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APPLICATION NUMBER:

022407Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

January 27, 2013

NDA: 22110/S004

Drug Product Name

Proprietary: VIBATIV™

Non-proprietary: Telavancin for Injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
October 3, 2012	October 3, 2012	November 19, 2012	November 19, 2012

Submission History (for amendments only) – N/A

Applicant/Sponsor

Name: Theravance Inc.

Address: 901 Gateway Blvd.,
San Francisco, CA 94080

Representative: Rebecca Coleman, Vice President, RAQ

Telephone: 650-808-6076

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: Recommend approval.

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Prior Approval Supplement
 2. **SUBMISSION PROVIDES FOR:** Comparability protocol for an alternate manufacturing site at Hospira, McPherson, Kansas.
 3. **MANUFACTURING SITE:** Hospira, McPherson, Kansas
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Sterile lyophilized powder for Injection.
 - Intravenous infusion.
 - 250 mg and 750 mg.
 5. **METHOD(S) OF STERILIZATION:** Sterile (b) (4)
(b) (4)
 6. **PHARMACOLOGICAL CATEGORY:** Antibiotic
- B. **SUPPORTING/RELATED DOCUMENTS:** None
- C. **REMARKS:** This electronic submission is a Prior Approval Supplement for a Comparability Protocol which provides for an alternate manufacturing site at Hospira, McPherson, Kansas. The drug product was previously manufactured at (b) (4). There are no changes in the overall manufacturing operation, product specifications and packaging. The Hospira, McPherson facility had a satisfactory FDA inspection for manufacture of injectable products using similar manufacturing processes (b) (4) in May 2012. On January 22, 2013, the Agency scheduled a meeting with the sponsor for clarification on the proposed CBE-0 submission and the contents of the interim report. Based on the discussion at the meeting it was agreed that the sponsor will amend the current Supplement for Comparability Protocol NDA 22-110/S004. The amendment was received on January 24, 2013. The amendment is described in Section P of this review.

filename: N022110S004R1

Executive Summary

I. Recommendations

- A. Recommendation on Approvability – Recommend approval**
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A**

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –** A comparability protocol is submitted to support the proposed (b) (4) operation at the alternate manufacturing site at Hospira, McPherson, Kansas. (b) (4) will be used for this product.
- B. Brief Description of Microbiology Deficiencies -** None
- C. Assessment of Risk Due to Microbiology Deficiencies –** N/A

III. Administrative

- A. Reviewer's Signature** _____
Vinayak B. Pawar, Ph.D., NDMS, OPS, CDER
- B. Endorsement Block** _____
Bryan S. Riley, Ph.D., NDMS, OPS, CDER
- C. CC Block**
N/A

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

/s/

VINAYAK B PAWAR
01/31/2013

BRYAN S RILEY
01/31/2013
I concur.

Division of Anti-Infective Products Clinical Microbiology Review

NDA: 22-407, Telavancin for injection

Date Company Submitted: 12 July 2012
Date received by CDER: 12 July 2012
Date Assigned: 12 July 2012
Date Completed: 13 December 2012
Reviewer: Kerry Snow MS

NAME AND ADDRESS OF APPLICANT:

Theravance, Inc.
901 Gateway Boulevard
South San Francisco, California USA

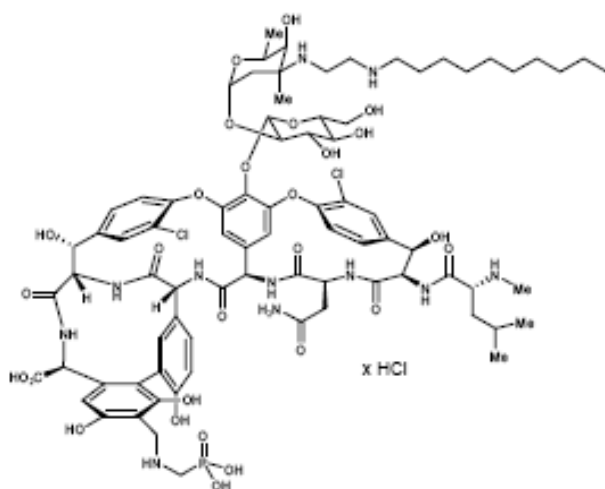
CONTACT PERSON:

Rebecca Coleman, Pharm.D.
Phone: 650-808-6076

DRUG PRODUCT NAMES:

Proprietary Name: Vibativ
Code Name: TD-6424
Established Name: Telavancin hydrochloride
Molecular Weight: 1755.6
Chemical Name: vancomycin, N3" [2 (decylamino) ethyl] 29 [[(phosphono-methyl) amino] methyl]
hydrochloride

STRUCTURAL FORMULA:



Telavancin hydrochloride

MOLECULAR FORMULA:

$C_{80}H_{106}Cl_2N_{11}O_{27}P \cdot xHCl$ (where $x = 1$ to 3)

MOLECULAR WEIGHT:
1755.6

DRUG CATEGORY:
Antibacterial

PROPOSED DOSAGE FORM AND STRENGTH:
Sterile, lyophilized powder for intravenous infusion in two dosage forms, 250 mg/vial and 750 mg/vial

ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT:

Proposed dosing is 10 mg/kg over a 60-minute period by intravenous infusion once every 24 hours for 7 to 14 days (in patients with normal renal clearance). For renally impaired patients, the following dosage adjustments are recommended by the Applicant:

Dosage Adjustment in Adult Patients with Renal Impairment

Creatinine Clearance* (mL/min)	Telavancin Dose and Dosage Interval
> 50	10 mg/kg every 24 hours
30-50	7.5 mg/kg every 24 hours
< 30 and hemodialysis	10 mg/kg every 48 hours

DISPENSED:
Rx

PROPOSED INDICATION:

Treatment of patients with nosocomial pneumonia, including ventilator-associated pneumonia (VAP), caused by susceptible isolates of the following gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and –resistant isolates) or *Streptococcus pneumoniae* (penicillin susceptible isolates)

RELATED DOCUMENTS:
IND 60,237
NDA 22-110

TYPE OF SUBMISSION:
New Drug Application

PURPOSE OF SUBMISSION:

This New Drug Application (NDA) is submitted to seek approval for the use of Telavancin (Vibativ) as an intravenous infusion (10mg/kg administered over 60 minutes) for the treatment of nosocomial pneumonia, including ventilator-associated pneumonia. This review addresses the development testing criteria and quality control parameters proposed by the applicant for the *in vitro* testing of telavancin. Supportive data, reviewed here, include *in vitro* drug characteristics (including mechanism of action, drug interaction, and development of resistance), pharmacokinetic/pharmacodynamic analysis, and correlation of *in vitro* activity with clinical outcomes.

REMARKS:

The Applicant has referenced NDA 22-110, which was submitted on 6 December 2006. That Application was submitted to seek approval for the use of telavancin (Vibativ) as an intravenous infusion (10 mg/kg administered over 60 minutes) for the treatment of complicated skin and skin structure infections (cSSSI), and addressed the development of testing criteria and quality control parameters for susceptibility testing of telavancin. The application for the use of telavancin for the treatment of cSSSI was approved by the Agency on 11 September 2009.

The current Application was originally filed on 23 January 2009. A Complete Response (CR) letter was issued on 23 November 2009. The Applicant responded to the CR letter on 21 December 2009, but was advised by the Agency that the response was incomplete (26 January 2010). On 30 June 2010, the Applicant resubmitted the Application, which was denied approval on 21 December 2010. The current submission includes a post-hoc analysis of mortality data.

This review is based largely on the original submission (23 January 2009). No additional clinical microbiology data or reports have been included in later submissions to this NDA.

SUMMARY AND RECOMMENDATIONS:

1) From the clinical microbiology perspective, this NDA submission may be approved, provided that the Applicant makes the changes in the microbiology subsection of the proposed label recommended by the Agency (included below; deletions to the proposed text are indicated by double strikethrough, additions are indicated by bold font).

2) From the clinical microbiology perspective, the data provided by the Applicant support the Applicant's proposed breakpoints for the susceptibility breakpoints for all pathogens included in the proposed indications.

3) The Agency proposes that *Streptococcus pneumoniae* be removed from the proposed indications for telavancin for the treatment of nosocomial pneumonia, including ventilator-associated pneumonia (VAP).

3) Recommended changes to package insert:

12.4 Microbiology

Telavancin is a semisynthetic, lipoglycopeptide antibiotic. Telavancin exerts concentration-dependent, bactericidal activity against gram-positive organisms *in vitro*, as demonstrated by time-kill assays and MBC/MIC ratios (minimum bactericidal concentration/minimum inhibitory concentration) using broth dilution methodology. *In vitro* studies demonstrated a telavancin post-antibiotic effect ranging from 1 to 6 hours against *S. aureus* and other gram-positive pathogens.

Although telavancin is approximately 90% protein bound, the presence of human serum or human serum albumin has minimal impact on the *in vitro* activity of telavancin against staphylococci, streptococci, and vancomycin-susceptible enterococci.

Mechanism of Action:

Telavancin inhibits cell wall biosynthesis by binding to late-stage peptidoglycan precursors, including lipid II. Telavancin also binds to the bacterial membrane and disrupts membrane barrier function.

Interactions with Other Antibiotics:

In vitro investigations demonstrated no antagonism between telavancin and amikacin, aztreonam, cefepime, ceftriaxone, ciprofloxacin, gentamicin, imipenem, meropenem, oxacillin, piperacillin/tazobactam, rifampin, and trimethoprim/sulfamethoxazole **when tested in various combinations against telavancin-susceptible staphylococci, streptococci, and enterococci. This information is not available for other bacteria.**

(b) (4)

Cross-Resistance:

Some vancomycin-resistant enterococci have reduced susceptibility to telavancin. There is no known cross-resistance between telavancin and other classes of antibiotics.

Antibacterial Activity

Telavancin has been shown to be active against most isolates of the following microorganisms both in vitro and in clinical infections as described in the Indications and Usage section [see *Indications and Usage*]:

Facultative Gram-Positive Microorganisms

Staphylococcus aureus (including methicillin-resistant isolates)

(b) (4)

Enterococcus faecalis (vancomycin-susceptible isolates only)

Streptococcus agalactiae

Streptococcus anginosus group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*)

(b) (4)

Greater than 90% of the following microorganisms exhibit an in vitro MIC less than or equal to the telavancin-susceptible breakpoint for organisms of similar genus shown in Table (b) (4). The safety and effectiveness of telavancin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Facultative Gram-Positive Microorganisms

Enterococcus faecium (vancomycin-susceptible isolates only)

Staphylococcus haemolyticus

Streptococcus dysgalactiae subsp. *equisimilis*

(b) (4)

Staphylococcus epidermidis

Susceptibility Test Methods:

When available, the clinical microbiology laboratory should provide cumulative results of the *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting (b) (4)

Dilution technique

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure [see *References (15)*]. Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of telavancin powder. The MIC values should be interpreted according to the criteria provided in Table (b) (4).

Diffusion technique

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations [see *References (15)*]. This procedure uses paper disks impregnated with 30 mcg of telavancin to test the susceptibility of microorganisms to telavancin. The disk diffusion interpretive criteria are provided in Table (b) (4).

