nonclinical developmental studies there were minor fetal effects. After reviewing the data from all developmental studies, an independent expert concluded that the primary evidence

of an adverse developmental effect was a reduction in litter weight in a study in rats and that there was no clear evidence of teratogenicity in any of the developmental studies. After evaluating the few observed limb defects, he noted that there was no embryologically coherent mechanism by which a common malformation syndrome could be postulated to have been caused by telavancin.

Telavancin offers an important addition to the therapeutic armamentarium for the treatment of serious infections due to resistant Gram-positive pathogens, particularly MRSA. With appropriate consideration of the potential risks in individual patients and the use of renal function monitoring in all patients, the benefits of telavancin outweigh the risks for the treatment of cSSSI caused by susceptible strains of the following Gram-positive microorganisms: *S. aureus* (including methicillin-resistant strains [MRSA]), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius* and *S. constellatus*), and *Enterococcus faecalis* (vancomycin-susceptible isolates only).

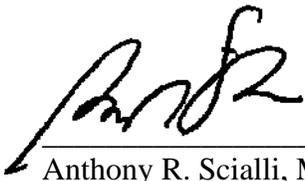
12 APPENDICES

- Appendix 1: Evaluation of the Developmental Toxicology Data on Telavancin
- Appendix 2: Narratives for Patients Who Died During Study
- Appendix 3: Narratives for Patients Who Had Serious Renal Adverse Events

**APPENDIX 1: EVALUATION OF THE DEVELOPMENTAL TOXICOLOGY DATA ON
TELAVANCIN**

Evaluation of the Developmental Toxicology Data on Telavancin (AMI-6424)

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6/27/07

Anthony R. Scialli, M.D.

date

Evaluation of the Developmental Toxicology Data on Telavancin (AMI-6424)

Introduction

I am a board-certified obstetrician-gynecologist with subspecialty training in Reproductive and Developmental Toxicology. I have spent most of my career as a faculty member in the Department of Obstetrics and Gynecology at Georgetown University Medical Center and, separately, as Director of the Reproductive Toxicology Center, A non-profit foundation located in Bethesda, Maryland. The Reproductive Toxicology Center operates a computerized data base called REPROTOX®, which contains information on the reproductive and developmental effects of several thousand agents and which is used by genetic counselors, physicians, industrial hygienists, and public health personnel around the world. I am a past president of the Teratology Society and Founding Editor of the peer-reviewed journal, *Reproductive Toxicology*, which is the official journal of the European Teratology Society. I have provided consulting services to government and industry in the area of reproductive and developmental toxicology. I am familiar with the conduct and interpretation of studies in this field and with the current FDA regulations on pregnancy labeling.

I have evaluated developmental toxicology study reports on telavancin (AMI-6424), a medication that has been evaluated in rat, rabbit, and minipig. As discussed below, these study reports clearly support Pregnancy Category C labeling.

The Rat Developmental Toxicity Study

The rat developmental toxicology study was performed at Covance Laboratories and was reported in April, 2003.¹ The test article was given to pregnant Sprague Dawley rats intravenously at 0, 50, 100, or 150 mg/kg bw/day (25 dams/group) on gestation day (GD) 6–17 (confirmation of mating = GD 0). There were two control groups, one of which received diluent and one of which received a placebo for telavancin. The animals were killed on GD 20. All fetuses were weighed and evaluated for external abnormalities. Half of the fetuses were evaluated for visceral abnormalities using the Wilson technique, and half of the fetuses were evaluated for skeletal anomalies using alizarin red S staining of bone. This design was compliant with regulations in force at the time of the study.

There were decreases in mean maternal body weight on GD 8–20 and in mean maternal body weight gain on GD 6–18, 6–20, and 0–20 in the high dose group. There was a decrease in terminal body weight corrected for uterine weight in the high dose dams. There was a decrease in food consumption in the mid and high dose groups. According to the study report, there was a decrease in fetal weight in the mid and high dose group; however, this analysis appears to have used the fetus as the experimental unit.² In additional analysis conducted for this review, using

¹ Fisher BR. Intravenous injection rat developmental toxicity study with AMI-6424. Covance Study Number 7057-126, April 4, 2003.

² The methods section indicates that ANCOVA was used with litter size as the covariant. This analysis takes the fetus as the statistical unit and considers litter effects only insofar as pups are lighter when litters are larger. The analysis does not consider maternal health and well-being as a mediator of fetal weight. The consequence of using a fetus-based analysis is an inflation of degrees of freedom in the statistical testing and greater ease in identifying differences as statistically significant (Type 1 error).

litter weights (Appendix 8) analyzed with ANOVA and post-hoc Tukey test, there was a significant difference between the high dose group and the diluent control, but not between the mid dose group and either control. Fetal soft tissue and skeletal variations were reported in the text as increased in the mid and high dose groups but these alterations appear based on the Tables 15 and 17 to have been increased in all dose groups on a litter basis. There was no increase in fetuses or litters with malformations at any dose. Two fetuses with malformations were noted. One fetus in the mid dose group had protruding tongue, “brachymelia” of the left hindlimb, syndactyly of the left hindlimb, and anophthalmia. One fetus in the high dose group had “brachymelia” of the left hindlimb. The LOAEL for maternal toxicity was 150 mg/kg bw/day, based on the body weight effects. In my opinion, the LOAEL for developmental toxicity was 150 mg/kg bw/day based on the decrement in litter weight.

The study author indicates that the “brachymelia” (short limb) noted on external examination in 1 high-dose and 1 mid-dose fetus was considered treatment-related because this abnormality has not been noted in historical control databases. I do not agree with this assessment for two reasons.

First, the observation of short limb on external examination is nonspecific and potentially unreliable. Typically, short limb can be a sign that one or more long bones are missing or under-developed. This finding should be confirmed on skeletal examination of the fetus. In the mid-dose fetus with “brachymelia” (Fetus 9, Dam B50748), no long-bone abnormalities were noted on skeletal examination, calling into question whether there was a limb malformation at all. The high-dose fetus (Fetus 5, Dam N50753) with “brachymelia” was not evaluated skeletally, because it was selected by coin toss for visceral evaluation. Therefore, an actual limb abnormality cannot be confirmed in this fetus.

Second, the term “brachymelia” is less commonly used than the term, “micromelia.” It is likely that the author would have been more successful finding the more common term in the historical control databases. If one fetus in each dose group had had micromelia, the author likely would have concluded that this finding was within the historical control range.³ Regardless, it is not clear that either of the fetuses in this study truly had a limb-shortening abnormality.

The Rabbit Developmental Toxicity Study

The rabbit developmental toxicology study was performed at Covance Laboratories and reported in October, 2003.⁴ The test article was administered to New Zealand white rabbits at 0, 60, or 75 mg/kg bw/day (20 females/group) on GD 7–20 (confirmation of mating = GD 0). Does were killed on GD 29. All fetuses were evaluated for external abnormalities, visceral abnormalities (by fresh dissection), and skeletal abnormalities (alizerin red S staining).

Maternal toxicity occurred in the televancin-treated does as manifested by a decrease in body weight on GD 7–9 and a decrease in body weight gain on GD 7–21. Body weight change over

³ According to the control data base of the Mid-Atlantic Regional Teratology Society, micromelia can occur as background in 1 fetus in 1 litter of a 20–22 control litter study.

⁴ Weaver EW. Intravenous injection rabbit developmental toxicity study with AMI-6424. Covance Study Number 7057-175, October 23, 2003

the course of pregnancy was not affected by treatment. There were decreases in maternal food intake at intervals in the high dose group. Fetal weight was not altered by treatment. There were no statistically significant increases in external, visceral, or skeletal malformations. There was a fetus in the high-dose group with limb abnormalities (including brachymelia) consisting of absence of the ulna and absence of 1 digit. This fetus also had gastroschisis, diaphragmatic hernia, and gallbladder agenesis. A second high-dose fetus from a different litter had an umbilical hernia. Three additional fetuses from three different high-dose litters had fusion of the sternbrae and one additional fetus in a separate litter had a bipartite vertebral centrum, fusion of a pair of ribs, and forking of a rib. Although the sternbral, vertebral, and rib abnormalities were considered malformations, their clinical significance is doubtful. Fused sternbrae for example, occurs spontaneously in control litters and has also been associated with maternal toxicity in rat and rabbit studies. Notwithstanding, the author considered 75 mg/kg bw/day an effect level based on what was characterized as the number and severity of fetal malformations seen at this dose level. The author considered 75 mg/kg bw/day an effect level for maternal toxicity based on the body weight loss and decreased food consumption at intervals in this group.

In my opinion, there were only three fetuses with clinically significant malformations in this study. One fetus in the control group had cardiomegaly, one fetus in the high-dose group had multiple malformations, and one fetus in a separate litter had umbilical hernia. Given the diverse nature of these malformations, it is difficult to make a case for a treatment-related effect. Consideration of 75 mg/kg bw/day as an effect level for developmental toxicity would be abundantly cautious.

The Minipig Developmental Toxicity Study

The minipig developmental toxicology study was performed at LAB Scantox and reported in June, 2006.⁵ The test article was given intravenously to pregnant Göttingen minipigs on GD 11-35 (the day after 3 successful matings or the first day of refusal to mate was GD 1). Fourteen animals per group were given diluent, placebo, or telavancin 25, 50, or 75 mg/kg bw/day. The females were killed on GD 109–111. All fetuses were examined for external, visceral, and skeletal abnormalities.

There were no statistically significant effects of treatment on maternal weight, fetal weight, or incidence of malformations. There was an increase in the number of late resorptions in the mid and high dose litters, but this increase was discounted by the study author because the rate was within the historical control range. There were fetuses with limb abnormalities in one of the control groups, in the low-dose group, and in the mid-dose group. The limb abnormalities were primarily polydactyly, which is known to occur spontaneously in the minipig. Polydactyly was seen in one fetus in the control group, 4 fetuses in 3 litters in the low-dose group, and 5 fetuses in 3 litters in the mid-dose group. One of the fetuses with polydactyly in the mid-dose group appeared to have a misshapened leg due to absence of the radius. Another mid-dose fetus, in a litter not otherwise affected, had syndactyly. The author indicated that because these abnormalities occur spontaneously in the minipig and because the high-dose group was not

⁵ Kledal T. Telavancin: Study for effects on embryo-fetal development in the minipig. LAB Scatox Study number 58857, reported June 16, 2006.

affected, the abnormalities were not treatment related. The authors considered 75 mg/kg bw/day a no-effect level.

Additional malformations were described in aborted fetuses; however, due to autolytic and postmortem positional abnormalities in aborted fetuses, I do not believe the assessment of these abnormalities is reliable or informative.

The minipig study is a difficult study to interpret because of the poor reproductive performance of all the groups and the small number of litters available for assessment. Pregnancy rates were low, ranging from 57% in one of the control groups to 79% in the other control group and the low-dose group. Pregnancy rates to term were lower, from 36% in a control and in the high-dose group to 64% in the low-dose group. The number of pregnant sows available for evaluation at term was at most 9 (in the low-dose group) and at the least 5 (in one of the controls and in the high-dose group). It is an important problem that reproductive performance was so poor in one of the control groups, and I would discount the minipig study altogether in my assessment of the developmental toxicity potential of telavancin.

Is There a Limb Signal in this Dataset?

Limb defects were reported in the rat, rabbit, and minipig studies. The question of whether these observations constitute a signal that telavancin interferes with limb development depends on whether the limb defects arise from embryologic events through a common mechanism.

In the rat study, there were two fetuses described as having brachymelia. One of these fetuses did not have an abnormality confirmed by skeletal examination. The other fetus was not evaluated skeletally, and it is not possible to know what underlying abnormality, if any, caused the impression of limb shortening.

There are diverse mechanisms of limb shortening. Embryonic limb outgrowth is dependent on the function of the apical ectodermal ridge, a specialized group of cells at the distal tip of the limb bud. The apical ectodermal ridge produces a protein (fibroblast growth factor 8) that maintains the subjacent mesenchyme in an undifferentiated state. This mesenchyme is called the progress zone and is the source of proliferating cells that increase limb length. These mesenchymal cells make fibroblast growth factor 10, which maintains the apical ectodermal ridge. As the limb grows outward, the more proximal cells in the progress zone become distant from the source of fibroblast growth factor 8, resulting in differentiation of these cells and cessation of growth. If the apical ectodermal ridge is damaged or prematurely stops producing fibroblast growth factor 8 or if the subjacent mesenchyme produces inadequate fibroblast growth factor 10, limb outgrowth will be reduced, often in association with failure of more distal structures to develop. During the fetal period, limb growth in the proximal-distal axis is also dependent on cell division at the epiphyseal plates. Impaired cell division at these plates or premature closure of the plates can produce a short limb.

Shortening of the limb can also be associated with absence or hypoplasia of one of the long bones. The proximal long bone (humerus, femur) may depend on Hoxd-9 and Hoxd-10, and the distal long bones (radius, ulna, tibia, fibula) may depend on gradients of Hoxd-9–13 in the

anteroposterior axis. Agenesis of one of the distal long bones, as occurred in one of the rabbit fetuses and one of the minipig fetuses, may be due to a disruption in the gradient or may be due to a subsequent vascular accident.