Table (b) (4) Susceptibility Interpretive Criteria for Telavancin

	Susceptibility Interpretive Criteria ^a					
	Minimal Inhibitory Concentration (µg/mL)			Disk Diffusion Zone Diameter (mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i> (including methicillin-resistant isolates)	≤ 1	--	--	≥ 15	--	--
(b) (4) <i>Streptococcus pyogenes</i> <i>Streptococcus agalactiae</i> <i>Streptococcus anginosus</i> group	≤ 0.12	--	--	≥ 15	--	--
<i>Enterococcus faecalis</i> (vancomycin-susceptible isolates only)	≤ 1	--	--	≥ 15	--	--

a. The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding results other than susceptible should be subjected to additional testing.

A report of "Susceptible" indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to monitor the performance of the supplies and reagents used in the assay and the techniques of the individuals performing the test. Standard telavancin powder should provide the range of values noted in Table (b) (4).

Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains used for microbiological quality control are not clinically significant.

Table (b)
(4) Acceptable Quality Control Ranges for Telavancin to be Used in Validation of Susceptibility Test Results

	Acceptable Quality Control Ranges	
	Minimal Inhibitory Concentration (µg/mL)	Disk Diffusion Zone Diameter (mm)
<i>Enterococcus faecalis</i> ATCC 29212	0.12-0.5	Not applicable
<i>Staphylococcus aureus</i> ATCC 29213	0.12-1	Not applicable
<i>Staphylococcus aureus</i> ATCC 25923	Not applicable	16-20
<i>Streptococcus pneumoniae</i> ATCC 49619 ^a	0.004-0.03	17-24
^a This organism may be used for validation of susceptibility test results when testing <i>Streptococcus</i> spp. other than <i>S. pneumoniae</i> .		

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EXECUTIVE SUMMARY

I. IN VITRO INFORMATION

MECHANISM OF ACTION

Investigations of telavancin generally support the claim for two distinct mechanisms of action, and for enhanced activity, compared to vancomycin and other comparators. Studies by the Applicant demonstrate substrate-dependent inhibition of PG biosynthesis, both with regard to formation of immature PG and to cross-linking of mature PG strands. Inhibition of PG biosynthesis appears to be enhanced, compared to vancomycin; an effect that may be attributable to a higher affinity of telavancin for cell membrane components. In investigations that linked mechanisms of action to antibacterial activity, MICs for telavancin-treated bacteria were lower than glycopeptide comparators (vancomycin and/or teicoplanin). In the current submission, the Applicant has provided data that supports the contention that the second mechanism of action, depolarization of the microbial cell membrane, occurs at attainable drug levels, in the absence of cell lysis, and is dependent on association of telavancin with Lipid II.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

Data submitted from large prospective surveillance studies and other investigations of in vitro activity, including investigations conducted in support of NDA 22110, support the applicant's claim of activity against the pathogens generally associated with hospital acquired pneumonia, (b) (4). MIC values for all tested strains of *S. aureus* and *S. pneumoniae* (including isolates resistant to other classes of antimicrobials, and stains with specific virulence profiles) were below attainable drug levels.

RESISTANCE STUDIES

The Applicant has provided, as reference to NDA 22110 and in information from investigations undertaken since that submission, sufficient data to demonstrate a low potential for development of resistance to bacterial species considered in the proposed indications. Data presented in this Application suggest that telavancin is an inducer of the VanA operon, but does not induce activity of the VanB operon. Population analysis profiles have not detected heteroresistance to telavancin in isolates of *S. aureus*. No resistance to telavancin was noted in isolates collected in clinical trials.

ANTIMICROBIAL INTERACTION STUDIES

In data presented in this Application as well as in NDA 22110, the Applicant has demonstrated modest synergy of telavancin with β -lactams, rifampin, ciprofloxacin, and gentamicin, against isolates of *S. aureus*, including methicillin-resistant and vancomycin-non-susceptible phenotypes. Telavancin activity is additive with other studied drug combinations. No antagonism has been demonstrated with telavancin and any tested antimicrobial.

EFFECTS OF MISCELLANEOUS FACTORS ON ACTIVITY

Telavancin is approximately 90% protein bound, primarily by albumin. Studies presented in this Application and in NDA 22110 indicate that telavancin retains in vitro activity against the principle respiratory pathogens sought in the proposed indication, in the presence of albumin or human serum. Recent studies also suggest that telavancin activity is not inhibited by pulmonary surfactant. Telavancin is active against isolates of *S. aureus* in stationary growth phase, and has

demonstrated activity against isolates of *S. aureus*, *S. epidermidis*, and *E. faecalis* in a biofilm model. The postantibiotic effect of telavancin, against isolates of *S. aureus* (including methicillin-susceptible and –resistant isolates, as well as vancomycin-non-susceptible isolates) ranges from one to six hours. The observed MIC values of the three primary telavancin metabolites (AMI-11352, AMI-11353, and AMI-11355) are ≥ 8 -fold higher than that of telavancin.

BACTERICIDAL ACTIVITY

The Applicant has submitted data, in NDA 22110 and this Application, from time-kill kinetic studies to support a claim of bactericidal activity of telavancin against a variety of strains of *S. aureus*, including methicillin-susceptible and –resistant phenotypes, as well as isolates non-susceptible to vancomycin, and against isolates of *S. pneumoniae*. This activity generally occurs at low multiples of the MIC and at concentrations consistent with therapeutic levels, even at trough concentrations. Telavancin demonstrated modest bactericidal activity against strains of enterococcus, with killing occurring only at high drug concentrations. Telavancin bactericidal activity against enterococci was superior to comparators, though, in most cases.

II. HUMAN AND ANIMAL STUDIES

ANIMAL DISEASE MODELS

The applicant has submitted data from animal *in vitro* studies that supports the use of $AUC_{(0-24)}/MIC$ as the best PK/PD predictor of antimicrobial efficacy for unbound (free) telavancin. Data from neutropenic mouse thigh models suggest that an $AUC_{(0-24)}/MIC$ ratio of 219 results in a one log₁₀ reduction in CFU/g against methicillin-resistant *S. aureus* with an MIC of 1 mcg/ml. Animal models of infection suggest that immune status may play a minor role in telavancin efficacy.

PHARMACOKINETIC / PHARMACODYNAMIC STUDIES

In NDA 22110, the applicant provided data from a variety of studies to support the proposed pharmacokinetic parameters. Monte Carlo simulation, based on the proposed dosage (10 mg/kg) supports a susceptible breakpoint as high as 2 µg/ml (based on > 99% target attainment at that concentration). Additional information, provided in this Application, suggests that telavancin is concentrated in human alveolar macrophages (exceeding 10 mcg/ml) and that the AUC of the antimicrobial in epithelial lining fluid (in uninfected lung tissue) is approximately 75% that of AUC_{plasma} .

III. CLINICAL TRIALS

Data from the two Phase 3 clinical trials indicate that telavancin is effective against the pathogens in the proposed indications. Specimen types, subject demographics, and bacterial isolates were similar between the telavancin and vancomycin arms of the trials. The majority of principle pathogens were recovered from non-invasive specimens (sputum and endotracheal aspiration), and a majority of specimens yielded a single gram-positive pathogen. Methicillin-resistant *S. aureus* was the predominant pathogen isolated. Using breakpoints proposed in this Application, no telavancin-nonsusceptible isolates were recovered in the clinical trials. No subjects with vancomycin-non-susceptible isolates were treated in the clinical trials. No development of telavancin resistance was observed during the trials.

IV. SUSCEPTIBILITY TEST METHODS

Telavancin MIC distributions from clinical trials and survey studies are unimodal for *S. aureus* (both methicillin-susceptible and methicillin-resistant strains), *E. faecalis*, and *S. pneumoniae*.

Distributions derived from clinical studies, for these pathogens, are similar to those derived from survey studies, although the percentage of clinical isolates with higher telavancin MIC values appears to trend higher, for isolates of *S. aureus* and *E. faecalis*, compared to survey isolates, particularly at higher MIC values. Since this may imply developing resistance among these pathogens, continued surveillance is warranted.

Correlation studies comparing the disk diffusion method of susceptibility testing with the minimum inhibitory concentration method support the zone size recommendations of the Applicant.

Data from reference laboratory reports, reviewed in NDA 22110, suggest that susceptibility testing of telavancin, using solid media techniques, may result in values that are difficult to reproduce or vary from acceptable quality control ranges. This may be due to the size of the telavancin molecule and its diffusion properties. Susceptibility testing by the agar diffusion method is not recommended. Data presented in this Application suggests that modest alterations in the pH of test media and inoculum size may result in unreliable telavancin susceptibility results for *S. pneumoniae*.

Data from quality control studies do not support vancomycin as a class-representative surrogate for telavancin susceptibility testing.

INTRODUCTION

LIPOGLYCOPEPTIDE CLASS OF ANTIBIOTICS

The glycopeptides of the vancomycin class and teicoplanin class are naturally occurring products, derived from various species of soil actinomycetes (Kahne 2005). Glycopeptides are known to inhibit synthesis of the bacterial cell wall, by binding to the D-alanyl-D-alanine terminus of lipid II, the GlcNAc-MurNAc disaccharide (linked to an undecaprenyl pyrophosphate carrier) that is the peptidoglycan precursor for most bacterial species of clinical interest. The stable complex that is formed by the glycopeptide and the lipid II molecule results in steric hindrance of the glycosylase and transpeptidase enzymes that are necessary for cell wall synthesis (Perkins 1974). The glycopeptides are generally bactericidal.

Lipoglycopeptides include naturally occurring antibiotics (e.g. teicoplanin) and semi-synthetic derivatives (e.g. dalbavancin and oritavancin). Lipoglycopeptides share the basic mechanism of action of the glycopeptide class, described above.

The glycopeptides and lipoglycopeptides are large, complex molecules. Because of their considerable molecular mass (the molecular weight of vancomycin is 1485.73 and the molecular weight of telavancin is 1755.6), members of the class are unable to cross the outer membrane of gram-negative bacteria, limiting their activity to gram-positive pathogens. Both Vancomycin (the only glycopeptide approved for use in the United States) and Daptomycin (the only approved lipoglycopeptide) have broad-spectrum activity against gram-positive microorganisms, including most staphylococcal species, most streptococci (including all strains of *S. pyogenes*, *S. agalactiae*, and *S. pneumoniae*), *Bacillus* species (including *B. anthracis*), most *Corynebacterium* species (including *C. jeikeium*), and many anaerobic gram-positive pathogens (including *Clostridium difficile*) (Mandell 2005). The activity of vancomycin against some strains of enterococci has decreased in recent years, possibly as a result of more widespread use of the antimicrobial against methicillin-resistant *S. aureus* (MRSA). The gene cluster responsible for this increased resistance has been identified in rare instances of staphylococcal infection (VRSA). Reduced activity of vancomycin against *S. aureus* (GISA, hGISA) has been noted more frequently than VRSA, and may result from a mechanism other than that mediated by the Vana gene cluster. Daptomycin appears to retain activity against vancomycin-resistant strains of enterococci (VRE) and staphylococci (both GISA and VRSA), and exhibits rapid, bactericidal activity against these pathogens (Akins 2001).

The glycopeptides have poor bioavailability and are difficult to administer intramuscularly. They are approved for intravenous administration. The most predictive pharmacodynamic parameter for both vancomycin and daptomycin is the AUC/MIC ratio. Daptomycin exhibits a prolonged postantibiotic effect (PAE), where the PAE of vancomycin against staphylococcal and enterococcal species is relatively short.

The resurgence of interest in the glycopeptides, since the beginning of the 1980s, corresponds to the concurrent increases in nosocomial infections caused by gram-positive pathogens, the emergence and spread of resistant strains, and improvements in the purification and dosing of vancomycin (Bryskier 2005). Rising rates of vancomycin treatment failures (Moise 2000), the increasing spread of resistance in enterococci and staphylococci, and the emergence of heterogeneous vancomycin-intermediate *S. aureus* (hVISA) continue to spur research for improved glycopeptide antimicrobials.

Telavancin (formerly TD-6424; proprietary name, Vibativ) is a semisynthetic derivative of vancomycin, substituted on the vancosamine sugar by a decylamino-ethyl hydrophobic side chain, and on the resorcinol moiety of the cyclic peptidic core by a phosphonomethyl aminomethyl side chain. The lipid side chain is credited with the increased activity of telavancin

against MRSA and VanA enterococci, compared to vancomycin, while the polar side chain improves tissue distribution (Kanafani 2006). Telavancin hydrochloride is available as a sterile lyophilized powder for injection.

HOSPITAL ACQUIRED PNEUMONIA

Hospital acquired pneumonia (HAP) is defined as pneumonia that occurs 48 hours or more after admission [Niederman 2005]. HAP may be differentiated by hospital location of onset (ICU vs. ward) and time of occurrence (early onset vs. late onset). Infections with multi-drug resistant (MDR) pathogens are more commonly associated with late-onset HAP and VAP (ventilator-associated pneumonia). HAP is an important cause of morbidity and mortality and accounts for approximately 25% of ICU infections [Richards 1999]. Mortality attributable to HAP is estimated to be between 33 and 50%.

Bacterial pathogens commonly associated with HAP include *Staphylococcus aureus* (particularly methicillin-resistant isolates), *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, and *Acinetobacter* species. The rates of polymicrobial infections and of infections by multi-drug resistant isolates are increasing [Fridkin 2001]. Over 50% of *S. aureus* infections in ICU environments are methicillin-resistant. *S. aureus* clinical isolates that are non-susceptible to vancomycin are currently rare, and most are susceptible to linezolid. Aspiration of oropharyngeal bacteria is the primary endogenous route of pathogen movement to the lower respiratory tract. Exogenous sources of infection include transmission from health care workers, nebulizers, biofilms, and ventilatory circuits.

Diagnosis of HAP should include collection and culture of lower respiratory secretions prior to antibiotic treatment. Acceptable samples include expectorated sputum, endotracheal aspirates, bronchoalveolar lavage samples, and bronchoalveolar brushes. Gram stains should be performed, and reports should include quantitation of epithelial cells and polymorphonuclear leukocytes. Bacteria present in the Gram stain preparation should be reported semi-quantitatively, with Gram stain morphology described. Culture media should include sheep blood agar, an enriched media for the recovery of fastidious bacteria and *Haemophilus* species (e.g. chocolate agar), and a medium designed to select Gram negative pathogens (e.g. MacConkey agar). Additional media and staining techniques should be included if specific etiologic agents are suspected (e.g. mycobacteria, *Legionella* sp., etc.).

Current recommendations for empiric therapy of HAP are grouped according to disease severity and risk factors for MDR pathogens. Patients with late onset HAP and with identified risk factors for MRSA should be treated with vancomycin or linezolid, according to guidelines published by the American Thoracic Society and the Infectious Diseases Society of America. Recent studies have demonstrated a high number of vancomycin treatment failures, possibly related to under-dosing [Moise 2000]. In a recent retrospective analysis [Wunderink 2003], patients with HAP due to MRSA had significantly better clinical cure and survival rates when treated with early-therapy linezolid, compared to those treated with vancomycin.

IN VITRO INFORMATION

MECHANISM OF ACTION

Glycopeptides inhibit biosynthesis of peptidoglycan (PG) by binding to the terminal D-alanyl-D-alanine dipeptide of the lipid II molecule. This binding results in steric hindrance of transglycosylases (which catalyze the transfer of Lipid II to growing PG strands) and transpeptidases (which catalyze peptide cross-linking) (Van Bambeke 2004). The blockage of PG biosynthesis results in inhibition of growth and eventual cell death (Bryskier 2005).

Because of their large size, glycopeptides are not able to cross the outer membrane of gram-negative bacteria, so their antimicrobial activity is limited to gram-positive organisms.

In addition to the mechanism described above, telavancin exhibits a second mechanism of action, which appears to involve disruption of the bacterial plasma membrane (described below).

Data from investigations of telavancin submitted in NDA 22110 generally support the claim for two distinct mechanisms of action, and for enhanced activity, compared to vancomycin and other comparators. Those studies demonstrated substrate-dependent inhibition of PG biosynthesis, both with regard to formation of immature PG and to cross-linking of mature PG strands. Inhibition of PG biosynthesis appeared to be enhanced, compared to vancomycin, an effect that may be attributable to a higher affinity of telavancin for cell membrane components. Investigations that linked mechanisms of action to antibacterial activity demonstrated MICs for telavancin-treated bacteria that were lower than glycopeptide comparators (vancomycin and/or teicoplanin). While the second proposed mechanism of action, disruption of the microbial cell membrane, appeared to play a role in the bactericidal activity of telavancin, it was unclear from the submitted studies that this mechanism was significant at obtainable free concentrations of the drug. Although increases in membrane permeability and disruption of membrane potential were observed at concentrations as low as 2 µg/ml (4X MIC), significant membrane alterations were not seen until telavancin concentrations approached 64X – 128X MIC (32 – 64 µg/ml).

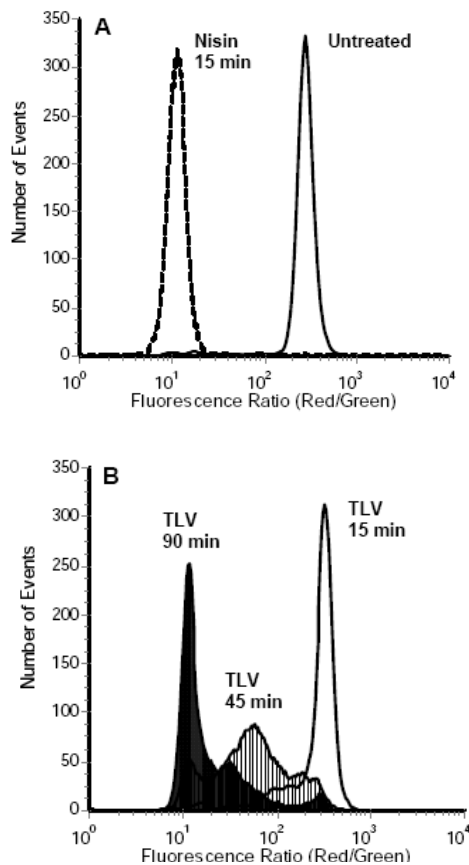
The Applicant has submitted information from a recent study, intended to further describe the mechanism of action of telavancin, specifically with regard to the molecule's effect on the bacterial cell membrane.

Investigators [Lunde 2009] measured bacterial membrane potential changes resulting from exposure to telavancin (and comparators). A flow cytometry assay, using diethyloxacarbocyanine dye, DiOC₂(3), as a fluorescent indicator, was employed to measure depolarization with greater accuracy than that reported in previous, similar, experiments. Observed bacterial isolates included a variety of *Staphylococcus aureus* phenotypes, including isolates susceptible to glycopeptides (ATCC 29213), methicillin-resistant isolates (MRSA, ATCC 33591), heterogeneous vancomycin-intermediate isolates (hVISA Mu3, ATCC 700698), vancomycin-intermediate isolates (VISA Mu50, ATCC 700699), and isolates nonsusceptible to daptomycin (MED2034, obtained from Theravance).

The investigators controlled for the possible effect on membrane potential caused by weakening of the cell wall by limiting the depolarization assay to 90 minutes, a time determined by experimental evidence involving timed inhibition of cell wall biosynthesis by penicillin G. Membrane potential was tested under conditions normally employed for antibiotic susceptibility testing (using cation-adjusted Mueller Hinton broth, physiologic temperature, and cell concentrations of 10⁶ CFU/ml).

Depolarization of the bacterial membrane by nisin (A), a pore-forming lantibiotic, and telavancin (B) are shown in Figure 1. Cells were exposed to 8 mcg/ml of telavancin. Depolarization was time-dependent, with broad depolarization observed at 90 minutes.

Figure 1: Dissipation of *S. aureus* Membrane Potential Measured by Flow Cytometry with DiOC₂(3)



Cell populations exhibiting depolarization appear towards the left on the x-axis. (A) Fully polarized (untreated) and depolarized (nisin, 8 µg/mL) *S. aureus* (ATCC 29213). (B) *S. aureus* incubated for 15, 45, and 90 min in the presence of 8 µg/mL telavancin.

Source: This submission, Section 5.3.5.4.1.2.2.1

The investigators compared concentration-dependent depolarization of telavancin, nisin, and vancomycin. Using nonlinear regression to derive IC₅₀ values from concentration response curves, the investigators demonstrated similar membrane depolarization activity of nisin and telavancin (IC₅₀ values of 2.9 mcg/ml and 3.6 mcg/ml, respectively). No IC₅₀ value could be determined for vancomycin (up to 96 mcg/ml). Against *S. aureus* isolates non-susceptible to other glycopeptides (vancomycin and daptomycin), telavancin demonstrated membrane depolarization activity comparable to that observed in glycopeptide-susceptible isolates (Table 1).

Table 1: Telavancin depolarization activity against phenotypically diverse *S. aureus*

Strain	Relevant phenotype	Depolarization (%) ^a
ATCC 33591	MRSA	77 ± 7
ATCC 700699	VISA (Mu50)	61 ± 3
ATCC 700698	hVISA (Mu3)	78 ± 4
MED2034	Daptomycin non-susceptible	77 ± 5

^a Percent depolarization is reported for treatment with 32 mcg/ml telavancin, and represents the mean ± standard deviation from three independent experiments

Source: Lunde 2009

In order to establish a role for Lipid-II binding in the observed depolarization of the bacterial membrane, the investigators conducted depolarization assays in the presence of a Lipid II competitor, N,N'-diacetyl-L-Lys-D-Ala-D-Ala (dKAA). In this experiment, concentration-dependent antagonism of the depolarization effect was observed, suggesting that Lipid II is required for telavancin-induced depolarization of the bacterial membrane. The dependence on Lipid-II for telavancin-induced membrane depolarization was also investigated using assays that measured depolarization in cells with altered levels of Lipid II. In this investigation (Table 2), decreased depolarization was noted in cells where Lipid II levels were decreased by treatment with fosfomycin, D-cycloserine, or bacitracin.