Polydactyly is produced by a mechanism distinct from the different mechanisms of limb shortening. Polydactyly is an abnormality of the distal limb in which the normal gradient of digit-inducing signals is impaired. The gradient is established by sonic hedgehog in the “zone of polarizing activity” on the posterior (pinky) side of the limb bud. Sonic hedgehog induces a gradient of bone morphogenetic proteins in the limb bud. In addition, *Gli3* and *Alx4* are expressed on the anterior (thumb) aspect of the limb bud, perhaps setting up a counter-gradient. Disruption of *Gli3* in mice causes polydactyly, as does ectopic anterior expression of sonic hedgehog.

The limb observations in the rat, rabbit, and minipig study are embryologically distinct. The limb observations in the rat study are difficult to evaluate, because one instance of “brachymelia” was not confirmed and the other instance was not investigated. The rabbit study had one fetus with absent ulna, and the minipig study had a fetus with absent radius and a non-dose related distribution of polydactyly, which is not unusual in this species. Because these abnormalities are etiologically distinct, it is unlikely that the same factor (telavancin treatment) caused them. The fact that the observations are situated in the same part of the body (the limb) does not make them etiologically similar any more than a clogged drain and a leaky faucet are the same because they are both located in the sink.

The Category C Designation

The Pregnancy Categories are described in 21 CFR 201.57:

If animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks, the labeling shall state: “Pregnancy Category C. (Name of drug) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (name(s) of species) when given in doses (x) times the human dose. There are no adequate and well controlled studies in pregnant women. (Name of drug) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.” The labeling shall contain a description of the animal studies.

Telavancin produced an adverse effect on rat fetuses, namely a decrease in litter weight at a maternal dose of 150 mg/kg bw/day. This dose produced plasma concentrations (AUC) about 2.2 times the plasma concentration in humans receiving telavancin 10 mg/kg/day (774 µg·hr/mL). In the rabbit study, fetal effects at 75 mg/kg bw/day were not convincing, but taking this dose level as an effect level would give a multiple of the human exposure level of 1.8, again based on AUC comparisons. The minipig study is not interpretable due to the poor reproductive performance of control animals.

The Category C designation has typically been used for medications with similar or more alarming preclinical findings. For example, the label for clarithromycin (Biaxin®) states:

Pregnancy Category C. Four teratogenicity studies in rats (three with oral doses and one with intravenous doses up to 160 mg/kg/day administered during the period of major organogenesis) and two in rabbits at oral doses up to 125 mg/kg/day (approximately 2 times the recommended maximum human dose based on mg/m^2) or intravenous doses of 30 mg/kg/day administered during gestation days 6 to 18 failed to demonstrate any teratogenicity from clarithromycin. Two additional oral studies in a different rat strain at similar doses and similar conditions demonstrated a low incidence of cardiovascular anomalies at doses of 150 mg/kg/day administered during gestation days 6 to 15. Plasma levels after 150 mg/kg/day were 2 times the human serum levels. Four studies in mice revealed a variable incidence of cleft palate following oral doses of 1000 mg/kg/day (2 and 4 times the recommended maximum human dose based on mg/m^2 , respectively) during gestation days 6 to 15. Cleft palate was also seen at 500 mg/kg/day. The 1000 mg/kg/day exposure resulted in plasma levels 17 times the human serum levels. In monkeys, an oral dose of 70 mg/kg/day (an approximate equidose of the recommended maximum human dose based on mg/m^2) produced fetal growth retardation at plasma levels that were 2 times the human serum levels.

The label for pyrimethamine (Daraprim®) states:

Pregnancy Category C. Pyrimethamine has been shown to be teratogenic in rats when given in oral doses 7 times the human dose for chemoprophylaxis of malaria or 2.5 times the human dose for treatment of toxoplasmosis. At these doses in rats, there was a significant increase in abnormalities such as cleft palate, brachygnathia, oligodactyly, and microphthalmia. Pyrimethamine has also been shown to produce terata such as meningocele in hamsters and cleft palate in miniature pigs when given in oral doses 170 and 5 times the human dose, respectively, for chemoprophylaxis of malaria or for treatment of toxoplasmosis.

Alternative Categories

Of the alternative categories, Category A and D require human data, which is not available for telavancin. Category B requires either human data or experimental animal studies that do not show adverse fetal effects, and this category would not be appropriate for telavancin. Category X requires that “the risk of use of the drug in a pregnant woman clearly outweighs any possible benefit.”

Category X is used when there is clear evidence of adverse fetal outcome in humans and the potential benefits to the pregnant woman are non-existent or less important than the risk. For example, isotretinoin has a Category X designation because it has been shown to increase the risk of malformations in humans after therapeutic use during pregnancy, and because the treatment of cystic acne during pregnancy is not considered sufficiently important to justify exposing a fetus to the risk. By contrast, valproic acid also is known to increase the risk of malformation after therapeutic use during pregnancy, but valproic acid is Category D because two of the conditions for which it is indicated (mania and epilepsy) may require treatment during pregnancy for the health of the mother and, perhaps, of the fetus.

Category X is also used in the absence of human data when there is evidence of fetal harm in experimental animal studies and there is no conceivable use for the medication during pregnancy. HMG CoAse reductase inhibitors (“statins”) were given Category X designations when there were no human data, because it was considered unnecessary to lower cholesterol during pregnancy, a condition during which serum cholesterol is physiologically increased.

As indicated in the CFR, the Category X designation is used when the risk “clearly outweighs” the benefit. The risk-benefit analysis for most medications is typically performed by the prescribing clinician and the patient, but in the case of Category X drugs, this analysis is performed by the label-writer. Although the CFR does not define the risk-benefit weighing process, it is reasonable to infer that the intent is for the risk-benefit to be so clearly tilted toward risk that a reasonable practitioner and a reasonable patient would decline to use the medication during pregnancy.

The data for telavancin do not support a Category X designation. On the risk side, the finding of decreased litter weight in the face of maternal weight gain decrements as in the telavancin rat study does not portend much risk. The rabbit findings do not suggest an adverse effect on embryo development; consideration of 75 mg/kg bw/day as an effect level is a conservative stance but appears to be based at least in part on the belief that “brachymelia” occurred in both species. It is not clear, in fact, that limb shortening occurred at all in the rat study or, if it did, that it was by a mechanism similar to that in the rabbit study.

On the benefit side, the drug is intended for the treatment of complicated infections with gram positive bacteria, including methicillin-resistant staphylococci. These infections can be serious and untreated or inadequately treated infection may have adverse effects on pregnancy outcome.

It is not possible to conclude, then, that for telavancin, the risk clearly outweighs the benefit. One practitioner or patient might conclude that the risk outweighed the benefit, another practitioner or patient might reasonably decide that the benefit outweighed the risk. As for other Category C drugs, it would be appropriate to leave this determination with respect to telavancin to the practitioner and the patient.

Conclusion

Telavancin has been evaluated in two interpretable experimental animal developmental studies, one in rats and one in rabbits. There was clear evidence of developmental toxicity in the rat study at a maternal dose level of 150 mg/kg bw/day (2.2 times the human dose on an AUC basis), manifested as a reduction in litter weight. There was no increase in developmental toxicity in the rabbit study; however, study authors identified an effect level at a maternal dose level of 75 mg/kg bw/day (1.8 times the human dose on an AUC basis), based apparently on the erroneous belief that a single malformed rabbit fetus had the same malformation as two of the rat fetuses. There is no embryologically coherent mechanism by which a common malformation syndrome can be postulated to be caused by telavancin. Category C is the appropriate Pregnancy Category for these data.

APPENDIX 2: NARRATIVES FOR PATIENTS WHO DIED DURING STUDY

Telavancin Deaths:

Patient ID: 0017-02010-0546

SAE (MedDRA PT): Ventricular arrhythmia

Drug Relationship: Possibly/probably related

Outcome: Death

Patient 0017-02010-0546, a 65-year old white male, was enrolled in Study 0017 and randomized to telavancin on 13 Oct 2005 for the treatment of cellulitis and minor infected wounds. The subject received a single dose of study drug (telavancin) on Day 1.

The patient's medical history is significant for deep cellulitis and minor infected wounds in swollen legs attributed to right heart failure secondary to COPD. In addition, the patient had epilepsy, diabetes mellitus, coronary artery disease, and hypercholesterolemia. Concomitant medications included: albuterol, tiotropium bromide, furosemide, isosorbide, glicazide, pravastatin, perindopril e, digoxin, coumadin, and phenytoin.

The patient was admitted to the hospital on Study Day 1 (13 Oct 2005) and had normal electrolytes at Baseline. Baseline electrocardiogram revealed a normal QT/QTc interval with incomplete right bundle branch block, ventricular conduction delay and non-specific ST/T wave abnormalities. The patient was randomized to telavancin and received one dose of study drug on 13 October 2005. Despite estimated creatinine clearance of 63 mL/min, telavancin was not administered on 14 Oct 2005. The patient was found dead in his hospital bed the morning of 15 Oct 2005. Therefore, the patient received only one active dose of study medication in the 24 to 36 hours before death.

The investigator assessed the fatal event of acute ventricular dysrhythmia (coded as ventricular arrhythmia) as possibly/ probably related to study medication. The investigator noted that the diagnosis of acute ventricular dysrhythmia is presumptive, and in all likelihood secondary to hypoxia, cor pulmonale, coronary artery disease, and COPD. However, the investigator could not rule out an association between the event and administration of study medication.

Theravance's comment: Since the terminal event(s) in this patient were not witnessed, and in view of this patient's multiple significant medical problems and pharmacologic treatments, the precise cause of this patient's death cannot be determined from the available data. Both study medications have a pharmacological half life of less than 9 hours. Therefore, it would be expected that this patient would have had low plasma concentrations of either study medication at the time of death. The sponsor supports the investigator's conclusion regarding the complexity of this patient and the uncertain relationship of the events to the patient's single dose of study drug given more than 24 hours before the patient's death. However, it is considered a remote possibility that the study medication may have been a contributor due to temporal factors.

The fatal event of ventricular arrhythmia was reported as an expedited safety report (MCN 200500072(1.0)).

Patient ID: 0017-04004-0677

SAE (MedDRA PT): Systemic inflammatory response syndrome

Drug Relationship: Not related

Outcome: Death

Patient 0017-04004-0677, a 49-year old white female, was enrolled in Study 0017 and randomized to telavancin on 10 Dec 2005 for the treatment of a right knee abscess. Treatment ended on 13 Dec 2005, for a total exposure of 4 days.

The patient's medical history is significant for epilepsy, alcohol abuse, heart failure, hepatic failure, renal failure, candidal UTI, cholecystolithiasis, acute respiratory distress syndrome, anemia, diarrhea, obesity, obstipation, and systemic inflammatory response syndrome (SIRS) that started approximately one week prior to study enrollment. Concomitant medications at the time of the event included: hydrocortisone, insulin, lactulose, ranitidine, cisatracurium, phenytoin, dobutamine, norepinephrine, fluconazole, morphine, and glucose. In addition she was on hemodialysis.

Prior to study entry, the patient received ampicillin as antibacterial therapy on 10 Dec 2005, for one day only. On admission, the patient was in multi-organ failure and had a diagnosis

of SIRS. Telavancin was erroneously dosed at 10 mg/kg every 48 hours rather than 10 mg/kg every 24 hours, as serum creatinine was normal at baseline. One day after enrollment, *Candida albicans* was recovered from the skin as well as from the urine. The multi-organ failure and SIRS continued to worsen, and the patient died on Study Day 5.

The investigator assessed the fatal event of worsening SIRS as not related to study medication.

Patient ID: 0017-27010-0474

SAE (MedDRA PT): Cerebrovascular accident

Drug Relationship: Not related

Outcome: Death

Patient 0017-27010-0474 a 65 year-old white female, was enrolled in Study 0017 and randomized to telavancin on 12 Sep 2005 for the treatment of multiple infected burns on the left leg and foot. Treatment ended on 26 Sep 2005, for a total exposure of 15 days.

The patient's medical history is significant for multiple strokes, arterial hypertension, chronic heart failure, and vascular encephalopathy. Concomitant medications at the time of the event include: enalapril, atenolol, hydrochlorothiazide, aspirin, metamizole, prednisolone, strophanthin, ranitidine, heparin, and methyluracilum.

Prior to study entry, the patient received cefazolin (19 August 2005 to 12 Sept 2005) and amikacin (26 Aug 2005 to 12 Sept 2005) as antibacterial therapy. The patient was hospitalized on 16 Aug 2005 due to multiple infected burns of the left leg, arms and chest caused by boiling water. The burn surface area was approximately 15 %. The patient underwent dermal autoplasty with engraftment. Telavancin was started on 12 Sep 2005 along with aztreonam (administered from Study Day 1 through 15). The patient responded well and completed study treatment on 26 Sep 2005. On 05 Oct 2005 (Study Day 24), the patient died due to an acute stroke in the right hemisphere. An autopsy was performed, with the findings of an acute ischemic stroke in the left hemisphere, as well as bilateral pneumonia, acute respiratory and heart failure, and second-to-third degree thermal burns of the left arm, chest, and left hip.