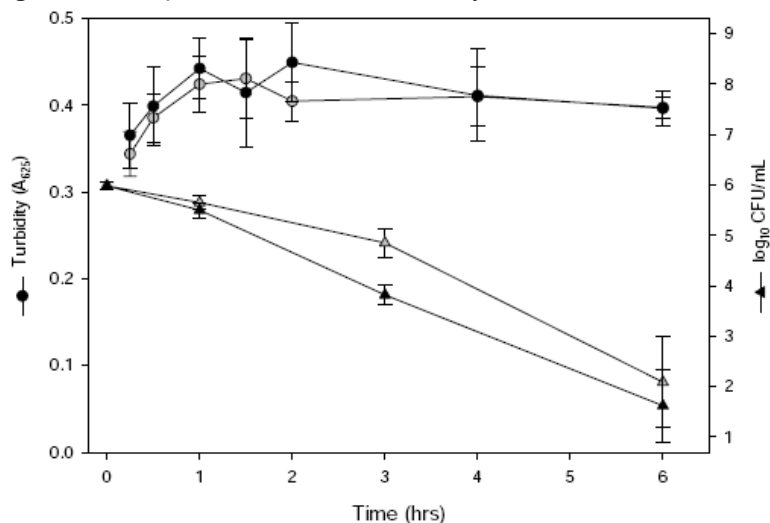
Table 2: Effect of Lipid II Synthesis on Depolarization of *S. aureus* by Telavancin

Antibiotic	Depolarization (%) ^a	
	Telavancin	Nisin
None	100	100
Fosfomycin	29	26
D-Cycloserine	38	36
Bacitracin	27	2

^a*S. aureus* (ATCC 29213) cells were pretreated 10 min prior to the addition of telavancin or nisin, and depolarization was calculated relative to control sample without pretreatment.
Source: This submission, Section 5.3.5.4.1.2.2.2

The same investigators examined the relationship of telavancin-induced membrane depolarization to cell lysis. Cell lysis was determined spectroscopically. Measured at 625 nm, cells exposed to concentrations of telavancin (and vancomycin) or 8 and 32 mcg/ml for 6 hours showed no significant change in optical density. The results are summarized in Figure 3 (vancomycin data not shown).

Figure 3: Comparison of Culture Turbidity to Viable Counts in *S. aureus* Exposed to Telavancin



Curves represent turbidity (circles) and viable counts (triangles) for cultures exposed to 8 µg/mL (grey) and 32 µg/mL (black) telavancin.
Source: This submission, Section 5.3.5.4.1.2.2.3

In Summary:

Investigations of telavancin generally support the claim for two distinct mechanisms of action, and for enhanced activity, compared to vancomycin and other comparators. Studies by the Applicant

demonstrate substrate-dependent inhibition of PG biosynthesis, both with regard to formation of immature PG and to cross-linking of mature PG strands. Inhibition of PG biosynthesis appears to be enhanced, compared to vancomycin; an effect that may be attributable to a higher affinity of telavancin for cell membrane components. In investigations that linked mechanisms of action to antibacterial activity, MICs for telavancin-treated bacteria were lower than glycopeptide comparators (vancomycin and/or teicoplanin). In the current submission, the Applicant has provided data that supports the contention that the second mechanism of action, depolarization of the microbial cell membrane, occurs at attainable drug levels, in the absence of cell lysis, and is dependent on association of telavancin with Lipid II.

Mechanism of Action Studies ~ Conclusions:

The applicant has provided data to support the principle mechanism of telavancin, involving interruption of late-stage glycopeptide synthesis, with concomitant cell wall disruption followed by cell death. The applicant has also provided acceptable data regarding the proposed second mechanism of action, involving disruption of the cell membrane in gram-positive bacteria of interest, including bacteria that are non-susceptible to vancomycin. Investigations support the contention that these mechanisms occur at attainable drug concentrations, in vivo.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

The following surveillance studies were conducted prior to release of telavancin to the market.

In NDA 22-110, the Applicant submitted data from two large prospective studies and seventeen other investigations of *in vitro* activity conducted to support the applicant's claim of activity against the pathogens generally associated with complicated skin and skin structure infections, including all organisms listed in that indication. MIC values for all tested isolates of *S. aureus* (including isolates resistant to other classes of antimicrobials, and isolates with specific virulence profiles), *S. pyogenes*, *S. agalactiae*, *S. anginosus*, *S. intermedius*, *S. constellatus*, and vancomycin-susceptible *E. faecalis* were all below the attainable drug levels, based on pharmacokinetic/pharmacodynamic analyses and Monte Carlo modeling, also submitted in that Application. Telavancin activity against vancomycin-intermediate *S. aureus* (VISA), heteroresistant vancomycin-intermediate *S. aureus*, and vancomycin-resistant *S. aureus* (VRSA), in those studies, was superior to vancomycin.

The current Application includes data from five new surveillance studies. The new studies are listed in Table 3. The largest study conducted in support of this NDA was an international prospective study conducted in 2007 (10,700 isolates). Other investigations included a study of 1500 methicillin-resistant *Staphylococcus aureus* (MRSA) isolates collected in Japan in 2006 [Hatano 2006], a study of 1005 streptococcal isolates (*Streptococcus pneumoniae*, β -hemolytic streptococci, and viridans group streptococci) from international surveillance studies, collected mainly between 2004-2007 [JMI Laboratories 2007], and two prospective bacteremia studies conducted in the UK and Ireland in 2005-2006 (2639 isolates) [Theravance Study Reports 08-6424-MCB-01 and 08-6424-MCB-02].

Table 3: Summary of Five Recent Studies of In Vitro Activity of Telavancin Against gram-positive Clinical Isolates

Study No.	Study Name	Reference	Sources of Isolates	No. of Isolates	No. of Centers	Methods	Gram-positive Total	<i>S. aureus</i>	CoNS and other staphylococci ^a	<i>S. pneumoniae</i>	<i>S. pyogenes</i>	Other β -hemolytic staphylococci	Bovis group streptococci	Viridans group streptococci	Enterococci	Miscellaneous Aerobes	Anaerobes
21	BSAC 2005	(74)	Blood	2705	25 ^b	Agar dilution	1330	244	205	230	88	140	21	159	243	0	0
22	BSAC 2006	(75)	Blood	2644	25 ^b	Agar dilution	1309	242	203	231	85	144	21	145	238	0	0
23	JMI Streptococcus Study 2007	(41)	Blood Skin Unknown	1005	94	Broth microdilution (frozen)	1005	0	0	205	0	300	0	500	0	0	0
24	Japanese Surveillance 2006	(36)	Respiratory Unknown	1500	1	Broth microdilution (frozen)	1500	1500	0	0	0	0	0	0	0	0	0
25	International Surveillance 2007	(40)	Blood Skin Respiratory Unknown	10700	105	Broth microdilution (dry-from)	10700	5895	1030	984	242	337	18	197	1949	41	7
Grand Total				16554	225		15844	7881	1438	1650	415	921	60	1001	2430	41	7

^a Includes non-spectated staphylococci.

^b The same centers were used for the BSAC 2005 and 2006 studies (74, 75).

Source: This submission, Section 5.3.5.4.1.4.2.2, Table 1

The large, 2007 international surveillance study (Protocol #07-AST-01) was performed by JMI Laboratories (North Liberty, IA), as part of the SENTRY Antimicrobial Surveillance Program. The majority (44.7%) of isolates analyzed in the study was collected in the US (geographic distribution of isolates is summarized in Table 4). All isolates were from clinical sources, with 10% from hospitalized patients with pneumonia (including hospital-acquired pneumonia).

Table 4: Geographic Sources of Isolates, 2007 International Surveillance Study

Geographic Region	Number of Sites	Number of Isolates	Percent of Total
United States	38	4782	44.7%
Canada	1	52	0.5%
Europe ^a	25	2673	25.0%
Latin America ^b	10	796	7.4%
Asia/South Pacific	31	2397	22.4%

^a: Includes Israel

^b: Includes Mexico and South America

Source: International Surveillance Study Report (40)

Of the 10,700 isolates analyzed, 55.1% (5,895) were *Staphylococcus aureus*, 9.6% (1,030) were coagulase-negative staphylococci, 18.2% (1,949) were *Enterococcus* species, 5.4% (579) were β -hemolytic streptococci, 1.8% (197) were viridans group streptococci, 9.2% (984) were *Streptococcus pneumoniae*, and 0.6% (66) were identified as "other gram-positive species."

All isolate identification was confirmed by JMI laboratories, using the Vitek Identification System (bioMerieux, Hazelwood, MO). Susceptibility testing was performed by microbroth dilution techniques approved by CLSI, using frozen panels supplied by (b) (4). Cation-adjusted Mueller-Hinton broth was supplemented with 2-5% lysed horse blood for testing of *S. pneumoniae* and other fastidious streptococci. Interpretive criteria for comparator agents were those of CLSI M100-S18; 2008. Quality control was performed on each day of testing, using methods and quality control strains approved by CLSI. All but one quality control result were within acceptable ranges (the one discrepant result was re-tested and found acceptable). Quality control results are summarized in Table 5.

Table 5: Telavancin Quality Control Results, JMI Surveillance Study, 2007

Organism	Broth MIC (ug/ml)	Frequency	Acceptable CLSI Range
<i>E. faecalis</i> ATCC 29212	0.06 0.12 0.25	1 73 3	0.12 - 0.5
<i>S. aureus</i> ATCC 29213	0.12 0.25	61 21	0.12 - 1
<i>S. pneumoniae</i> ATCC 49619	≤0.015 0.03	43 21	0.004 - 0.03

Source: Study 07-AST-01

The results of the study are summarized in Table 6.

The telavancin MIC₉₀ value for *Staphylococcus aureus* isolates, including methicillin-resistant and –susceptible isolates) was 4-fold lower than those seen for vancomycin (0.25 mcg/ml for telavancin and 1.0 mcg/ml for vancomycin) and 8-fold lower than that seen for linezolid (2.0 mcg/ml). Telavancin MIC₉₀ values against all staphylococcal species were generally lower than all comparators, including vancomycin, teicoplanin, clindamycin, daptomycin, linezolid, and quinupristin/dalfopristin. Activity of telavancin against *S. aureus* isolates exclusively recovered from respiratory tract infections (predominantly hospital acquired pneumonia) was similar to that observed against all *S. aureus* isolates tested (all sources). Oxacillin resistance had no effect on telavancin potency in either *S. aureus* isolates or coagulase negative staphylococcal species. All staphylococcal isolates tested were inhibited by telavancin at ≤ 0.05 mcg/ml.

Against *Streptococcus pneumoniae* (including isolates non-susceptible to penicillin), the MIC₉₀ for telavancin was 0.03 mcg/ml (the vancomycin MIC₉₀ was ≤ 1 mcg/ml, the linezolid MIC₉₀ was 1 mcg/ml). Penicillin non-susceptibility had no effect on telavancin potency against isolates of *S. pneumoniae*. The MIC₉₀ value for *S. pneumoniae* isolates collected exclusively from respiratory sources was identical to that of the entire *S. pneumoniae* collection. All isolates of *S. pneumoniae* were inhibited by telavancin at ≤ 0.06 mcg/ml.

All vancomycin-susceptible enterococci, tested in this study, were inhibited by telavancin at ≤1 mcg/ml. Among vancomycin-resistant enterococcal isolates, 26.8% had a telavancin MIC of ≤1 mcg/ml and 76.6% had a telavancin MIC of ≤2 mcg/ml.

All viridans group streptococci and β-hemolytic streptococci (including *S. pyogenes*, *S. agalactiae*, and *Streptococcus* groups C and G) were inhibited by telavancin concentrations of ≤0.25 mcg/ml.

Table 6: MIC Statistics of Telavancin and Selected Comparators vs. Gram-Positive Organisms from the 2007 International Surveillance Study

Organism (no. tested)	Agent	MIC (µg/mL)			%
		Range	50%	90%	Susceptible ^a
<i>S. aureus</i>					
All <i>S. aureus</i> (5895)	Telavancin	0.03-0.5	0.12	0.25	- ^b
	Vancomycin	≤ 0.12-4	1	1	> 99
	Teicoplanin ^c	≤ 2 - 8	≤ 2	≤ 2	100
	Clindamycin ^c	≤ 0.25 - > 2	≤ 0.25	>2	78
	Daptomycin	≤ 0.06 - 2	0.25	0.5	> 99
	Linezolid	0.25 - > 8	1	2	> 99
	Quinu/Dalfo ^d	≤ 0.25 - > 2	≤ 0.25	0.5	> 99
MRSA ^e (2658)	Telavancin	0.03 - 0.5	0.12	0.25	-
	Vancomycin	0.25 - 4	1	1	> 99
	Teicoplanin	≤ 2 - 8	≤ 2	≤ 2	100
	Clindamycin	≤ 0.25 - >2	≤ 0.25	> 2	56
	Daptomycin	≤ 0.06 - 2	0.25	0.5	> 99
	Linezolid	0.25 - > 8	1	2	> 99
	Quinu/Dalfo	≤ 0.25 - >2	0.5	0.5	> 99
MSSA ^f (3237)	Telavancin	0.03 - 0.5	0.12	0.25	-
	Vancomycin	≤ 0.15 - 2	1	1	100
	Teicoplanin	≤ 2 - 4	≤ 2	≤ 2	100
	Clindamycin	≤ 0.25 - >2	≤ 0.25	≤ 0.25	95
	Daptomycin	≤ 0.06 - 1	0.25	0.5	100
	Linezolid	0.25 - 2	1	2	100
	Quinu/Dalfo	≤ 0.25 - 2	≤ 0.25	0.5	> 99
Coagulase-negative staphylococci (CoNS)					
All CoNS (1030)	Telavancin	≤ 0.015 - 0.5	0.12	0.25	-
	Vancomycin	≤ 0.12 - 8	1	2	> 99
	Teicoplanin	≤ 2 - > 16	≤ 2	4	99
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	65
	Oxacillin	≤ 0.25 - > 2	> 2	> 2	22
	Daptomycin	≤ 0.06 - 4	0.25	0.5	> 99
	Linezolid	≤ 0.06 - 8	0.5	1	99
	Quinu/Dalfo	≤ 0.25 - > 2	≤ 0.25	0.5	99

Source: This submission, Section 5.3.5.4.1.4.3.1, Table 7

Table 6: MIC Statistics of Telavancin and Selected Comparators vs. Gram-Positive Organisms from the 2007 International Surveillance Study (cont'd)

Organism (no. tested)	Agent	MIC (µg/mL)			% Susceptible ^a
		Range	50%	90%	
<i>S. epidermidis</i> (326)	Telavancin	0.03 - 0.25	0.12	0.12	-
	Vancomycin	≤ 0.12 - 4	2	2	100
	Teicoplanin	≤ 2 - 8	≤ 2	4	100
	Oxacillin	≤ 0.25 - > 2	> 2	> 2	15
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	61
	Daptomycin	≤ 0.06 - 1	0.25	0.5	100
	Linezolid	≤ 0.06 - > 8	0.5	1	99
	Quinu/Dalfo	≤ 0.25 - > 2	≤ 0.25	≤ 0.25	98
<i>S. haemolyticus</i> (58)	Telavancin	0.03 - 0.5	0.12	0.25	-
	Vancomycin	0.25 - 2	1	2	100
	Teicoplanin	≤ 2 - > 16	≤ 2	8	97
	Oxacillin	≤ 0.25 - > 2	> 2	> 2	16
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	71
	Daptomycin	≤ 0.06 - 0.5	0.25	0.5	100
	Linezolid	0.5 - 1	1	1	100
	Quinu/Dalfo	≤ 0.25 - 1	≤ 0.25	0.5	100
<i>S. hominis</i> (52)	Telavancin	≤ 0.015 - 0.12	0.12	0.12	-
	Vancomycin	0.5 - 2	1	2	100
	Teicoplanin	≤ 2 - 8	≤ 2	4	98
	Oxacillin	≤ 0.25 - > 2	> 2	> 2	23
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	83
	Daptomycin	≤ 0.06 - 0.5	0.25	0.25	100
	Linezolid	≤ 0.06 - 2	1	1	100
	Quinu/Dalfo	≤ 0.25 - 0.5	≤ 0.25	0.5	100
Other <i>Staphylococcus</i> spp. ⁹ (594)	Telavancin	≤ 0.015 - 0.5	0.12	0.25	-
	Vancomycin	≤ 0.12 - 8	1	2	> 99
	Teicoplanin	≤ 2 - > 16	≤ 2	4	99
	Oxacillin	≤ 0.25 - > 2	> 2	> 2	28
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	68
	Daptomycin	≤ 0.06 - 4	0.25	0.5	> 99
	Linezolid	0.25 - > 8	1	1	99
	Quinu/Dalfo	≤ 0.25 - 1	≤ 0.25	0.5	> 99

Source: This submission, Section 5.3.5.4.1.4.3.1, Table 7

Table 6: MIC Statistics of Telavancin and Selected Comparators vs. Gram-Positive Organisms from the 2007 International Surveillance Study (cont'd)

Organism (no. tested)	Agent	MIC (µg/mL)			%
		Range	50%	90%	Susceptible ^a
<i>S. pneumoniae</i>					
All <i>S. pneumoniae</i> (n=984)	Telavancin	≤ 0.015 - 0.06	0.03	0.03	-
	Vancomycin	≤ 0.12 - ≤ 1	≤ 1	≤ 1	100
	Teicoplanin ^h	≤ 2	≤ 2	≤ 2	-
	Erythromycin	≤ 0.25 - > 2	≤ 0.25	> 2	61
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	79
	Levofloxacin	≤ 0.5 - > 4	1	1	99
	Linezolid	≤ 0.12 - 2	1	1	100
<i>S. pneumoniae</i> , Penicillin-NS ^j (368)					
	Telavancin	≤ 0.015 - 0.06	0.03	0.03	-
	Vancomycin	≤ 1	≤ 1	≤ 1	100
	Teicoplanin ^k	≤ 2	≤ 2	≤ 2	-
	Erythromycin	≤ 0.25 - > 2	> 2	> 2	25
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	53
	Levofloxacin	≤ 0.5 - >4	1	1	> 99
	Linezolid	≤ 0.12 - 2	1	1	100
β-Hemolytic Streptococci					
<i>S. pyogenes</i> (242)					
	Telavancin	≤ 0.015 - 0.25	0.03	0.06	-
	Vancomycin	≤ 0.12 - 0.5	0.25	0.5	100
	Teicoplanin	≤ 2	≤ 2	≤ 2	-
	Erythromycin	≤ 0.25 - > 2	≤ 0.25	≤ 0.25	92
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	≤ 0.25	98
	Levofloxacin	≤ 0.5 - 2	≤ 0.5	1	100
	Linezolid	0.25 - 2	1	1	100
	Daptomycin	≤ 0.06 - 0.25	≤ 0.06	≤ 0.06	100
<i>S. agalactiae</i> (260)					
	Telavancin	0.03 - 0.25	0.06	0.06	-
	Vancomycin	0.25 - 1	0.5	0.5	100
	Teicoplanin	≤ 2	≤ 2	≤ 2	-
	Erythromycin	≤ 0.25 - > 2	≤ 0.25	> 2	73
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	82
	Levofloxacin	≤ 0.5 - > 4	≤ 0.5	1	97
	Linezolid	0.5 - 2	1	1	100
	Daptomycin	≤ 0.06 - 0.25	0.12	0.25	100

Source: This submission, Section 5.3.5.4.1.4.3.1, Table 7

Table 6: MIC Statistics of Telavancin and Selected Comparators vs. Gram-Positive Organisms from the 2007 International Surveillance Study (cont'd)

Organism (no. tested)	Agent	MIC (µg/mL)			% Susceptible ^a
		Range	50%	90%	
<i>Streptococcus</i> Group G (35)	Telavancin	0.03 - 0.12	0.03	0.06	-
	Vancomycin	0.25 - 0.5	0.25	0.5	100
	Teicoplanin	≤ 2	≤ 2	≤ 2	-
	Erythromycin	≤ 0.25 - > 2	≤ 0.25	> 2	71
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	92
	Levofloxacin	≤ 0.5 - > 4	≤ 0.5	1	94
	Linezolid	0.5 - 2	1	1	100
	Daptomycin	≤ 0.06 - 0.12	≤ 0.06	≤ 0.06	100
<i>S. dysgalactiae</i> /Group C ^l (30)	Telavancin	0.03 - 0.12	0.03	0.06	-
	Vancomycin	0.25 - 1	0.25	0.5	100
	Teicoplanin	≤ 2	≤ 2	≤ 2	-
	Erythromycin	≤ 0.25 - > 2	≤ 0.25	≤ 0.25	90
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	≤ 0.25	97
	Levofloxacin	≤ 0.5 - > 4	≤ 0.5	1	97
	Linezolid	0.5 - 1	1	1	100
	Daptomycin	≤ 0.06 - 0.25	≤ 0.06	0.12	100
Other β-hemolytic species ^m (12)	Telavancin	0.03 - 0.12	0.03	0.06	-
	Vancomycin	0.25 - 1	0.25	0.5	100
	Teicoplanin	≤ 2 - 4	≤ 2	≤ 2	-
	Erythromycin	≤ 0.25 - > 2	≤ 0.25	> 2	50
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	75
	Levofloxacin	≤ 0.5 - 1	≤ 0.5	1	100
	Linezolid	0.5 - 1	1	1	100
	Daptomycin	≤ 0.06 - 0.25	≤ 0.06	0.12	100

Source: This submission, Section 5.3.5.4.1.4.3.1, Table 7

Table 6: MIC Statistics of Telavancin and Selected Comparators vs. Gram-Positive Organisms from the 2007 International Surveillance Study (cont'd)