The investigator assessed the fatal event of cerebrovascular accident as not related to study medication, but related to the patient's concurrent illness.

Patient ID: 0017-38001-0693

SAE (MedDRA PT): Pulmonary embolus

Deep vein thrombosis

Ovarian cancer

Drug Relationship: Not related to any of above

Outcome: Death

Patient 0017-38001-0693, a 96-year old white female, was enrolled in Study 0017 and randomized to telavancin 10 mg/kg on 20 Dec 2005 for the treatment of deep, extensive cellulitis of the lower left leg and foot. Treatment ended on 27 Dec 2005, for a total exposure of 8 days.

The patient's medical history was significant for hypertension, allergies to Macrodantin and Celebrex, macular degeneration, GERD, degenerative joint disease, left hip replacement, lumbar spine surgery, temporal arteritis, congestive heart failure, anemia, and hypothyroidism. Concomitant medications included: hydromorphone, theragran, pantoprazole, atenolol, hydrochlorothiazide, levothyroxine, isosorbide dinitrate, sublingual nitroglycerin, macrogol, bisacodyl, omeprazole, docusate sodium, paracetamol, Maalox, Fleet's enemas, prochlorperazine, furosemide, lorazepam, and oxycocet.

Prior to study entry, the patient received vancomycin (19 Dec 2005 only) and cefalexin (14 Dec 2005 to 19 Dec 2005). Baseline calculated creatinine clearance was 24 mL/min, and the patient was dosed appropriately with telavancin beginning on 20 Dec 2005. Hemoglobin was low (7.8 g/dL) throughout hospitalization. Doppler examination was negative for deep vein thrombosis. Because the patient's cellulitis had improved, treatment with study medication was completed on Study Day 8, and she was discharged to a rehabilitation center. Four days after completing study medication (31 Dec 2005), she experienced increasing fatigue, abdominal pain, shortness of breath, and flank and back pain. She was brought to the Emergency Room and found to be anemic (hemoglobin 7.5 g/dL), and

hypoxic (oxygen saturation approximately 75% on room air). An ultrasound performed on her swollen left lower extremity revealed extensive venous thrombosis, and a lung perfusion scan revealed a pulmonary embolus. CT scan of the abdomen revealed extensive ascites. MRI confirmed a pelvic mass, and paracentesis was performed to drain the intra-abdominal hemorrhage. The patient died on 21 Jan 2006, with the cause of death listed as pulmonary embolism and previously undiagnosed ovarian cancer.

The investigator assessed the fatal events of pulmonary embolus, deep vein thrombosis and ovarian cancer as not related to study medication. However, the events were submitted as an expedited safety report due to the patient's death (MCN 200600013).

Patient ID: 0017-38002-0428

SAE (MedDRA PT): Renal failure

AE (MedDRA PT): Renal insufficiency

Drug Relationship: Possibly/probably related

Outcome: Death

Patient 0017-38002-0428, an obese (425 lbs) 70-year old white male, was enrolled in Study #0017 and randomized to telavancin on 18 Aug 2005 for the treatment of cellulitis of the left calf. Treatment was discontinued on 23 Aug 2005 for a total exposure of 6 days.

The patient's medical history is significant for morbid obesity (428 lbs), chronic atrial fibrillation, congestive heart failure, left atrial clot, hypertension, unstable angina, extrapulmonary tuberculosis, diabetes, appendectomy, thoracotomy, and sleep apnea. The patient had an automatic implantable cardioverter/defibrillator placed in Feb 2005. An echocardiogram performed in Feb 2005 showed an ejection fraction of 35-40%. Concomitant medications at the time of the event included: furosemide, nitrofurantoin, phenazopyridine, carvedilol, clopidogrel, insulin, warfarin, lactulose, quinapril hydrochloride, simvastatin, paracetamol, and panadeine co.

The patient was admitted to the hospital on 14 Aug 2005 for work-up of unstable angina and congestive heart failure. He developed cellulitis of the left calf and treated with piperacillin with tazobactam (17 Aug to 18 Aug 2005) and ampicillin (18 Aug 2005). He was enrolled in

the study on 18 Aug 2005 and randomized to telavancin. Baseline calculated creatinine clearance was 85 mL/min. Beginning on 22 Aug 2005 (Study Day 5), the patient's urine output decreased. Serum creatinine increased from 1.0 mg/dL (Day 1) to 2.7 mg/dL (Study Day 7). Although the initial dose of telavancin was appropriate according to the calculated creatinine clearance, the dose of telavancin was not modified (decreased) to reflect the new calculated creatinine clearance of less than 50 mL/min. Telavancin was stopped on Study Day 6 due to renal insufficiency; on that day, serum potassium was 5.3 mEq/L, creatinine was 2.7 mg/dL, and urea was 63 mg/dL. Due to the patient's underlying condition, his status was changed two days later (26 Aug 2005) to "do not resuscitate/comfort care only" (including no hemodialysis). The patient died on 27 Aug 2005 due to renal failure.

The investigator assessed the fatal event of renal failure as possibly/probably related to study medication. The investigator stated that the increased creatinine may have been secondary to diuresis. In addition, at the time of this event, the patient was receiving furosemide, phenazopyridine, carvedilol, clopidogrel, and quinapril hydrochloride, which may have played a role in this event. However, a relationship of the renal failure to study medication could not be excluded, and the report was submitted as an expedited safety report (MCN 200500044).

Patient ID: 0018-01002-2474

SAE (MedDRA PT): Cardiac arrest

Drug Relationship: Possibly/probably related

Outcome: Death

Patient 0018-01002-2474, a 75-year-old white post-menopausal female, was enrolled in Study 0018 and randomized to telavancin on 08 Nov 2005 for the treatment of cellulitis of the left hand resulting from a thermal burn. Treatment ended on 13 Nov 2005, for a total exposure of 6 days.

The patient's medical history is significant for diabetes, peripheral vascular disease, cholecystectomy, and hypertension. Concomitant medications at the time of the event included: heparin, enalapril, acetylsalicylic acid, pethidine, insulin, ibuprofen, clonazepam, morphine, furosemide, ranitidine, dipirone, dexiopopoxiphen, metformin.

Prior to study entry, the patient received cefalothin (05 Nov – 07 Nov 2005) and clindamycin (05 Nov 2005 only) as antibacterial therapy for deep cellulitis of the left hand. On 07 Nov 2005, the patient was hospitalized for continued treatment. Admission labs were normal (Hemoglobin 11.3 g/dL, creatinine 0.8 mg/dL). ECGs recorded prior to initiating study medication showed a mean QTcF of 451 msec and evidence of right bundle branch block (RBBB). The patient began therapy with telavancin, aztreonam, and metronidazole on 08 Nov 2005. ECGs on Study Day 4 still showed evidence of RBBB with a mean QTcF of 479 msec, for an increase from baseline of 28 msec. The hemoglobin was 8.8 g/dL and creatinine was 1.3 mg/dL; the latter value was reported as acute renal failure of moderate severity. On Study Day 5, the patient was accidentally overdosed with morphine (dose administered unknown). Four hours later the patient complained of moderate weakness and moderate asthenia, and a mild fall was reported. Telavancin dosage was decreased from 10 mg/kg q 24 hr to 7.5 mg/kg q 24 hr. On Study Day 6, the patient was determined to have a poor response of the local cellulitis to treatment. However, the abscess had minimal purulent drainage with no erythema or induration. On Study Day 7, the subject was found dead with no underlying cause. No autopsy was performed.

The investigator assessed the fatal event of cardiac arrest as possibly/probably related to study medication. Since the terminal event(s) in this patient was not witnessed, and in view of this patient's multiple medical problems, the precise cause of death cannot be determined from the available data. Contributing events, as described by the investigator, include ventricular arrhythmia secondary to hypoxemia, pulmonary thromboembolism, or coronary heart disease. It should be noted that the ECGs from baseline to 3 days before death were not significantly changed. Hence, it is not possible from the data available to define the cause of death or ascertain whether the study medication was a contributor. This event was submitted as an expedited safety report (MCN 200500091(1.0))

Patient ID: 0018-19006-2894

SAE (MedDRA PT): Cardiorespiratory arrest

Drug Relationship: Not related

Outcome: Death

Patient 0018-19006-2894, an 84 year-old white male, was enrolled in Study 0018 and randomized to telavancin on 01 Mar 2006 for the treatment of extensive cellulitis of the left foot. Treatment ended on 09 Mar 2006, for a total exposure of 9 days.

The patient's medical history is significant for poorly controlled diabetes mellitus, rheumatoid arthritis, hypertension, left femoral-iliac bypass (15 Dec 2005), hepatic carcinoma (follow-up information from the investigator), and amputation of the 2nd finger. Concomitant medications included furosemide, captopril, acetylsalicylic acid, insulin, ranitidine, paracetamol with codeine, albumin, and hydrocortisone.

On 27 Feb 2006, the patient was hospitalized due to extensive cellulitis of the left foot and on 01 Mar 2006 (Study Day 1) therapy with telavancin was initiated. The dose of telavancin was 10 mg/kg every 24 hours despite a baseline creatinine clearance < 30 mL/min (peak plasma concentration 28 µg/mL, AUC₀₋₂₄: 556 µg.hr/mL), but was adjusted appropriately on 05 Mar 2006 to 10 mg/kg every 48 hr. Aztreonam was added on 02 Mar 2006. On this same day (02 Mar 2006), hydrocortisone was administered for hypotension, but this was not reported as an adverse event. The patient was anemic with a hemoglobin of 7.1 g/dL on Study Day 7. Baseline ECG was abnormal with first degree AV block, and had a mean QTcF of 440 msec that did not significantly increase during the study. ECGs on 05 Mar 2006 showed new right bundle branch block. Telavancin was discontinued on Study Day 9 due to resolution of cellulitis.

Two adverse events of increases in ALT and AST were reported on 09 Mar 2006 (Study Day 9). The central laboratory measurements on Study Day 7 (07 Mar 2006) were: ALT 47 U/L, AST 48 U/L, bilirubin of <3 umol/L, and alkaline phosphatase of 270 U/L. Local laboratory values on 09 Mar 2006 were reportedly AST 818 UI/L and GPT 1186 UI/L. According to the Investigator (from follow-up information), the patient had hepatic cirrhosis from hepatic carcinoma.

On 10 Mar 2006, ECG showed new atrial fibrillation. On Study Day 11, two days after the last dose of study drug, the patient died due to cardio-respiratory arrest. An autopsy was not performed.

The investigator assessed the fatal event of cardio-respiratory arrest as not related to study medication.

Patient ID: 0018-38160-2501

SAE (MedDRA PT): Myocardial infarction, Acute respiratory failure

Drug Relationship: Not related

Outcome: Death

Patient 0018-38160-2501, a 77 year-old white male, was enrolled in Study 0018 and randomized to telavancin on 16 Nov 2005 for the treatment of cellulitis of the left hand. Treatment ended on 20 Nov 2005, for a total exposure of 5 days.

The patient's medical history is significant for COPD, hypertension, pulmonary fibrosis, asthma, supraventricular tachycardia, congestive heart failure, angina, pneumonia (Oct 2005), rheumatoid arthritis, and silicosis. Concomitant medications included: metronidazole, aztreonam, prednisone, levosalbutamol, glipizide, irbesartan, lorazepam, vicodin, paracetamol, ipotassium chloride, insulin, and furosemide.

The patient's pretreatment serum creatinine was 1.7 mg/dL, which did not increase during the study, and the calculated creatinine clearance was 30.7 mL/min. Telavancin dosing was appropriately adjusted to approximately 7.5 mg/kg q 24 hr. On 18 Nov 2005 (Study Day 3), the patient underwent surgical excision of an underlying hand cyst. On 19 Nov 2005 (Study Day 4), he developed fever and an increased white blood cell count. No other clinically significant abnormalities were seen in the chemistry and hematology analytes. All Gram stains and cultures from the wound were negative. Blood cultures were also negative. In the morning of 20 Nov 2005 (Study Day 5), the patient was found to be improving; he was afebrile, responsive and eating. However, by mid-morning the patient developed acute respiratory failure, and heparin was started for pulmonary embolus prophylaxis. He was also treated with morphine, ipratropium, and diltiazem for congestive heart failure. The patient was transferred to ICU for mechanical ventilation; however, the patient and his family refused mechanical ventilation, and the patient was made DNR status. He continued on study drug, acute care, and comfort measures. The patient died that evening with cause of death of myocardial infarction, based on troponin I level of 4.76 ng/mL (normal <0.4).

The investigator assessed the fatal events of myocardial infarction and acute respiratory failure as not related to study medication. The report was submitted as an expedited safety report due to the patient's death (MCN 200500104).

Vancomycin Deaths:

Patient ID: 0017-02001-0257

SAE (MedDRA PT): Pulmonary Embolism

Drug Relationship: Not Related

Outcome: Death

Patient 0017-02001-0257, a 46-year-old white male, was enrolled in Study 0017 and randomized to vancomycin on 13 May 2005 for the treatment of an infection at the site of a below-the-knee amputation. Treatment ended on 17 May 2005, for a total exposure of 5 days.