Organism (no. tested)	Agent	MIC (µg/mL)			%
		Range	50%	90%	Susceptible ^a
Bovis group Streptococci					
<i>S. bovis</i> group ⁿ (18)	Telavancin	≤ 0.015 - 0.06	0.03	0.06	-
	Vancomycin	0.25 - 0.5	0.25	0.5	100
	Teicoplanin	≤ 2 - 4	≤ 2	≤ 2	-
	Erythromycin	≤ 0.25 - > 2	≤ 0.25	> 2	50
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	72
	Levofloxacin	≤ 0.5 - > 4	2	> 4	83
	Linezolid	0.5 - 1	1	1	100
	Daptomycin	≤ 0.06	≤ 0.06	≤ 0.06	100
Viridans Group Streptococci					
All viridans group Streptococci (197)	Telavancin	≤ 0.015 - 0.12	0.03	0.06	-
	Vancomycin	≤ 0.12 - 1	0.5	1	100
	Teicoplanin	≤ 2	≤ 2	≤ 2	-
	Erythromycin	≤ 0.25 - > 2	0.5	> 2	53
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	87
	Levofloxacin	≤ 0.5 - > 4	1	2	95
	Linezolid	0.12 - 2	1	1	100
	Daptomycin	≤ 0.06 - 2	0.25	0.5	> 99
Viridans group Streptococci, Penicillin-NS ⁱ (56)	Telavancin	≤ 0.015 - 0.12	0.03	0.06	-
	Vancomycin	0.25 - 1	0.5	0.5	100
	Teicoplanin	≤ 2	≤ 2	≤ 2	-
	Erythromycin	≤ 0.25 - > 2	2	> 2	30
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	80
	Levofloxacin	≤ 0.5 - > 4	1	2	95
	Linezolid	0.25 - 1	1	1	100
	Daptomycin	≤ 0.06 - 2	0.25	1	98

Source: This submission, Section 5.3.5.4.1.4.3.1, Table 7

Table 6: MIC Statistics of Telavancin and Selected Comparators vs. Gram-Positive Organisms from the 2007 International Surveillance Study (cont'd)

Organism (no. tested)	Agent	MIC (µg/mL)			% Susceptible ^a
		Range	50%	90%	
<i>S. anginosus/milleri</i> (36)	Telavancin	≤ 0.015 - 0.06	0.03	0.06	-
<i>S. constellatus</i> (10)	Telavancin	0.03 - 0.06	0.03	0.06	-
<i>S. gordonii</i> (2)	Telavancin	0.06	-	-	-
<i>S. intermedius</i> (2)	Telavancin	0.03 - 0.06	-	-	-
<i>S. mitis</i> (14)	Telavancin	0.03 - 0.06	0.03	0.06	-
<i>S. mutans</i> (3)	Telavancin	0.03	-	-	-
<i>S. oralis</i> (7)	Telavancin	≤ 0.015 - 0.06	-	-	-
<i>S. parasanguis</i> (3)	Telavancin	0.03	-	-	-
<i>S. salivarius</i> (6)	Telavancin	0.03 - 0.06	-	-	-
<i>S. sanguis</i> (6)	Telavancin	0.03 - 0.06	-	-	-
<i>S. vestibularis</i> (1)	Telavancin	0.03	-	-	-
<i>Streptococcus</i> spp. (107)	Telavancin	≤ 0.015 - 0.12	0.03	0.06	-
Enterococci					
<i>E. faecalis</i> (1229)	Telavancin	0.03 - > 2	0.25	0.5	-
	Vancomycin	≤ 0.12 - > 16	1	2	97
	Teicoplanin	≤ 2 - > 16	≤ 2	≤ 2	98
	Ampicillin	≤ 1 - > 16	≤ 1	2	> 99
	Linezolid	0.25 - > 8	1	2	> 99
	Daptomycin	≤ 0.06 - 8	1	2	> 99
<i>E. faecalis</i> , vancomycin-S ^o (1197)	Telavancin	0.03 - 1	0.25	0.5	-
	Vancomycin	≤ 0.12 - 4	1	2	100
	Teicoplanin	≤ 2	≤ 2	≤ 2	100
	Ampicillin	≤ 1 - > 16	≤ 1	2	> 99
	Linezolid	0.25 - > 8	1	2	> 99
	Daptomycin	≤ 0.06 - 8	1	2	> 99

Source: This submission, Section 5.3.5.4.1.4.3.1, Table 7

Table 6: MIC Statistics of Telavancin and Selected Comparators vs. Gram-Positive Organisms from the 2007 International Surveillance Study (cont'd)

Organism (no. tested)	Agent	MIC (µg/mL)			% Susceptible ^a
		Range	50%	90%	
<i>E. faecalis</i> , vancomycin-R ^P (30)	Telavancin	0.25 - >2	>2	>2	-
	Vancomycin	>16	>16	>16	0
	Teicoplanin	≤ 2 - > 16	>16	>16	17
	Ampicillin	≤ 1 - 8	≤ 1	2	100
	Linezolid	0.5 - 2	1	2	100
	Daptomycin	0.25 - 2	0.5	1	100
<i>E. faecium</i> (680)	Telavancin	≤ 0.015 - > 2	0.12	2	-
	Vancomycin	0.5 - > 16	1	> 16	55
	Teicoplanin	≤ 2 - > 16	≤ 2	> 16	60
	Ampicillin	≤ 1 - > 16	> 16	> 16	7
	Linezolid	0.5 - > 8	1	2	99
	Daptomycin	0.12 - 4	2	4	100
<i>E. faecium</i> , vancomycin-S ^O (377)	Telavancin	≤ 0.015 - 1	0.06	0.12	-
	Vancomycin	0.5 - 4	0.5	1	100
	Teicoplanin	≤ 2 - > 16	≤ 2	≤ 2	> 99
	Ampicillin	≤ 1 - > 16	> 16	> 16	12
	Linezolid	0.5 - > 8	2	2	> 99
	Daptomycin	0.12 - 4	2	4	100
<i>E. faecium</i> , vancomycin-R ^P (295)	Telavancin	0.03 - > 2	2	>2	-
	Vancomycin	>16	>16	>16	0
	Teicoplanin	≤ 2 - > 16	>16	>16	9
	Ampicillin	16 - > 16	>16	>16	0
	Linezolid	0.5 - > 8	1	2	98
	Daptomycin	0.25 - 4	2	2	100
<i>Enterococcus</i> spp. ^q (40)	Telavancin	0.03 - 1	0.25	0.5	-
	Vancomycin	0.25 - 8	1	8	88
	Teicoplanin	≤ 2	≤ 2	≤ 2	100
	Ampicillin	≤ 1 - > 16	≤ 1	4	93
	Linezolid	0.5 - 2	1	2	95
	Daptomycin	≤ 0.06 - 4	1	2	100

Source: This submission, Section 5.3.5.4.1.4.3.1, Table 7

Table 6: MIC Statistics of Telavancin and Selected Comparators vs. Gram-Positive Organisms from the 2007 International Surveillance Study (cont'd)

Organism (no. tested)	Agent	MIC (µg/mL)			%
		Range	50%	90%	Susceptible ^a
Miscellaneous Gram-positive Aerobes					
<i>Bacillus</i> spp. (6)	Telavancin	0.03 - 0.25	-	-	-
<i>Corynebacterium</i> spp. (21)	Telavancin	≤ 0.015 - 0.06	0.03	0.03	-
<i>Erysipelothrix</i> spp. (1)	Telavancin	0.06	-	-	-
<i>Kocuria kristinae</i> (1)	Telavancin	≤ 0.015	-	-	-
<i>Lactobacillus</i> spp. (2)	Telavancin	> 2	-	-	-
<i>Lactococcus</i> spp. (3)	Telavancin	0.03 - 0.06	-	-	-
<i>Leuconostoc</i> spp. (1)	Telavancin	> 2	-	-	-
<i>Listeria monocytogenes</i> (2)	Telavancin	0.03	-	-	-
<i>Micrococcus</i> spp. (2)	Telavancin	≤ 0.015	-	-	-
<i>Turicella otiditis</i> (2)	Telavancin	≤ 0.015	-	-	-
Gram-positive Anaerobes					
<i>Aerococcus</i> spp. (5)	Telavancin	≤ 0.015 - 0.25	-	-	-
<i>Gemella</i> spp. (2)	Telavancin	0.03	-	-	-

^a Susceptibility based on CLSI breakpoints, where available (13).

^b Not available or not applicable.

^c Teicoplanin and clindamycin MIC statistics determined for 5,894 isolates.

^d Quinupristin/Dalfopristin.

^e MRSA, methicillin-resistant *Staphylococcus aureus*.

^f MSSA, methicillin-susceptible *Staphylococcus aureus*.

^g Includes *S. auricularis* (3 isolates), *S. capitis* (18), *S. caprae* (4), *S. cohnii* (3), *S. intermedius* (3), *S. lugdunensis* (14), *S. saprophyticus* (16), *S. simulans* (16), *S. warneri* (10), *S. xylosus* (14), *Staphylococcus* spp. (493).

^h Teicoplanin MIC statistics determined for 318 isolates.

ⁱ Penicillin-NS, penicillin-non-susceptible.

^j Penicillin breakpoint for meningitis ($S \leq 2$ µg/mL).

^k Teicoplanin MIC statistics determined for 230 isolates.

^l Includes *S. dysgalactiae* ssp. *equisimilis* (4 isolates).

^m Includes Streptococcus Group F (6 isolates), *Streptococcus* spp. (6).

ⁿ Includes *S. bovis* (15 isolates), *S. equinus* (2), *S. gallolyticus* (1).

^o Vancomycin-S, vancomycin-susceptible.

^p Vancomycin-R, vancomycin-resistant.

^q Includes *E. avium* (10 isolates), *E. casseliflavus* (12), *E. durans* (3), *E. gallinarum* (10), *E. hirae* (4), and *Enterococcus* spp. (1).

Source: This submission, Section 5.3.5.4.1.4.3.1, Table 7

Telavancin was tested in 2005 and 2006 in the ongoing BSAC (British Society for Antimicrobial Chemotherapy) Bacteremia Resistance Surveillance Programme, against gram-positive cocci. Theravance has included summary reports from this ongoing study as Report 08-6424-mcb-01 (2005) and Report 08-64240-mcb-02 (2006). The study employed susceptibility testing methods not approved by CLSI and the study did not fall within the scope of the FDA Good Laboratory Practice Regulations. Isolates were collected from clinical centers in the United Kingdom and Ireland. Susceptibility testing was performed using the BSAC agar dilution method. In 2005, 1,330 isolates were evaluated against telavancin. In 2006 1,309 isolates were tested. Testing was performed at a central laboratory. Quality control procedures were performed on each day of testing, using BSAC guidelines.

In the 2005 survey, there were 449 staphylococcal isolates tested (244 *S. aureus*, 129 *S. epidermidis*, 21 *S. haemolyticus*, 7 *S. capitis*, 23 *S. hominis*, 4 *S. warneri*, and 21 "unspeciated" staphylococci). The telavancin MIC₉₀ for all staphylococcal species tested was 0.25 mcg/ml. Against *S. aureus*, the MIC₉₀ was 0.5 mcg/ml (identical in oxacillin-susceptible and –resistant isolates, analyzed as sub-populations). The MIC values against *S. aureus* were normal and unimodal. The telavancin MIC₉₀ for coagulase-negative staphylococci was 0.25 mcg/ml (the vancomycin MIC₉₀ against the same collection was 2 mcg/ml), with no noted difference in oxacillin-susceptible and –resistant subpopulations. Telavancin was more active than all comparators (including cefoxitin, ciprofloxacin, clindamycin, daptomycin, erythromycin, fusidic acid, gentamicin, linezolid, minocycline, oxacillin, penicillin, piperacillin-tazobactam, rifampin, teicoplanin, tetracycline, tigecycline, trimethoprim, and vancomycin) against isolates of coagulase-negative staphylococci and "unspeciated" staphylococci.