The patient's medical history is significant for peripheral vascular disease (1993) and atrial fibrillation (1998). He underwent a right popliteal arterial embolectomy and fasciotomy (1993). Concomitant medications include: heparin, paracetamol, tramadol, oxycodone, digoxin and amitriptyline.

On 29 Apr 2005, the patient's right leg was amputated below the knee. A chest x-ray performed on 03 May 2005 was normal. On 09 May 2005, the patient's amputation site was debrided. Two days later (11 May 2005), a methicillin-resistant *Staphylococcus aureus* wound infection was diagnosed and the patient started study drug (vancomycin) on 13 May 2005.

On 17 May 2005 (Study Day 5), the patient was found slumped in his wheelchair, he was cold and clammy and short of breath. The patient was treated for this event with prolonged advanced life support and resuscitation attempts, including administration of 1200 µg of atropine and 4 mg of adrenaline for electro-mechanical dissociation. The patient died on 17 May 2005 of a cardiac arrest secondary to a pulmonary embolus. An autopsy report indicated that there was a large saddle embolus obstructing the pulmonary trunk.

The investigator assessed the fatal event of pulmonary embolism as not related to study medication; however, the event was submitted as an expedited safety report due to the patient's death (MCN 200500012).

Patient ID: 0017-38016-0824

SAE (MedDRA PT): Pulmonary embolism
Cardiopulmonary arrest*

Drug Relationship: Not related

Outcome: Death

Patient 0017-38016-0824, a 49-year-old white female, was enrolled in Study 0017 and randomized to vancomycin on 22 Feb 2006 for the treatment of an abscess to the lower left quadrant. Treatment ended on 23 Feb 2006, for a total exposure of 2 days.

The patient's medical history was significant for morbid obesity (366 lbs, ht 5' 7"), diabetes, and herpes type II. Concomitant medications included morphine sulfate, regular insulin, famotidine, heparin, promethazine, paracetamol, azetreonam, and metronidazole.

On 22 Feb 2006, the patient began treatment for an abscess to the lower left quadrant radiating to the supra-pubic areas with drainage, redness, and swelling. Lab values on 22 Feb 2006 included: WBC 8.2/mm³ and glucose 370 mg/dl. A urine dipstick test was positive for ketones 1+, glucose 4+, blood 1+. On 23 Feb 2006, the patient was getting out of bed and became suddenly unresponsive. The patient was moved to bed with no pulse. CPR was performed with 5 rounds of epinephrine and atropine. The patient briefly regained pulse two times. Dopamine was started. The patient remained unresponsive to therapy and died. Pathology results at autopsy indicated the cause of death to be pulmonary embolism secondary to abdominal abscess.

The investigator assessed the life-threatening events of pulmonary embolism and cardiopulmonary arrest as not related to study medication; however, the event was submitted as an expedited safety report due to the patient's death (MCN 200600083).

*The event of cardio-pulmonary arrest was incorrectly recorded in the clinical database as 'non-serious'.

Patient ID: 0017-38024-0695

SAE (MedDRA PT): Respiratory failure

Cardiac failure congestive

Drug Relationship: Possibly/probably related

Outcome: Death

Patient 0017-38024-0695, a 53 year-old male, was enrolled in Study #0017 and randomized to vancomycin on 20 Dec 2005 for the treatment of chronic non-healing leg ulcers. Treatment was discontinued on 02 Jan 2006, for a total exposure of 14 days.

The patient's medical history was significant for pulmonary hypertension, secondary polycythemia, ventricular septal defect, hypothyroidism, renal insufficiency, hypertension, and seizure disorder. Concomitant medications included aztreonam, warfarin, levothyroxine, lidocaine, silver sulfadiazine, furosemide, esomeprazole, mirtazapine, acetaminophen w/codeine, losartan, atenolol and tegretol.

The patient had been previously admitted with chronic non-healing leg ulcers, from which methicillin-resistant Staphylococcus aureus (MRSA) and Pseudomonas were recovered on bacterial culture. Baseline calculated creatinine clearance was 32 mL/min. The patient was discharged on 30 Dec 2005, but outpatient administration of study drug continued. The patient was re-admitted to the hospital on 04 Jan 2006 with shortness of breath. A chest x-ray performed on the same date, revealed bilateral pleural effusion and interstitial pulmonary edema consistent with congestive heart failure. The patient died on 05 Jan 2006.

The investigator assessed the life-threatening events of respiratory and cardiac failure as not related to study medication; however, the events were submitted as an expedited safety report due to the patient's death (MCN 200600027).

Patient ID: 0017-38271-0659

SAE (MedDRA PT): Hepatic coma

Respiratory failure

Cariorespiratory arrest

Drug Relationship: Not related (all events)

Outcome: Death

Patient 0017-38271-0659, a 47-year-old white male, was enrolled in Study #0017 and randomized to vancomycin on 25 Nov 2005 for the treatment of right leg cellulitis. Treatment ended on 30 Nov 2005, for a total exposure of 6 days.

The patient's medical history is significant for hypertension, hepatitis C infection, depression, open reduction and internal fixation of a compound fracture of the left tibia/fibula (1987) with bone graft in 1988, removal of external fixator in 1989, skin graft left lower extremity 1990, cardiomegaly, alcohol abuse, cirrhosis with ascites/encephalopathy/coagulopathy/hyperbilirubinemia/anasarca 10 Nov 2005), and allergy to Demerol. Concomitant medications during study drug administration included aztreonam, metronidazole, atenolol, potassium chloride, vicodin, morphine, diphenhydramine, amlodipine, lactulose, pantoprazole, spironolactone, folic acid, benazepril, magnesium oxide and sulfate, phytomenadione, temazepam.

Cefazolin and ampicillin were administered in the two days prior to study entry. Study drug treatment was started on 25 Nov 2005 for cellulitis of the right leg. On 30 Nov 2005, the patient's liver function tests were as follows (pre-treatment Baseline values in parentheses): ALT 27 u/L (25 U/L), AST 71 U/L (65 U/L), total bilirubin (39 umol/L (41 mg/dL umol/L), alkaline phosphatase (120 U/L (140 U/L). Study drug was discontinued on 30 Nov 2005 due to the presence of aztreonam-resistant Gram-negative bacteria. Subsequent antibacterial therapy included levofloxacin (30 Nov – 06 Dec 2005), trimethoprim-sulfamethoxazole (01 – 02 Dec 2005), vancomycin (03 – 06 Dec 2005), ampicillin/sulbactam (04 – 05 Dec 2005), and ampicillin (04 – 06 Dec 2005). Additional therapies initiated after study drug discontinuation included levothyroxine, diphenhydramine, haloperidol, heparin, guaifenesin, lactulose, sucralfate, and octreotide.

On 03 Dec 2005 (3 days after last dose of study drug), the patient had an episode of oxygen desaturation that did not improve with increased oxygen via 5L nasal cannula. The patient was started on biphasic positive airway pressure (BIPAP), and required norepinephrine, phenylephrine, midodrine and albumin for hypotension as well as atropine and epinephrine for bradycardia over the next days. Diagnoses included hepatic coma and respiratory failure. On 05 Dec 2005, the patient was transferred to the ICU after he became apneic and required mechanical ventilation, levosalbutamol, and opatropium for hypoxia. On 07 Dec 2005, the patient had a fatal cardiopulmonary arrest.

The investigator assessed the fatal events of hepatic coma and respiratory failure as not related to study medication, but the events were submitted as an expedited safety report due to the patient's death (MCN 200500116).

Patient ID: 0017-38271-1010

SAE (MedDRA PT): Respiratory Distress

Drug Relationship: Not Related

Outcome: Death

Patient 0017-38271-1010, a 90-year-old white male, was enrolled in Study #0017 and randomized to vancomycin on 13 May 2006 for the treatment of cellulitis. Treatment ended on 26 May 2006, for a total exposure of 14 days.

The patient's medical history is significant for insulin-dependent Type II diabetes mellitus with polyneuropathy, hypertension, chronic renal failure, benign prostatic hypertrophy, hyperlipidemia, myocardial infarction (April 12 2006) , mild Alzheimer's Disease, chronic anemia, unsteady gait, depression, penicillin allergy, and peripheral vascular disease including high grade stenosis of the proximal superficial femoral artery with absence of pulses and osteopenia. Concomitant medications at the time of the serious adverse event included aztreonam, metronidazole, amlodipine, heparin-fraction, insulin, pantoprazole, folic acid, lisinopril, morphine, zolpidem, Accuzyme, moracizine, clopidogrel, paracetamol, epoetin alfa, lactulose, furosemide, megestrol, ASA, simvastatin, tamsulosin, iron and calcium supplements.

The patient was hospitalized on 12 May 2006 for cellulitis of the left foot and study drug was started the next day, 13 May 2006. While hospitalized, the patient was treated for aspiration pneumonia, congestive heart failure, renal insufficiency, sepsis, and had the left second toe amputated. The patient developed respiratory distress after vomiting what was described as brown colored digested food. The patient had rales with crackles. The respiratory therapist placed the patient on 3L/min oxygen via nasal cannula. Oxygen saturation was 71%. Patient was placed on a bilevel positive airway machine. The patient's oxygen saturation improved to 89-91% the morning following placement on the machine. The patient's renal function continued to decline (creatinine increased to 3.6 mg/dl on 22 May from a Baseline value of 1.7 mg/dl). On 24 May 2006, hemodialysis was performed and he required dopamine and phenylephrine for hypotension. The patient was improving with a planned transfer back to the nursing home on 02 Jun 2006. At 0225 on 02 Jun 2006, the patient developed labored respirations and an episode of ventricular tachycardia. The patient had requested a chemical code only. The patient died on 02 Jun 2006.

The investigator assessed the fatal event of respiratory distress as not related to study medication, but related to the patient's concurrent illness.

Patient ID: 0018-22000-2742

SAE (MedDRA PT): Cardiac insufficiency, Atrial fibrillation

Drug Relationship: Not related

Outcome: Death

Patient 0018-22000-2742, a 55-year-old white male, was enrolled in Study 0018 and randomized to vancomycin on 13 Jan 2006 for the treatment of cellulitis. Treatment ended on 14 Jan 2006, for a total exposure of 2 days.

The patient's medical history is significant for dermal T-lymphoma, diagnosed 14 Sep 2004, and hypoproteinemia. In the summer of 2005 the patient developed multiple, ulcer-like skin wounds for which he received 3 courses of chemotherapy. The patient had multiple skin lesions on the thorax, abdomen, upper and lower limbs. Concomitant medications included: metamizol, ketorolac, morphine, and Nutrison (all started on 13 Jan 2006).

On 10 Jan 2006, the patient was admitted; he received ampicillin from 10 Jan to 13 Jan 2006. On 13 Jan 2006, study drug (vancomycin) was started for wound infection/cellulitis that was culture-positive for MSSA. Baseline laboratory data showed: WBC $13.7 \times 10^9/L$, platelets $325 \times 10^9/L$, hemoglobin 99 g/L, C-reactive protein 454 mg/L, creatinine 107 $\mu\text{mol/L}$, total protein 48.8 g/L. Pre-treatment electrocardiograms revealed sinus tachycardia with a short QT interval. On 14 Jan 2006, a cardiologist diagnosed atrial fibrillation and cardiac insufficiency. The patient was treated for this event with metoprolol, aspirin, albumin, and furosemide and a normal sinus rhythm returned. However, on 15 Jan 2006, anuria developed, cardiac insufficiency progressed, and the patient died.

The investigator assessed the fatal events of cardiac insufficiency and atrial fibrillation as not related to study medication. These events were submitted as an expedited safety report due to the patient's death (MCN 200600034).

Patient ID: 0018-30907-2323

SAE (MedDRA PT): Septic shock, Cardiogenic shock, Pulmonary edema

Drug Relationship: Not related

Outcome: Death

Patient 0018-30907-2323, a 66-year-old white female, was enrolled in Study 0018 and randomized to vancomycin on 29 Sep 2005 for the treatment of right arm cellulitis. Treatment continued until the patient's death on 01 Oct 2005 for a total exposure of 3 days.

The patient's medical history was significant for hypertension, aortic aneurysm repair (2002), small bowel obstruction requiring laparotomy and enterolysis (June 2005), and chronic coughing. Concomitant medications included: aztreonam, opium alkaloids, diclofenac, paracetamol, heparin fraction, paracetamol, Omnopon, diclofenac, paracetamol, dobutamine, and phenylephrine.

On 29 Sep 2005, the patient presented to the emergency room with cellulitis of the right arm at the peripheral intravenous infusion site from a previous hospitalization and was started on study drug (vancomycin). Pre-treatment blood cultures grew *Staphylococcus aureus*. Baseline ECGs showed ectopic supraventricular tachycardia. Beginning 30 Sep 2005, the

patient became progressively hypotensive and tachycardic. On 01 Oct 2005, she developed hypoxemia due to pulmonary edema. Septic shock was considered as well as cardiogenic shock. Her kidney function had also deteriorated progressively since 20 Sep 2005. The patient was intubated, and treated with dobutamine, phenylephrine, hetastarch, furosemide, and midazolam/flumazenil for sedation for intubation. All efforts to resuscitate the patient were unsuccessful and the patient died on 01 Oct 2005.

There was no action taken with vancomycin due to the event.

The investigator assessed the fatal events of cardiogenic shock, septic shock and pulmonary edema as not related to study medication. The events were submitted as an expedited safety report due to the patient's death (MCN 20050061).

Patient ID: 0018-38260-2555

SAE (MedDRA PT): Cardiac arrest, Renal failure chronic, Ascites

Drug Relationship: Possibly/probably related

Outcome: Death (due to Cardiac Failure)

Patient 0018-38260-2555, a 53-year old, black, male was enrolled in Study 0018 and randomized to vancomycin on 23 Nov 2005 for the treatment of leg abscess/cellulitis. On 23 Nov 2005, one dose of vancomycin was given. The patient died before the next scheduled dose of vancomycin was to be given. However, because of the patient's renal status, vancomycin serum levels were expected to be in the therapeutic range for up to 1 week.

The patient's medical history was significant for cirrhosis with ascites, congestive heart failure, atrial fibrillation, gout, hypertension, anxiety, and end-stage renal disease requiring hemodialysis. Concomitant medications included: digoxin, carvedilol, clonidine, pantoprazole, Epogen, cyproheptadine, promethazine, paracetamol, temazepam, metoprolol, allopurinol, and morphine.

On 22 Nov 2005, the patient was hospitalized with leg abscess/cellulitis of both legs for which he was enrolled into study. On 23 Nov 2005, an incision and drainage was performed and the patient was discharged the following day (24 Nov 2005). On 27 Nov 2005, he was

re-admitted due to leg pain and ascites. The serious adverse events of worsening of end-stage renal disease and worsening of ascites were reported. However, the serum creatinine of 9.7 mg/dL on 28 Nov 2005 showed little change from the pre-treatment level of 9.6 mg/dL. On 30 Nov 2005, the patient underwent removal of double valve peritoneal subclavian venous shunt and was transferred to the ICU. The patient was started on amiodarone as an anti-arrhythmic and was dialyzed. Vancomycin serum levels were as follows: 19.9 mg/L on 25 Nov, 14.9 mg/L on 26 Nov, 10.6 mg/L on 28 Nov, and 8.7 mg/L on 30 Nov. Prior to the next schedule dose of vancomycin, the patient died on 01 Dec 2005.

The investigator assessed the fatal event of cardiac failure, and serious events of chronic renal failure and ascites as not related to study medication. The events were submitted as an expedited safety report due to the patient's death (MCN 200500111).

Patient ID: 202b-903-9037

SAE (MedDRA PT): Septic shock, Liver failure, Renal failure, Respiratory Failure

Drug Relationship: Not related

Outcome: Death

Patient 903-9037 was a 41-year-old female with a wound infection of the left foot. The patient was randomized to standard therapy (vancomycin) and started study drug on 09 June 2004. Concomitant medications during the study included paracetamol, aztreonam, and metronidazole. On 08 June 2004, the patient was admitted to the hospital with an approximately 1-week history of progressively enlarging ulcer of the left foot following a minor trauma. After study enrollment the patient was found to be anemic (hemoglobin 7.4 g/dL) with abnormal liver function test results (bilirubin 78 µmol/L, alkaline phosphatase 344 U/L, AST 109 U/L, and GGT 396 U/L). The patient admitted chronic alcohol use. Subsequently, the patient was found to be septicemic, and study drug was augmented with aztreonam and metronidazole. The patient's liver function continued to deteriorate, as well as her renal function. Study drug was discontinued on 14 June 2004. Laboratory results on 15 June 2004 included bilirubin 152 µmol/L, alkaline phosphatase 285 U/L, ALT 169 U/L, AST 94 U/L, creatinine 200 µmol/L, and potassium 2.3 µmol/L. The patient developed

respiratory distress and circulatory failure and died on 19 June 2004. The investigator assessed the events of multiorgan failure as not related to study drug.

**APPENDIX 3: NARRATIVES FOR PATIENTS WHO HAD SERIOUS RENAL ADVERSE
EVENTS**

Telavancin Renal SAEs:

Patient ID: 0017-38117-0240

SAE (MedDRA PT): Acute renal failure

Drug Relationship: Not related

Outcome: Recovered

Patient 0017-38117-0240, a 51 -year old black female, was enrolled in Study 0017 and randomized to telavancin on 21 Jun 2005 for the treatment of a right axillary methicillin-resistant *Staphylococcus aureus* (MRSA) abscess. Study drug was discontinued on 26 Jun 2005, for a total exposure of 6 days.

The patient's medical history was significant for morbid obesity, discoid lupus erythmatosus, diabetes, pulmonary hypertension, renal disease, iron deficiency anemia, rheumatic heart disease, mitral and aortic valve insufficiency, chronic airway obstruction, spinal stenosis, rheumatoid arthritis, and allergy to pork insulin. Concomitant medications at the time of the event included: insulin, morphine, hydroxychloroquine, tramadol, Oxycocet, temazepam, prednisone, amlodipine, lisinopril, hydrochlorothiazide, amitriptyline, erythropoietin, ferrous gluconate, famotidine, glyceryl trinitrate, mupirocin, atenolol, and glipizide.

Prior to study entry, the patient had received cefazolin as antibacterial therapy (20 Jan –21 Jan 2005, Study Days -1 to 1). She was randomized to study drug (telavancin) on 21 Jun 2005. At study Baseline, the patient's calculated creatinine clearance was 81 mL/min. However, she inadvertently received approximately double the recommended dose of telavancin (2000 mg q24h instead of 1100 mg q24h). She had the following Baseline renal laboratory values: BUN 33 mg/dL and serum creatinine 1.1 mg/dL. On 23 Jun 2005 (Study Day 3), BUN and creatinine were 36 mg/dL and 0.8 mg/dL, respectively, felt to be consistent with mild dehydration. On 24 Jun 2005 (Study Day 4), the patient underwent a CT scan of the abscess with IV contrast. The next day (25 Jun 2005, Study Day 5), she had renal failure reported. On 26 Jun 2005 (Study Day 6), BUN and creatinine had risen to 43 mg/dL and 2.7 mg/dL (local laboratory results), respectively. Study drug (telavancin) was discontinued on the same date and was unblinded to the investigator by the site pharmacist.

On 27 Jun 2005 (Study Day 7), BUN was 54 mg/dL and creatinine, 3.1 mg/dL. The event was noted as resolved on 03 Jul 2005 (Study Day 13). The patient received subsequent antibacterial therapy with vancomycin (01 Jul – 04 Jul 2005). On 08 Jul 2005 (Study Day 18), BUN and creatinine were 18 mg/dL and 1.0 mg/dL, respectively.

The investigator assessed the life-threatening serious event of acute renal failure as not related to study medication but secondary to receiving IV contrast.

Patient ID: 0017-38271-0953

SAE (MedDRA PT): Worsening Renal function (Renal Impairment)

Drug Relationship: Not related

Outcome: Recovered

Patient 0017-38271-0953, a 93-year-old white male, was enrolled in Study 0017 and randomized to telavancin on 23 Mar 2006 for the treatment of cellulitis of the right lower extremity. Treatment was completed on 01 Apr 2006, for a total exposure of 9 days.

The patient's medical history is significant for congestive heart failure, chronic atrial fibrillation, aortic stenosis, old anteroseptal myocardial infarction, hypercholesterolemia, hypertension, chronic renal failure, hyperkalemia, peripheral vascular disease, deep vein thrombosis of the right leg, bilateral pain, edema, and chronic cellulitis of the lower extremities with *Staphylococcus Aureus*, mild dementia, tobacco and alcohol use, and mild anemia. The patient's concomitant medications included heparin, warfarin sodium, lovastatin, warfarin, atenolol, lisinopril, bumetanide, metolazone, paracetamol, temazepam, Panafil, magnesium hydroxide, bisacodyl, Kayexalate (sodium polystyrene sulfonate), and pantoprazole.

Prior to study entry, the patient had received clindamycin and ceftriaxone as antibacterial therapies (each for one day only on 22 Mar 2006, Study Day -1). The patient, who was primarily bedridden and lived in a boarding-care facility, was hospitalized on 22 Mar 2006 with a diagnosis of right lower extremity cellulitis and atrial fibrillation. He was randomized to telavancin on 23 Mar 2006. Baseline calculated creatinine clearance was 28 mL/min, baseline creatinine was 1.5 mg/dL, and telavancin was dosed appropriately. The patient's treatment with study drug (telavancin) was successful, and he received his end of treatment

visit on 01 Apr 2006 (Study Day 10), at which time he was considered a cure. However, the patient remained in the hospital for monitoring of anemia and worsening renal function. On 31 Mar 2006, the patient's serum creatinine had increased to 2.3 mg/dL from a Baseline of 1.5 mg/dL, and the patient was transfused with packed red blood cells due to decreased hemoglobin (hgb) and hematocrit (HCT) (8.2 g/ dL and 25.6 %, respectively). Laboratory values on 01 Apr 2006 (Study Day 10) were: creatinine 2.2 mg/ dL, Hgb 9.4 g/ dL, and HCT 34 %. The patient was treated with IV fluids. and serum creatinine levels began to decrease: 2.9 mg/dL on 03 Apr 2006 (Study Day 12); 2.0 mg/dL on 07 Apr 2006 (Study Day 16) ; 1.6 mg/dL on 10 Apr 2006 (Study Day 19). On 07 Apr 2006 (Study Day 16), the patient was discharged from the hospital. Serum creatinine returned to baseline by 10 Apr 2006 (Study Day 19), at which time the patient was considered recovered from the event.

The investigator assessed the serious adverse event of worsening renal function, which prolonged hospitalization, as not related to study medication.

Patient ID: 0017-38002-0428

SAE (MedDRA PT): Renal failure

AE (MedDRA PT): Renal insufficiency

Drug Relationship: Possibly/probably related

Outcome: Death

Patient 0017-38002-0428, an obese (425 lbs) 70-year old white male, was enrolled in Study #0017 and randomized to telavancin on 18 Aug 2005 for the treatment of cellulitis of the left calf. Treatment was discontinued on 23 Aug 2005 for a total exposure of 6 days.

The patient's medical history is significant for morbid obesity (428 lbs), chronic atrial fibrillation, congestive heart failure, left atrial clot, hypertension, unstable angina, extrapulmonary tuberculosis, diabetes, appendectomy, thoracotomy, and sleep apnea. The patient had an automatic implantable cardioverter/defibrillator placed in Feb 2005. An echocardiogram performed in Feb 2005 showed an ejection fraction of 35-40%. Concomitant medications at the time of the event included: furosemide, nitrofurantoin, phenazopyridine, carvedilol, clopidogrel, insulin, warfarin, lactulose, quinapril hydrochloride, simvastatin, paracetamol, and panadeine co.

The patient was admitted to the hospital on 14 Aug 2005 for work-up of unstable angina and congestive heart failure. He developed cellulitis of the left calf and treated with piperacillin with tazobactam (17 Aug to 18 Aug 2005) and ampicillin (18 Aug 2005). He was enrolled in the study on 18 Aug 2005 and randomized to telavancin. Baseline calculated creatinine clearance was 85 mL/min. Beginning on 22 Aug 2005 (Study Day 5), the patient's urine output decreased. Serum creatinine increased from 1.0 mg/dL (Day 1) to 2.7 mg/dL (Study Day 7). Although the initial dose of telavancin was appropriate according to the calculated creatinine clearance, the dose of telavancin was not modified (decreased) to reflect the new calculated creatinine clearance of less than 50 mL/min. Telavancin was stopped on Study Day 6 due to renal insufficiency; on that day, serum potassium was 5.3 mEq/L, creatinine was 2.7 mg/dL, and urea was 63 mg/dL. Due to the patient's underlying condition, his status was changed two days later (26 Aug 2005) to "do not resuscitate/comfort care only" (including no hemodialysis). The patient died on 27 Aug 2005 due to renal failure.

The investigator assessed the fatal event of renal failure as possibly/probably related to study medication. The investigator stated that the increased creatinine may have been secondary to diuresis. In addition, at the time of this event, the patient was receiving furosemide, phenazopyridine, carvedilol, clopidogrel, and quinapril hydrochloride, which may have played a role in this event. However, a relationship of the renal failure to study medication could not be excluded, and the report was submitted as an expedited safety report (MCN 200500044).

Patient ID: 0017-18001-0721

SAE (MedDRA PT): Renal Impairment

Drug Relationship: Possibly/Probably Related

Outcome: Continued

Patient 0017-18001-0721, a 46-year old white male, was enrolled in Study 0017 and randomized to telavancin on 03 Jan 2006 for the treatment of a left leg/foot cellulitis. Treatment was completed on 12 Jan 2006, for a total exposure of 9 days. Due to renal insufficiency (baseline calculated creatinine clearance was 19 mL/min), study medication was dosed every 2 to 3 days.

The patient's medical history is significant for heavy smoking, diabetes, diabetic nephropathy and retinopathy, hypertension, ischemic heart disease, normocytic and hypochromic anemia, hyperlipidemia, morbid obesity, chronic renal failure, insomnia, and allergy to amoxicillin with clavulanate. Concomitant medications included diltiazem, furosemide, heparin, insulin, atenolol, simvastatin, aspirin, omeprazole, domperidone, brotizolam, metamizole, and acetylsalicylic acid.