The telavancin MIC₉₀ for isolates of *S. pneumoniae* (n = 230) tested in the 2005 survey, was ≤ 0.03 mcg/ml. Only one penicillin-resistant isolate was identified, with a telavancin MIC of ≤ 0.03 mcg/ml. Thirty erythromycin-resistant isolates were identified, with a telavancin MIC₉₀ of ≤ 0.03 mcg/ml.

Results of the 2005 BSAC Survey are summarized in Table 7.

Table 7: Telavancin MIC₉₀ values for Gram-Positive pathogens analyzed in the 2005 BSAC Survey (species with ≥ 10 isolates tested)

Organism	MIC _{range} (mcg/ml)	MIC ₉₀ (mcg/ml)
All <i>S. aureus</i> (n = 244)	0.12 – 0.5	0.5
MRSA (n = 88)	0.12 – 0.5	0.25
MSSA (n = 156)	0.12 – 0.5	0.5
All CoNS (n = 184)	0.06 – 0.5	0.25
MRCoNS (n = 143)	0.06 – 0.5	0.25
<i>S. pneumoniae</i> (n = 230)	≤ 0.03 – 0.06	≤ 0.03
<i>S. pyogenes</i> (n = 88)	≤ 0.03 – 0.12	≤ 0.06
<i>S. agalactiae</i> (n = 65)	≤ 0.03 – 0.12	0.12
<i>S. dysgalactiae</i> (n = 12)	≤ 0.03 – 0.06	0.06
<i>S. oralis</i> (n = 63)	≤ 0.03 – 0.12	0.06
<i>S. salivarius</i> (n = 10)	≤ 0.03 – 0.12	0.12
<i>S. sanguis</i> (n = 17)	≤ 0.03 – 0.12	0.12
All <i>E. faecalis</i> (n = 138)	0.06 – 16	1
Vancomycin-susceptible <i>E. faecalis</i> (n = 136)	0.06 – 1	1
All <i>E. faecium</i> (n = 90)	≤ 0.03 – 8	4
Vancomycin-resistant <i>E. faecium</i> (n = 36)	0.06 – 8	8
Vancomycin-susceptible <i>E. faecium</i> (n = 54)	≤ 0.03 – 0.25	0.25

MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; CoNS = coagulase-negative Staphylococcus species; MRCoNS = methicillin-resistant coagulase-negative Staphylococcus species
Source: compiled from data in Study Report 08-6426-MCB-01

In the 2006 survey, there were 445 staphylococcal isolates tested, including 242 *S. aureus* isolates. The telavancin MIC₉₀ for all staphylococcal species tested was 0.5 mcg/ml. Against *S. aureus*, the MIC₉₀ was 0.5 mcg/ml (identical in oxacillin-susceptible and –resistant isolates, analyzed as sub-populations). The MIC values against *S. aureus* were unimodal. The telavancin MIC₉₀ for coagulase-negative staphylococci was 0.25 mcg/ml (the vancomycin MIC₉₀ against the same collection was 2 mcg/ml), with no noted difference in oxacillin-susceptible and –resistant subpopulations. Telavancin was more active than all comparators (identical to comparators in 2005 survey, above) against isolates of coagulase-negative staphylococci and "unspeciated" staphylococci.

The telavancin MIC₉₀ for isolates of *S. pneumoniae* (n = 231) tested in the 2006 survey, was ≤ 0.015 mcg/ml. Thirty-one erythromycin-resistant isolates were identified, with a telavancin MIC₉₀ of ≤ 0.015 mcg/ml.

Results of the 2006 BSAC Survey are summarized in Table 8.

Table 8: Telavancin MIC₉₀ values for Gram-Positive pathogens analyzed in the 2006 BSAC Survey (species with ≥ 10 isolates tested)

Organism	MIC _{range} (mcg/ml)	MIC ₉₀ (mcg/ml)
All <i>S. aureus</i> (n = 242)	0.12 – 0.5	0.5
MRSA (n = 109)	0.12 – 0.5	0.5
MSSA (n = 133)	0.12 – 0.5	0.5
All CoNS (n = 203)	0.03 – 0.5	0.25
MRCoNS (n = 158)	0.06 – 0.5	0.25
<i>S. pneumoniae</i> (n = 231)	≤ 0.008 – 0.12	0.015
<i>S. pyogenes</i> (n = 85)	≤ 0.03 – 0.12	0.06
<i>S. agalactiae</i> (n = 82)	≤ 0.03 – 0.25	0.12
<i>S. dysgalactiae</i> (n = 15)	≤ 0.03 – 0.06	0.06
<i>S. anginosus</i> (n = 21)	0.015 – 0.06	0.03
<i>S. oralis</i> (n = 49)	≤ 0.008 – 0.06	0.03
<i>S. parasanguis</i> (n = 13)	0.03 – 0.12	0.06
<i>S. sanguis</i> (n = 27)	0.015 – 0.06	0.06
All <i>E. faecalis</i> (n = 142)	0.03 – 8	0.5
Vancomycin-susceptible <i>E. faecalis</i> (n = 138)	≤ 0.03 – 0.5	0.5
All <i>E. faecium</i> (n = 81)	≤ 0.03 – 4	2
Vancomycin-resistant <i>E. faecium</i> (n = 26)	0.06 – 4	2
Vancomycin-susceptible <i>E. faecium</i> (n = 55)	≤ 0.03 – 0.25	0.12

MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; CoNS = coagulase-negative Staphylococcus species; MRCoNS = methicillin-resistant coagulase-negative Staphylococcus species
Source: compiled from data in Study Report 08-6426-MCB-02

The Applicant has provided the study report from an investigation of telavancin activity against 1500 MRSA isolates collected in Japan, primarily from respiratory sources [Hatano 2006]. Susceptibility testing was performed using microbroth dilution methods approved by CLSI. Quality control was performed on each day of testing, using *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212. Comparators included vancomycin, linezolid, daptomycin, and tigecycline. The collection of isolates included none that were vancomycin-intermediate (VISA), vancomycin-resistant (VRSA), or linezolid non-susceptible. The results of this investigation are summarized in Table 9. MIC₉₀ value of telavancin (0.5 mcg/ml) were similar to (within 1 doubling dilution) those observed for all comparators with the exception of linezolid (2 mcg/ml).

Table 9: MIC Statistics of Telavancin and Selected Comparators for 1500 MRSA Isolates Collected in Japan in 2006

Agent	MIC (µg/mL)		
	Range	50%	90%
Telavancin	0.12 - 0.5	0.25	0.5
Vancomycin	0.25 - 2	1	1
Linezolid	1 - 4	2	2
Daptomycin	0.12 - 2	0.5	0.5
Tigecycline	0.12 - 1	0.25	0.5

Source: This submission, Section 5.3.5.4.1.4.2.4.1, Table 10
JMI Laboratories (North Liberty, Iowa) conducted a study designed to investigate the activity of

telavancin against *S. pneumoniae* with defined antibiograms, including multidrug-resistant (MDR) patterns (n = 205), and eight other species of streptococci (100 isolates of each), including *S. anginosus* (aka *S. milleri*), *S. constellatus*, *S. intermedius*, *S. mitis*, *S. oralis*, *S. agalactiae* (group B), *S. dysgalactiae* sub. *equisimilis* (group C), and Group G β -hemolytic streptococci. Result of the study indicated that telavancin was active against viridans group streptococci (MIC₉₀ 0.03-0.06 mcg/ml), β -hemolytic streptococci group B, C, and G (MIC₉₀ 0.03-0.6 mcg/ml) and all tested resistant phenotypes of *S. pneumoniae* (MIC₉₀ 0.015 mcg/ml). The results for telavancin tested against resistant phenotypes of *S. pneumoniae* are summarized in Table 10.

Table 10: Telavancin MIC results for pneumococcal isolates having nine different patterns of resistance (n = 205)

Resistance pattern (no. tested) ^a	MIC (µg/ml):		
	50%	90%	Range
Pan-S (16)	0.015	0.015	0.008-0.015
PEN-NS (30)	0.008	0.015	0.008-0.015
PEN AND CXM-NS (10)	0.015	0.015	0.008-0.015
ERY-R (10)	0.008	0.015	0.008-0.015
LEVO-R (10)	0.015	0.015	0.008-0.015
TET-R (10)	0.015	0.015	0.008-0.015
T/S-R (11)	0.015	0.015	0.004-0.015
ERY, CM, TET-R (10)	0.015	0.015	0.008-0.015
Multidrug-R (98) ^b	0.015	0.015	0.008-0.015
All strains (205)	0.015	0.015	0.004-0.015

a. S = susceptible; R = resistant; NS = non-susceptible; PEN = penicillin; CXM = cefuroxime; ERY = erythromycin; LEVO = levofloxacin; TET = tetracycline; and T/S = trimethoprim/sulfamethoxazole; CM = clindamycin.

b. Multidrug-R = resistance to PEN, CXM, CM, ERY, TET and T/S (six drug classes).

Source: This application, Report 06-THE-02

In Summary:

In addition to summarized data originally submitted in support of NDA 22110, the Applicant has provided study reports from five investigations of the in vitro activity of telavancin, conducted since that submission. Telavancin overall activity against isolates of *S. aureus* and *S. pneumoniae* (the primary pathogens in the proposed indications), analyzed in these studies, is summarized in Tables 11 and 12, respectively.

Table 11: Summary of Activity of Telavancin Against *S. aureus*: Previously Reported and Recent Prospective Surveillance Studies

Study	No. Isolates	MIC (µg/mL)		
		Range	50%	90%
2004-2005 US Surveillance [31]	2299	0.03 - 1	0.25	0.5
2004-2005 EU Surveillance [30]	1785	≤ 0.015 - 1	0.25	0.5
BSAC 2005 [74]	244	0.12 - 0.5	0.25	0.5
BSAC 2006 [75]	242	0.12 - 0.5	0.25	0.5
Japanese Surveillance 2006 [36]	1500	0.12 - 0.5	0.25	0.5
International Surveillance 2007 [40]	5895	0.03 - 0.5	0.12	0.25

Source: This submission, Section 5.3.5.4.1.4.2.6, Table 14

Table 12: Summary of Activity of Telavancin Against *S. pneumoniae*: Previously Reported and Recent Prospective Surveillance Studies

Study	No. Isolates	MIC (µg/mL)		
		Range	50%	90%
2004-2005 US Surveillance {31}	276	0.002 - 0.06	0.015	0.03
2004-2005 EU Surveillance {30}	179	≤ 0.001 - 0.06	0.015	0.03
BSAC 2005 {74}	230	≤ 0.03 - 0.06	≤ 0.03	≤ 0.03
BSAC 2006 {75}	231	≤ 0.008 - 0.12	≤ 0.008	0.015
JMI Streptococcus Study {41}	205	0.004 - 0.015	0.015	0.015
International Surveillance 2007 {40}	984	≤ 0.015 - 0.06	0.03	0.03

Source: This submission, Section 5.3.5.4.1.4.2.6, Table 15

Overall telavancin activity, as reported in the large in vitro studies, against pathogens associated with HAP (including Enterococcus species, viridans group streptococci, β-hemolytic streptococci, and bovis group streptococci is summarized in Tables 13 and 14.