Three days prior to starting study medication, the patient's serum creatinine had increased from 3.8 mg/dL to 5.3 mg/dL (Study Day 1). During the study, serum creatinine levels continued to rise, and hemodialysis was started on Study Day 4. Despite hemodialysis, serum creatinine continued to increase, reaching 11.4 mg/dL on Study Day 6 and dropping to 10.8 mg/dL on Study Day 10.

There was no action was taken regarding study drug (telavancin) due to this event. However, study medication was discontinued on Study Day 10 due to resolution of the skin infection. At the follow-up visit, serum creatinine was 7.3 mg/dL, and at the last patient contact (2½ months later), it was 4.2 mg/dL.

The investigator assessed the life-threatening serious adverse event of renal impairment that required hospitalization and resulted in permanent disability as possibly/probably related to study medication. The report was submitted as an expedited safety report (MCN 200600025). The Sponsor notes that the patient's creatinine was increasing prior to patient's enrollment in the study, from 3.84 to 5.28 mg/dL, and therefore the pre-existing condition of the patient and other concomitant medications that affect kidney function (e.g., furosemide and cilazapril) may have been responsible for the increased creatinine experienced by this patient. However, the contribution of the study medication to the patient's renal impairment cannot be entirely ruled out.

Patient ID: 0018-06003-2353

SAE (MedDRA PT): Renal failure acute

Drug Relationship: Not related

Outcome: Recovered

Patient 0018-06003-2353, an 84-year-old white female, was enrolled in Study 0018 and randomized to telavancin on 06 Oct 2005 for the treatment of severe cellulitis of the right lower limb. Treatment was discontinued on 11 Oct 2005, for a total exposure of 6 days.

The patient's medical history is significant for diabetes mellitus, microcytic anemia, chronic renal failure, dyslipidemia, hypothyroidism, acute rheumatoid arthritis (1996), sigmoidectomy with colostomy (1997), cerebrovascular accident (26 Jul 2005), overactive bladder with chronic urinary tract infection, and hypertension. Concomitant medications included: glibenclamide, ergocalciferol, atenolol, pantoprazole, levothyroxine, prednisone, simvastatin, tolterodine, ramipril, insulin, dimenhydrinate, lactulose, chronic trimethoprim-sulfamethoxazole, and hydrochlorothiazide.

Upon admission the patient's blood pressure was 127/70 mmHg, calculated creatinine clearance was 21.9 mL/min, and serum creatinine was 1.7 mg/dL. Telavancin was dosed at 10 mg/kg every 48 hours. On 09 October 2005, hemoglobin was 9.3 g/dL. Three days after admission, systolic blood pressure fell to under 100 mmHg. On 10 Oct 2005, serum creatinine increased to 2.9 mg/dL and then to 3.0 mg/dL on 11 Oct 2005. Ramipril and hydrochlorothiazide were discontinued after her last dose of study medication on 11 Oct 2005. On 13 Oct 2005, serum creatinine was 1.9 mg/dL and hemoglobin dropped to 7.1g/dL with systolic blood pressure <100 mmHg. Abdominal CT scan was negative for hematoma. The patient received a blood transfusion and was treated with norepinephrine and furosemide for acute renal failure on 12 Oct 2005. Renal failure was noted to have resolved on 18 October 2005 (serum creatinine 1.2 mg/dL).

The investigator assessed the serious event of acute renal failure, which prolonged the patient's hospitalization, as possibly/probably related to study medication. The investigator's final assessment was that the elevation in creatinine, which was rapidly ameliorated with normalization of blood pressure as well as cessation of ramipril and study medications, was

primarily due to hypotension combined with the ACE inhibitor rather than to study medication. Other confounding factors include an elevated serum creatinine pre-treatment, a history of chronic renal failure and the use of other potentially nephrotoxic medications such as hydrochlorothiazide and trimethoprim-sulfamethoxazole. With further follow-up the investigator reassessed the renal failure as not related to study medication. The events were submitted as an expedited safety report (MCN 200500062(1.0)).

Patient ID: 0018-06003-2721

SAE (MedDRA PT): Acute renal failure, Hypoglycemia

Drug Relationship: Possibly/probably related

Outcome: Recovered

Patient 0018-06003-2721, a 56-year-old white post-menopausal female, was enrolled in Study 0018 and randomized to telavancin on 06 Jan 2006 for the treatment of cellulitis of the left leg. Treatment ended on 19 Jan 2006, for a total exposure of 14 days.

The patient's medical history is significant for iron deficiency anemia, hypertension, asthma, chronic obstructive pulmonary disease, morbid obesity, sleep apnea, diabetes mellitus, gastroesophageal reflux, dyslipidemia, venous insufficiency with chronic edema and stasis dermatitis, Factor V Leiden, deep thrombophlebitis, and insomnia. Concomitant medications included: montelukast, salbutamol, budesonide, diltiazem, gezor, furosemide, glivencamide, metformin, beclometasone, fluvastatin, naproxen, oxycodone, warfarin, flurazepam, pantopazole, insulin (07 Jan – 15 Jan 2006), heparin, ASA, potassium chloride, terbinafine and ferrous sulfate,

Prior to study entry, the patient had received ciprofloxacin and clindamycin (each from 29 Dec 2004 – 05 Jan 2005) as antibacterial therapy. The patient began treatment with telavancin and aztreonam on 06 January 2006. Baseline serum creatinine was 0.9 mg/dL. During hospitalization, the patient underwent a gastroscopy, colonoscopy, and a barium enema study, following which a diagnosis of mild diverticulosis was made. The patient was discharged to home care on Study Day 11. At that time, serum creatinine was 0.8 mg/dL. She completed treatment on Study Day 14 (peak plasma concentration: 94 µg/mL, AUC₀₋₂₄: 1277 µg.hr/mL) and was considered cured. On Study Day 14 (19 Jan 2005), the patient's

home health nurse noted that the patient was confused and not eating well. The next day (Study Day 15), she was readmitted to the hospital for severe hypoglycemia (glucose 1.7 mmol/L), confusion, diarrhea (8 to 10 episodes of diarrhea each day, with fecal testing positive for *C. difficile*), hypomagnesemia, hypokalemia, and dehydration. Acute renal failure was reported (serum creatinine 1.7 mg/dL). The patient was treated with IV fluids and received potassium and magnesium supplementation. The symptoms of hypoglycemia and confusion resolved within 36 hours, and the renal failure resolved on Study Day 19. Oral metronidazole was started. The patient was discharged on Study Day 22, at which time serum creatinine had fallen to 0.7 mg/dL.

The investigator assessed the serious events of acute renal failure and hypoglycemia, both of which required hospitalization, as possibly/probably related to study medication. Other factors contributing to this patient's course include dehydration from severe diarrhea due to *C. difficile* and underlying diabetes. Hypoglycemia may have been exacerbated by a lack of adjustment of dosage of glibenclamide and metformin. These events were submitted as an expedited safety report (MCN 20060036).

Patient ID: 0018-38160-3068

SAE (MedDRA PT): Acute renal failure

Drug Relationship: Possibly/probably related

Outcome: Continuing*

Patient 0018-38160-3068, a 95 year-old white male, was enrolled in Study 0018 and randomized to telavancin on 25 Apr 2006 for the treatment of left leg cellulitis. Treatment was completed on 01 May 2006, for a total exposure of 7 days.

The patient's medical history is significant for diabetes mellitus, congestive heart failure, coronary artery disease, rheumatic heart disease, severe aortic stenosis requiring replacement of the aortic valve on 2 occasions, endocarditis (1997), peripheral vascular disease with venous stasis ulcers and bilateral edema in the lower extremities, hypertension, intermittent atrial fibrillation, coronary artery disease, transient ischemic attacks, pacemaker placement for sick sinus syndrome, chronic renal insufficiency (Oct 2005), hiatal hernia with gastroesophageal reflux disease, simple hepatic cyst, benign

prostatic hypertrophy, transurethral prostatectomy, hemorrhoidectomy, recurrent urinary tract infections, and anemia. Concomitant medications included pioglitazone, carvedilol, Coumadin, furosemide, pantoprazole, warfarin, and insulin.

Prior to study entry, the patient received piperacillin with tazobactam (21 Apr to 25 Apr), and clindamycin (24 Apr to 25 Apr). He was received telavancin at a dosage of 10 mg/kg q 24 hr, beginning on 25 Apr 2006, despite a calculated creatinine clearance of 10.5 mL/min. Pre-treatment serum creatinine levels were elevated at 3.9 mg/dL and 4.1 mg/dL. Serum creatinine values continued to increase throughout study drug treatment and after treatment was discontinued. Creatinine values were as follows: 26 Apr 2006 (Study Day 2), 4.4 mg/dL; 28 Apr (Study Day 4), 5.5 mg/dL; 01 May (Study Day 7), 5.9 mg/dL; 02 May (Study Day 8), 6.5 mg/dL; and 03 May (Study Day 9), 7.6 mg/dL. On 02 May 2006 (Study Day 8), the patient became oliguric with elevated BUN and creatinine and severe lower extremity edema. A renal ultrasound on 02 May 2006 revealed small incidental cysts in the right and left kidneys but was otherwise unremarkable. An ultrasound of the lower extremities on 02 May 2006 was negative for deep venous thrombosis. The patient was aggressively diuresed and hydration was corrected, but the fluid challenge on 02 May and 03 May failed to resolve the patient's azotemia, thus excluding a pre-renal etiology. Additional laboratory values on 04 May 2006 were: hemoglobin 8.2 g/dL, hematocrit 24.3%, sodium 128 mmol/L, creatinine 7.8 mg/ dL, BUN 145 mg/ dL. Serum creatinine on 10 May was 10.3 mg/dL. The physician discussed the progressive renal failure with the patient and family, but the patient refused dialysis. The patient was placed on comfort measures only, and all of his usual medications were discontinued. His overall condition continued to deteriorate, and he died on 12 May 2006 (Study Day 18).

The investigator stated the likely cause of the fatal renal failure was excessive diuresis from furosemide and sustained renal hypoperfusion; however, the investigator assessed the event as possibly related to study medication as the contribution of study medication to the event could not be completely ruled out. This event was submitted as an expedited safety report (MCN 200600137).

* The outcome (death) of this patient occurred outside the protocol-defined collection period and was not captured in the clinical trial database.

Patient ID: 0018-38148-2498

SAE (MedDRA PT): Acute respiratory failure (Possibly/probably related), Elevated creatinine level (Possibly/probably related), BUN increased (Possibly/probably related), Altered mental status (Not related)

Drug Relationship: As described above

Outcome: Recovered (All events)

Patient 0018-38148-2498, a 47-year-old white female, was enrolled in Study 0018 and randomized to telavancin on 11 Nov 2005 for the treatment of a right lower extremity abscess and probable soft tissue abscess in the right knee. She was treated from 12 Nov to 13 Nov 2005, for a total exposure of 2 days.

The patient's medical history is significant for obesity, diabetes mellitus, hypertension, hypercholesterolemia, peripheral vascular disease, headaches, left below-the-knee amputation, peptic ulcer disease, mild COPD, bursitis, osteoarthritis, depression, hysterectomy, cholecystectomy, hypomagnesemia, hypocalcemia, anemia, overactive bladder, and smoking. There was also a history of allergies to multiple drugs, including penicillin, sulfa, aspirin, and cephalexin. Concomitant medications included morphine, magnesium sulfate, oxycocet, indomethacin, insulin, pravastatin, promethazine, pantoprazole, uetiapine, rosiglitazone, and topiramate.

On 11 Nov 2005, the patient underwent incision and drainage of the major right leg and knee abscess. The patient received rifampicin therapy for one day only on 12 Nov 2005, and telavancin on 12 Nov and 13 Nov 2005 (four doses total). On 14 Nov 2005, the patient's serum creatinine level was elevated to 2.7 mg/dl from a Baseline level of 0.7 mg/dl, and BUN level was elevated to 26 mg/dl from a baseline level of 17 mg/dl. Telavancin was discontinued, as was indomethacin and lisinopril. The patient was anemic (Hb 9.8 g/dL) and received a packed red blood cell transfusion. On 14 Nov 2005, moderate hypoxia and mild hyperkalemia were reported, and acute respiratory failure was reported on 15 Nov 2005. The patient was transferred to ICU and placed on mechanical ventilation. Upon return from hyperbaric oxygen therapy, the patient was found to be obtunded and nonverbal. The next

day, serum creatinine rose to 4.4 mg/dl. Mechanical ventilation was discontinued on Study Day 9, and the respiratory failure was considered resolved as of that date. By Study Day 10, the patient was transferred out of the ICU, and her mental status returned to Baseline.

On 23 Nov 2005, serum creatinine had fallen to 1.4 mg/dl and the BUN was still elevated at 58 mg/dl, and the patient was felt to have completely recovered from the renal adverse events. On 27 Nov 2005, serum creatinine was 1.2 mg/dl and BUN was 30 mg/dl. Approximately 2 months later, on 18 Jan 2006, the patient's BUN level was within normal range at 14 mg/dl.

The investigator assessed the life-threatening events of elevated creatinine and BUN levels and acute respiratory failure and as possibly/probably related to the study medication and the altered mental status, which resulted from the required medical intervention, as not related to study medication. The patient had major comorbidities for renal impairment (diabetes, hypertension, peripheral vascular disease, tobacco abuse, and anemia) and was receiving non-steroidal anti-inflammatories and ACE inhibitor as concomitant medication. The renal function improved after the packed cell transfusion and cessation of indomethacin and lisinopril as well as telavancin. The events were submitted as an expedited safety report (MCN 200500088).

Patient ID: 0018-38260-2099

SAE (MedDRA PT): Renal Insufficiency (Recovered)

AE (Discontinuation): Blood creatinine increased (Condition improving), Blood urea increased (Condition improving)

Drug Relationship: Possibly/probably related

Outcome: As noted above

Patient 0018-38260-2099, a 50 year-old black female, was enrolled in Study 0018 and randomized to telavancin on 03 Jun 2005 for the treatment of an abscess of the left leg/foot. Treatment was discontinued on 07 Jun 2005, for a total exposure of 5 days.

The patient's medical history is significant for lupus, fibromyalgia, seizure disorder, depression, mood disorder, hypothyroidism, hypercholesterolemia, allergic rhinitis, shortness of breath, 3-year history of chronic abscesses, and bilateral lower extremity edema. Concomitant medications included: hydroxychloroquine, tegaserod, simvastatin, hydroxychloroquine, montelukast, potassium chloride, topiramate, lansoprazole, levothyroxine, quetiapine, venlafaxine, hydrochlorothiazide, excitalopram, vicodin, lamotrigine, carisoprodol, salbutamol, tramadol, and lidocaine patch.

Prior to study entry, the patient received levofloxacin as antibacterial therapy (26 May – 02 Jun 2005). Study drug (telavancin) was started on 03 Jun 2005. Baseline (03 Jun 2005) laboratory values included: BUN 15 mg/dL, serum creatinine 1.1 mg/dL. By 05 Jun 2005 (Study Day 3), BUN and serum creatinine had increased to 30 mg/dL and 2.2 mg/dL, respectively. On 08 Jun 2005 (Study Day 6), BUN was 41 mg/dL and serum creatinine was 4.6 mg/dL. Telavancin was discontinued, and she was admitted to the hospital with a diagnosis of kidney failure on 10 Jun 2005 (Study Day 8). Identity of study drug was unblinded to the investigator by the site pharmacist. Laboratory values on that date were BUN 44 mg/dL and serum creatinine 6.0 mg/dL. She was given IV fluids while in the hospital and discharged on 14 Jun 2005 (Study Day 12). Renal insufficiency was considered resolved after follow-up tests on 21 Jun 2005 (Study Day 19) revealed BUN of 25 mg/dL and serum creatinine 1.8 mg/dL. On 28 Jun 2005 (Study Day 26), serum creatinine was 1.5 mg/dL. At the end of the study, the patient's increased blood creatinine and BUN were considered "improving."

The investigator assessed the serious event of kidney failure (i.e., renal insufficiency), which required hospitalization, as possibly/probably related to study medication. The event was submitted as an expedited safety report (MCN 200500024(1.0)).

Patient ID: 0018-38148-2359

SAE (MedDRA PT): Blood creatinine increased

Drug Relationship: Possibly/probably related

Outcome: Recovered

Patient 0018-38148-2359, a 57-year-old white female, was enrolled in Study 0018 and randomized to telavancin on 21 Oct 2005 for the treatment of cellulitis of the left leg. Treatment with study drug was discontinued on 24 Oct 2005, for a total exposure of 4 days.

The patient's medical history is significant for diabetes mellitus, hypertension, ARDS (Aug 2005), asthma, morbid obesity, arthritis, cholecystectomy, lumbar degenerative disc disease, chronic depression and anxiety, multi-level cervical spondylosis, bilateral knee replacement, acute hypoxemic hypercapnic respiratory failure with acute sepsis syndrome and septic shock (20 Jul 2005), dyslipidemia, and pharyngeal dysphagia, obstructive sleep apnea syndrome, and right hemidiaphragm paralysis. Concomitant medications included salbutamol, iproatropium, ascorbic acid, ASA, ferrous sulfate, furosemide, fluticasone, gabapentin, loratidine, naproxen, pantoprazole, pravastatin, multivitamins, verapamil, sertaline, alprazolam, paracetamol, benzonatate, tussionex, guaifenesin,

Prior to study entry, the patient received levofloxacin (12 Oct – 21 Oct 2005) and linezolid (22 Oct – 24 Oct 2005) as antibacterial therapy. On 21 October, the patient was randomized to telavancin, which she began concurrent with "septic shock". On 25 Oct 2005, serum creatinine had increased from 0.9 mg/dL at Baseline to 2.1 mg/dL and blood urea nitrogen had increased from 5.7 mmol/L at Baseline to 10.4 mmol/L. She was discontinued from telavancin and started on clindamycin for cellulitis. Eighteen days later (07 Nov 2005), serum creatinine had normalized to 1.0 mg/dL and blood urea nitrogen was 3.6 mmol/L.

The investigator assessed the life-threatening serious event of elevated creatinine level as possibly/probably related to study medication. The patient had significant medical conditions that can predispose to renal failure, e.g., hypertension, septic shock, and diabetes mellitus. She was also receiving numerous medications associated with elevated creatinine or renal failure (e.g., acetylsalicylic acid, naproxen, paracetamol, furosemide, and gabapentin). The events were submitted as an expedited safety report (MCN 200500074).

Patient ID: 0018-38322-2757

SAE (MedDRA PT): Renal failure acute

Drug Relationship: Possibly/probably related

Outcome: Recovered

Patient 0018-38322-2757, a 66 year-old white female, was enrolled in Study 0018 and randomized to telavancin on 19 Jan 2006 for the treatment of deep extensive cellulitis of the left leg and foot. Treatment was discontinued on 25 Jan 2006, for a total exposure of 7 days.

The patient's medical history is significant for hypertension, hypercholesterolemia, osteoarthritis, cholelithiasis and cholecystectomy, psoriasis, bilateral lower extremity edema, peripheral neuropathy, chronic diarrhea, depression, anxiety, seasonal allergies, neck pain, sleep apnea, bilateral varicose veins, impaired glucose tolerance without diagnosis of diabetes, GERD, endometriosis, hysterectomy with oophorectomy, restless leg syndrome, and a recent urinary tract infection (10 Jan –12 Jan 2006). Concomitant medications included: Tenoretic (atenolol plus chlorthalidone), estradiol, loperamide, rosuvastatin, pramipexole, bupropion, paracetamol, cyclobenzaprine, buspirone, and diflorasone ointment.

The patient began therapy with telavancin on 19 Jan 2005. Baseline lab values on 19 Jan 2006 included serum creatinine 0.6 mg/dL, and urea nitrogen 16 mg/dL. On 23 Jan 2006 (Study Day 5), she complained of a 1-day history of nausea and vomiting, as well as shortness of breath and malaise that had been ongoing since starting study drug. On 23 Jan 2006 (Study Day 5), serum creatinine was 3.7 mg/dL and urea nitrogen was 39 mg/dL.

Despite the positive response of the infection to study drug therapy, the patient was instructed to discontinue telavancin on 24 Jan 2006 (Study Day 6) due to rising serum creatinine. However, the patient continued to self-administer two additional doses: the first on the evening of 24 Jan 2006 (Study Day 6) and the second on the morning of 25 Jan 2006 (Study Day 7). Telavancin was therefore discontinued on 25 Jan 2006, 2 days after the onset of the event.

The patient was hospitalized for acute renal failure on 25 Jan 2006 (Study Day 7). Serum creatinine values were: 25 Jan 2006 (Study Day 7), 2.6 mg/dL and 26 Jan 2006 (Study Day 8), 2.4 mg/dL. Renal failure was considered resolved on 31 Jan 2006 (Study Day 13) [serum creatinine value unavailable], and the patient was discharged on 02 Feb 2006 (Study Day 15). At the Test-of-Cure visit on 03 Feb 2006 (Study Day 16), 10 days after discontinuation of study medication, serum creatinine was within normal limits (0.9 mg/dL).

The investigator assessed the serious event of acute renal failure, which required hospitalization, as possibly/probably related to study medication. This event was submitted as an expedited safety report (MCN 200500033(1.0)).

Patient ID: 202b-910-9058

AE Term: Renal Failure Acute (Acute Renal Failure [Early Stage])

Patient number 202b-910-9058 was a 28-year-old black male with a major abscess of the left gluteal region, supra-medial quadrant, positive for coagulase-negative *Staphylococci*, *Escherichia coli*, *Enterobacter spp*, and *Viridans Streptococcus*.

The patient had no relevant medical history. Concomitant medications used during the study included diclofenac and Myprodol (ibuprofen, paracetamol and codeine) (both 30 June to 02 July 2004). The patient received no antimicrobials prior to enrollment. Baseline serum creatinine was 1.0 mg/dL.

The patient was randomized to telavancin and started study drug on 29 June 2004. The patient completed study treatment on 03 July 2004 and was discharged from the hospital.

When results of laboratory testing from 30 June 2004 became available on 03 July, evidence of renal dysfunction was revealed (serum creatinine 159 $\mu\text{mol/L}$ (1.8 mg/dL); normal range 60-120 $\mu\text{mol/L}$). The investigator considered the event to be early-stage acute renal failure. Clinical examination on 03 July 2004 was within normal limits (blood pressure of 130/85 mmHg with no signs or symptoms of renal failure). Serum creatinine values

remained elevated with the highest value recorded on 03 July 2004 (256 $\mu\text{mol/L}$ [2.9 mg/dL]). Urea elevations were first noted on 02 July (9.4 mmol/L; normal range 2.1-7.1 mmol/L) and also peaked on 03 July (10 mmol/L). Clinical examination on 08 July 2004 was normal; blood pressure was 130/85 mmHg. The patient had no complaints; urinary output measured by the patient over more than 14 hours on 05 July was 1700 mL. On 13 July 2004, clinical examination was normal; blood pressure was 130/80 mmHg. Serum creatinine was 138 $\mu\text{mol/L}$ (1.6 mg/dL); urea was 7.6 mmol/L.

On 03 August 2004, at a follow-up visit, clinical examination was normal, with blood pressure 120/80 mmHg. Laboratory testing showed that serum creatinine and serum urea had returned to normal levels (100 $\mu\text{mol/L}$ [1.1 mg/dL] and 4.9mmol/L, respectively). As of 03 August 2004, the outcome of the early-stage acute renal failure was completely recovered.

The investigator assessed the event as serious because it required medical intervention and as possibly/probably related to study drug. The investigator stated that the impaired renal function was probably related to the study drug with additional effect of anti-inflammatory medications.

Patient ID: 0017-02008-0120

SAE (MedDRA PT): Respiratory failure (Possibly/probably related)
Respiratory distress (Possibly/probably related)
Renal failure (Possibly/probably related)
Pulmonary edema (Not related)
Sepsis (Not related)

AE (MedDRA PT): Hypotension (Possibly/Probably related)

Drug Relationship: As noted above

Outcome: Death

Patient 0017-02008-0120, an 82-year old white female was enrolled in Study 0017 and randomized to telavancin on 04 Feb 2005 for the treatment of venous ulcers and cellulitis of the right leg and foot. Treatment was discontinued on 13 Feb 2005, for a total exposure of 9 days.

The patient's medical history is significant for diabetes, bilateral leg edema, recalcitrant ulceration of the lower right leg, hypercholesterolemia, gout, hypertension, anaphylaxis to penicillin, bilateral cataracts, fluid retention, obesity, and urinary incontinence. Concomitant medications included: simvastatin, allopurinol, perindopril, metformin, glimepiride, furosemide, potassium chloride, magnesium sulfate, omeprazole, and sodium polystyrene sulfonate.

Prior to study entry and during the study, the patient received aztreonam (Study Day -1 to 10). The patient presented with venous ulcers and cellulitis of the right leg, and received telavancin 7.5 mg/kg in combination with aztreonam and metronidazole. The initial starting dosage was low at 7.5 mg/kg every 48 hours rather than every 24 hours, in view of creatinine clearance of approximately 40 mL/min. However, the patient responded well with minimal residual cellulitis. Serum creatinine on Study Day 7 was 0.7 mg/dL. On Study Day 8, the patient reported increasing shortness of breath and two days later (Study Day 10)

developed oliguria, increasing respiratory distress, and coffee ground hematemesis. Laboratory tests revealed hypoxemia, acidosis, and renal impairment. Blood urea (17.6 mmol/L) and creatinine (2.1 mg/dL) were elevated, with low arterial pO₂ (47 mmHg) and pH (7.23), and elevated pCO₂ (62 mmHg). On Study Day 11, the patient was transferred to the Intensive Care Unit because of severe hypotension. Study medication was discontinued on that day, and the investigator felt it necessary to unblind the study drug. Respiratory fatigue continued to worsen, and the patient was intubated on Study Day 11 (serum creatinine 3.2 mg/dL). Purulent secretions were noted, and the patient was thought to be septic. She was treated with vasopressor and antimicrobial (ciprofloxacin, aztreonam, and metronidazole) agents. Mechanical ventilation continued over the next 48 hours, during which time renal function improved. The patient was extubated on Study Day 14, although she still required noradrenaline to maintain her blood pressure. On Study Day 16, the patient experienced intermittent atrial fibrillation that required treatment with amiodarone. The patient's condition deteriorated and the patient died on that day.

The investigator assessed the fatal events as unlikely or not related (although possibly/probably related was checked on the CRF) to study medication but as related to a combination of pre-existing renal and cardiac disease, a component of chest infection, and tachyarrhythmia. In this case, the patient's age, underlying diseases, septic shock, and concomitant medications could all have contributed to the development of the renal failure. The events were submitted as an expedited safety report (MCN 200500002).

Patient ID: 0018-38160-2007
SAE (MedDRA PT): Acute tubular necrosis
Drug Relationship: Not related
Outcome: Resolved

Patient 0018-38160-2007, a 51 year-old white male, was enrolled in Study 0018 and randomized to telavancin on 21 Dec 2004 for the treatment of right leg cellulitis. Treatment ended on 30 Dec 2004, for a total exposure of 10 days.

The patient's medical history is significant for alcoholic liver disease with cirrhosis and ascites, chronic pancreatitis, hypertension, and Crohn's disease. Concomitant medications

included: metoprolol, magnesium sulfate, meperidine, lorazepam, oxycocet, spironolactone, torasemide, albumin, lorazepam, lansoprazole, potassium chloride, promethazine, multivitamin with thiamine, Fleet's enema, magnesium and lactobacillus/acidophilus.

On 21 Dec 2004, the patient was admitted for cellulitis of right leg and study drug treatment was initiated in concert with aztreonam. There was an ulceration noted on the dorsal aspect of the right foot with *E. coli*. The wound was debrided and cultures revealed methicillin-sensitive *Staphylococcus aureus*. Abdominal ultrasound revealed changes in the liver consistent with cirrhosis, gallbladder with wall thickening and cholelithiasis, and mild splenomegaly. There was a small amount of ascites noted and paracentesis was performed; ascites fluid was negative for growth. Ultrasound and X-ray of the right leg were negative for DVT. He was hypokalemic on 22 Dec 2004 and he was given potassium supplements. On 23 Dec 2004, the patient was noted to have an increased creatinine (2.6 mg/dL, increased from Baseline value of 0.9 mg/dL) and aztreonam was discontinued. A Foley catheter was placed for better management of fluid status and spironolactone was started for acute tubular necrosis that was thought to be secondary to sepsis-like syndrome from the cellulitis. Spironolactone was discontinued on 24 Dec 2004 and torasemide and normal saline were started on 25 Dec 2004. On 27 Dec 2005, the patient's creatinine reached a maximum level of 3.4 mg/dL. On 28 December 2004, the patient had nausea and amylase was elevated at 497. On 29 December 2004, the patient had watery diarrhea. On 30 Dec 2004, the patient received his last dose of telavancin due to resolution of baseline skin infection (creatinine was 2.6 mg/dL). A stool specimen was positive for occult blood. On 31 Dec 2004, the patient underwent colonoscopy and polyp/hemorrhoid removal. On 03 Jan 2005, *C. difficile* toxin was isolated from stool. The patient was discharged in stable condition on 05 Jan 2005. The acute tubular necrosis was considered resolved although the patient continued to have mild renal insufficiency (creatinine 1.9 mg/dL on 03 Jan 2005)

On 01 Mar 2005, the patient was readmitted in end-stage liver failure from continued alcohol abuse. The patient died on 25 Mar 2005 due to the liver failure.

The investigator assessed the acute tubular necrosis as not related to study medication, however the report was submitted as an expedited safety report due to the patient's death (MCN 200500020(1.0)).

Patient ID: 202b-101-7008

AE term: Acute Prerenal Failure (Pre Renal Azotemia); Blood Urea Increased (Elevated BUN); Blood Creatinine Increased (Elevated Creatinine); Renal Failure (Acute Renal Insufficiency)

Patient number 202b-101-7008 was a 76-year-old white female with a postoperative abscess at the amputation site of the left second phalange.

Medical history was significant for non-insulin-dependent diabetes mellitus, hypertension, osteoarthritis, amputation of second phalange (21 February 2004), cholecystectomy, and Cesarean section. Concomitant medications included acetaminophen with codeine, vitamin C, metformin, aztreonam, metronidazole, morphine sulfate, acetaminophen, ibuprofen, ketorolac, promethazine, and benazepril. The patient received ceftriaxone on 05 March 2004.

On 05 March 2004, the patient was admitted to the hospital for treatment of an abscess at the site of the amputation of the left second phalange. At baseline, calculated creatinine clearance was 69 mL/min per Cockcroft-Gault calculation with a baseline serum creatinine of 0.9 mg/mL. The patient was randomized to telavancin 7.5 mg/kg once daily and received study drug on 06-15 March 2004. An elevated urinary microalbumin was observed at baseline.

On 15 March 2004, the investigator was notified by the medical staff at the Study Coordinating Center that laboratory testing on 12 March 2004 revealed a serum creatinine of 3.1 mg/dL (central lab). Urinalysis on 12 March 2004 revealed specific gravity 1.030, 2+ blood, 11-20 WBCs/HPF, 3-7 fine granular casts/LPF, and 4+ bacteria with 3+ leukocyte esterase. On 15 March 2004, repeat testing of creatinine and BUN was performed at the local laboratory. Creatinine was 3.4 mg/dL and BUN was 64 mg/dL. Study drug was discontinued; the patient had already received the morning dose on 15 March 2004.

The patient was evaluated by a nephrology consultant, who felt that the acute renal insufficiency could be multifactorial; possible causes included prerenal azotemia, medication (study drug, benazepril, nonsteroidal anti-inflammatory drug), or renal artery stenosis. In

addition, other possibilities were considered, such as interstitial nephritis. Overall, the impression of the nephrologist was of possible acute renal failure.

All other antibiotic therapies were interrupted pending further evaluation of the patient's renal function. On 16 March 2004, the patient's creatinine had decreased to 3.2 mg/dL, and maintenance intravenous fluids were increased to alleviate symptoms of azotemia. A renal ultrasound on 16 March 2004 was normal. Vital signs remained stable. On 19 March 2004, serum creatinine decreased to 2.0 mg/dL. On 25 March 2004, serum creatinine was 1.2 mg/dL and BUN was 12 mg/dL, and the event was considered resolved.

The investigator assessed the event as possibly related to study drug.

Vancomycin Renal SAEs:

Patient ID: 0017-38005-0180

SAE (MedDRA PT): Creatinine increased

White blood cell count increased

Drug Relationship: Possibly/probably related

Outcome: Recovered

Patient 0017-38005-0180, a 77-year-old white female, was enrolled in Study 0017 and randomized to vancomycin on 14 Apr 2005 for the treatment of traumatic wound on right foot complicated by diabetes. Treatment was completed on 17 Apr 2005, for a total exposure of 3 days.

The patient's medical history was significant for diabetes mellitus, peripheral vascular disease, osteomyelitis, hypertension, hyperlipidemia, peripheral neuropathy, and anemia. Concomitant medications included aztreonam, metronidazole, pantoprazole, heparin, clotrimazole, methyldopa, lisinopril, glibenclamide, pravastatin, verapamil, insulin.

The patient was initially treated with levofloxacin for three days. After the infection worsened, the patient underwent an angiogram and percutaneous transluminal angioplasty to restore optimal circulation. One dose of vancomycin was administered. The infection site was noted to have had increased erythema, induration and new wounds present. Upon study entry, the patient's creatinine was noted to be above the normal range (1.4 mg/dL) and her calculated creatinine clearance was 24 mL/min. She remained hospitalized for the entire study period with right great toe amputation scheduled for 17 Apr 2005. On 18 Apr 2005, the patient's creatinine increased to 3.4 mg/dL and WBC increased to 18.7 GI/L (from 11.3 GI/L on 15 Apr 2005; local laboratory result). The patient also complained of nausea and diarrhea. The patient was considered recovered on 22 Apr 2005. On 25 Apr 2005, the patient's creatinine was 1.0 mg/dL and WBC to 12.1 GI/L.

The investigator assessed the serious events of increased creatinine and increased WBC as possibly/probably related to study medication and the events were submitted as an expedited safety report (MCN 200500010).

Patient ID: 0017-38024-0697

SAE (MedDRA PT): Blood creatinine increased

Drug Relationship: Possibly/probably related

Outcome: Recovered

Patient 0017-38024-0697, a 62-year-old Asian male, was enrolled in Study 0017 and randomized to vancomycin on 21 Dec 2005 for the treatment of an infected abdominal gunshot wound. Study drug was discontinued on 25 Dec 2005, for a total exposure of 5 days.

The patient's medical history is significant for hypertension, as well as a gunshot wound to the pelvis on 05 Dec 2005 with exploratory laparotomy, end-sigmoid colostomy, and partial urethral disruption at that time. Concomitant medications included: aztreonam, metoprolol, esomeprazole, oxycocet, ibuprofen, docusate, and heparin.

At Baseline, serum creatinine was 0.7 mg/dL and calculated creatinine clearance was 98 mL/min. On 25 Dec 2005 (Day 5 of study drug), the patient's serum creatinine level increased to 2.1 mg/dL (local laboratory result), and study drug was discontinued. On 27 Dec 2005, serum creatinine further increased to 3.0 mg/dL (central laboratory result). The event was considered resolved on 18 Jan 2006, when the patient's serum creatinine normalized to 1.0 mg/dL. Subsequent antibacterial therapy included nafcillin, then oxacillin.

The investigator assessed the serious event of increased serum creatinine as possibly/probably related to study medication and the report was submitted as an expedited safety report (MCN 200600012).

Patient ID: 0018-38260-2555

SAE (MedDRA PT): Cardiac arrest, Renal failure chronic, Ascites

Drug Relationship: Possibly/probably related

Outcome: Death (due to Cardiac Failure)

Patient 0018-38260-2555, a 53-year old, black, male was enrolled in Study 0018 and randomized to vancomycin on 23 Nov 2005 for the treatment of leg abscess/cellulitis. On 23 Nov 2005, one dose of vancomycin was given. The patient died before the next scheduled dose of vancomycin was to be given. However, because of the patient's renal status, vancomycin serum levels were expected to be in the therapeutic range for up to 1 week.

The patient's medical history was significant for cirrhosis with ascites, congestive heart failure, atrial fibrillation, gout, hypertension, anxiety, and end-stage renal disease requiring hemodialysis. Concomitant medications included: digoxin, carvedilol, clonidine, pantoprazole, Epogen, cyproheptadine, promethazine, paracetamol, temazepam, metoprolol, allopurinol, and morphine.

On 22 Nov 2005, the patient was hospitalized with leg abscess/cellulitis of both legs for which he was enrolled into study. On 23 Nov 2005, an incision and drainage was performed and the patient was discharged the following day (24 Nov 2005). On 27 Nov 2005, he was re-admitted due to leg pain and ascites. The serious adverse events of worsening of end-stage renal disease and worsening of ascites were reported. However, the serum creatinine of 9.7 mg/dL on 28 Nov 2005 showed little change from the pre-treatment level of 9.6 mg/dL. On 30 Nov 2005, the patient underwent removal of double valve peritoneal subclavian venous shunt and was transferred to the ICU. The patient was started on amiodarone as an anti-arrhythmic and was dialyzed. Vancomycin serum levels were as follows: 19.9 mg/L on 25 Nov, 14.9 mg/L on 26 Nov, 10.6 mg/L on 28 Nov, and 8.7 mg/L on 30 Nov. Prior to the next schedule dose of vancomycin, the patient died on 01 Dec 2005.

The investigator assessed the fatal event of cardiac failure, and serious events of chronic renal failure and ascites as not related to study medication. The events were submitted as an expedited safety report due to the patient's death (MCN 200500111).

Patient ID: 202b-903-9037

SAE (MedDRA PT): Septic shock, Liver failure, Renal failure, Respiratory Failure

Drug Relationship: Not related

Outcome: Death

Patient 202b-903-9037 was a 41-year-old female with a wound infection of the left foot. The patient was randomized to standard therapy (vancomycin) and started study drug on 09 June 2004. Concomitant medications during the study included paracetamol, aztreonam, and metronidazole. On 08 June 2004, the patient was admitted to the hospital with an approximately 1-week history of progressively enlarging ulcer of the left foot following a minor trauma. After study enrollment the patient was found to be anemic (hemoglobin 7.4 g/dL) with abnormal liver function test results (bilirubin 78 µmol/L, alkaline phosphatase 344 U/L, AST 109 U/L, and GGT 396 U/L). The patient admitted chronic alcohol use. Subsequently, the patient was found to be septicemic, and study drug was augmented with aztreonam and metronidazole. The patient's liver function continued to deteriorate, as well as her renal function. Study drug was discontinued on 14 June 2004. Laboratory results on 15 June 2004 included bilirubin 152 µmol/L, alkaline phosphatase 285 U/L, ALT 169 U/L, AST 94 U/L, creatinine 200 µmol/L, and potassium 2.3 µmol/L. The patient developed respiratory distress and circulatory failure and died on 19 June 2004. The investigator assessed the events of multiorgan failure as not related to study drug.