Table 13: Summary of Activity of Telavancin Against Vancomycin-susceptible Enterococcus Species: Previously Reported and Recent Prospective Surveillance Studies

Study	No. Isolates	MIC (µg/mL)		
		Range	50%	90%
<i>E. faecalis</i>, vancomycin-S				
2004-2005 US Surveillance {31}	429	0.12 - 1	0.25	0.5
2004-2005 EU Surveillance {30}	426	0.06 - 1	0.25	0.5
BSAC 2005 {74}	136	0.06 - 1	0.5	1
BSAC 2006 {75}	138	≤ 0.03 - 0.5	0.25	0.5
International Surveillance 2007 {40}	1197	0.03 - 1	0.25	0.5
<i>E. faecium</i>, vancomycin-S				
2004-2005 US Surveillance {31}	92	≤ 0.015 - 0.5	0.12	0.25
2004-2005 EU Surveillance {30}	276	0.03 - 1	0.12	0.25
BSAC 2005 {74}	54	≤ 0.03 - 0.25	0.12	0.25
BSAC 2006 {75}	55	≤ 0.03 - 0.25	0.06	0.12
International Surveillance 2007 {40}	377	≤ 0.015 - 1	0.06	0.12

Source: This submission, Section 5.3.5.4.1.4.2.6, Table 16

Table 14: Summary of Activity of Telavancin Against Individual Non-Pneumococcal *Streptococcus* Species: Previously Reported and Recent Prospective Studies

Group/Species	Study	No. Isolates	MIC (µg/mL)		
			Range	50%	90%
β-Hemolytic streptococci					
Group A (<i>S. pyogenes</i>)	2004-2005 US Surveillance [31]	68	0.015 - 0.12	0.03	0.06
	2004-2005 EU Surveillance [30]	54	0.015 - 0.12	0.03	0.03
	BSAC 2005 [74]	88	≤ 0.03 - 0.12	0.06	0.06
	BSAC 2006 [75]	85	≤ 0.03 - 0.12	0.06	0.06
	International Surveillance 2007 [40]	242	≤ 0.015 - 0.25	0.03	0.06
Group B (<i>S. agalactiae</i>)	2004-2005 US Surveillance [31]	45	0.03 - 0.12	0.06	0.06
	2004-2005 EU Surveillance [30]	48	≤ 0.008 - 0.12	0.06	0.06
	BSAC 2005 [74]	65	≤ 0.03 - 0.12	0.12	0.12
	BSAC 2006 [75]	82	≤ 0.03 - 0.25	0.06	0.12
	International Surveillance 2007 [40]	260	0.03 - 0.25	0.06	0.06
	JMI Streptococcus Study [41]	100	0.015 - 0.06	0.03	0.06
Group C (<i>S. dysgalactiae</i> , including ssp. <i>equisimilis</i>)	2004-2005 US Surveillance [31]	10	0.03 - 0.06	0.03	0.06
	2004-2005 EU Surveillance [30]	9	≤ 0.008 - 0.12	-- ^a	--
	BSAC 2005 [74]	13	≤ 0.03 - 0.12	0.06	0.06
	BSAC 2006 [75]	16	≤ 0.03 - 0.06	≤ 0.03	0.06
	International Surveillance 2007 [40]	30	0.03 - 0.12	0.03	0.06
	JMI Streptococcus Study [41]	100	0.015 - 0.06	0.03	0.03
Group F	2004-2005 US Surveillance [31]				
	and 2004-2005 EU Surveillance [30]	4	0.015 - 0.06	--	--
	combined	7	0.03 - 0.12	--	--
	International Surveillance 2007 [40]				
Group G	2004-2005 US Surveillance [31]	18	0.03 - 0.25	0.06	0.12
	2004-2005 EU Surveillance [30]	15	0.03 - 0.25	0.03	0.06
	BSAC 2005 [74]	62	≤ 0.03 - 0.12	0.06	0.06
	BSAC 2006 [75]	46	≤ 0.03 - 0.12	0.06	0.06
	International Surveillance 2007 [40]	35	0.03 - 0.12	0.03	0.06
	JMI Streptococcus Study [41]	100	0.015 - 0.12	0.03	0.06
Bovis Group Streptococci					
<i>S. bovis</i> group	BSAC 2005 [74]	21	≤ 0.03 - 0.12	0.06	0.12
	BSAC 2006 [75]	21	0.03 - 0.12	0.06	0.12
	International Surveillance 2007 [40]	15	≤ 0.015 - 0.06	0.03	0.06
<i>S. equinus</i>	International Surveillance 2007 [40]	2	0.03	--	--
<i>S. gallolyticus</i>	International Surveillance 2007 [40]	1	0.06	--	--
Viridans Group Streptococci					
Anginosus Group					
<i>S. anginosus/milleri</i>	2004-2005 EU Surveillance [30]	1	0.03	--	--
	BSAC 2005 [74]	26	≤ 0.03 - 0.12	≤ 0.03	0.06
	BSAC 2006 [75]	21	0.015 - 0.06	0.015	0.03
	International Surveillance 2007 [40]	36	≤ 0.015 - 0.06	0.03	0.06
	JMI Streptococcus Study [41]	100	0.002 - 0.06	0.03	0.03
<i>S. constellatus</i>	BSAC 2005 [74]	3	≤0.03	--	--
	BSAC 2006 [75]	4	0.015	--	--
	International Surveillance 2007 [40]	10	0.03 - 0.06	0.03	0.06
	JMI Streptococcus Study [41]	100	0.015 - 0.06	0.03	0.03
<i>S. intermedius</i>	2004-2005 US Surveillance [31]	2	0.03 - 0.06	--	--
	BSAC 2005 [74]	2	≤ 0.03	--	--
	BSAC 2006 [75]	5	0.015 - 0.03	--	--
	International Surveillance 2007 [40]	2	0.03 - 0.06	--	--
	JMI Streptococcus Study [41]	100	0.015 - 0.25	0.03	0.06

Source: This submission, Section 5.3.5.4.1.4.2.6, Table 17

Table 14: (cont'd)

Group/Species	Study	No. Isolates	MIC (µg/mL)		
			Range	50%	90%
Mitis Group					
<i>S. mitis</i>	2004-2005 US Surveillance [31]	1	0.12	--	--
	BSAC 2005 [74]	14	≤ 0.03 - 0.06	≤ 0.03	≤ 0.03
	BSAC 2006 [75]	7	≤ 0.008 - 0.015	--	--
	International Surveillance 2007 [40]	14	0.03 - 0.06	0.03	0.06
	JMI Streptococcus Study [41]	100	0.008 - 0.06	0.03	0.03
<i>S. oralis</i>	BSAC 2005 [74]	63	≤ 0.03 - 0.12	≤ 0.03	0.06
	BSAC 2006 [75]	49	≤ 0.008 - 0.06	0.03	0.03
	International Surveillance 2007 [40]	7	≤ 0.015 - 0.06	--	--
	JMI Streptococcus Study [41]	100	0.015 - 0.06	0.03	0.03
<i>S. parasanguis</i>	BSAC 2005 [74]	9	≤ 0.03 - 0.06	--	--
	BSAC 2006 [75]	13	0.03 - 0.12	0.03	0.06
	International Surveillance 2007 [40]	3	0.03	--	--
Mutans Group					
<i>S. mutans</i>	BSAC 2005 [74]	2	0.06 - 0.12	--	--
	BSAC 2006 [75]	1	0.12	--	--
	International Surveillance 2007 [40]	3	0.03	--	--
Sanguis Group					
<i>S. gordonii</i>	BSAC 2005 [74]	4	≤ 0.03	--	--
	BSAC 2006 [75]	6	0.03 - 0.06	--	--
	International Surveillance 2007 [40]	2	0.06	--	--
<i>S. sobrinus</i>	BSAC 2005 [74]	1	≤ 0.03	--	--
<i>S. sanguis</i>	BSAC 2005 [74]	17	≤ 0.03 - 0.12	≤ 0.03	0.12
	BSAC 2006 [75]	27	0.015 - 0.06	0.03	0.06
	International Surveillance 2007 [40]	6	0.03 - 0.06	--	--
Salivarius Group					
<i>S. salivarius</i>	BSAC 2005 [74]	10	≤ 0.03 - 0.12	≤ 0.03	0.12
	BSAC 2006 [75]	5	0.06	--	--
	International Surveillance 2007 [40]	6	0.03 - 0.06	--	--
<i>S. vestibularis</i>	BSAC 2005 [74]	8	≤ 0.03 - 0.12	≤ 0.03	--
	BSAC 2006 [75]	7	≤ 0.008 - 0.12	--	--
	International Surveillance 2007 [40]	1	0.03	--	--

^a MIC statistics not determined for N < 10 isolates

Source: This submission, Section 5.3.5.4.1.4.2.6, Table 17

Antimicrobial Spectrum of Activity Studies ~ Conclusions:

Data submitted from large prospective surveillance studies and other investigations of in vitro activity, including investigations conducted in support of NDA 22110, support the applicant's claim of activity against the pathogens generally associated with hospital acquired pneumonia,

(b) (4). MIC values for all tested isolates of *S. aureus* and *S. pneumoniae* (including isolates resistant to other classes of antimicrobials, and isolates with specific virulence profiles) were below attainable drug concentrations that can be achieved with the telavancin dosing regimen being proposed by the Applicant.

RESISTANCE STUDIES

Glycopeptide resistance in enterococci, first described in European isolates in 1988 [Courvalin 2006] has become widespread since that time. The resistance mechanisms have been characterized phenotypically and genotypically [Leclercq 1988]. Of the six different types of enterococcal vancomycin-resistance, VanA and VanB are the most common clinically observed varieties. Both are inducible and both may be transferred by mobile elements. Resistance is conferred by the production of peptidoglycan (PG) precursors that have a low affinity for glycopeptides, and by the elimination of high-affinity PG precursors (precursors with C-terminal D-Ala residues) that are the normal constituents of peptidoglycan polymerization. VanA

resistance is induced by a variety of glycopeptides (including teicoplanin and telavancin), while VanB appears to be primarily induced by vancomycin only.

Staphylococcal resistance to glycopeptides is rare. Vancomycin-resistant *S. aureus* (VRSA; MIC ≥ 16 $\mu\text{g/ml}$) has been isolated three times in the U.S., and all isolates were positive for the VanA gene cluster [Weigel 2003]. Vancomycin-intermediate *S. aureus* (VISA; MIC = 4 – 8 $\mu\text{g/ml}$) is seen more often than VRSA, but is also uncommon in clinical settings. VISA isolates appear to have decreased (or absent) levels of specific transpeptidases (PBP 4), which may result in a buildup of cell wall precursors. This excess concentration of uncross-linked precursors may act to absorb glycopeptides, effectively reducing the action of the antimicrobial. The isolation of GISA is most often associated with patients undergoing long-term vancomycin therapy. *Staphylococcus aureus* isolates may exhibit heteroresistance to glycopeptides, which is determined by the presence of resistant sub-populations in vitro. Heteroresistant vancomycin-intermediate *S. aureus* (hVISA) may represent a precursor to the development of VISA, and hVISA has been associated with vancomycin therapy failures (Moore 2003).

Glycopeptide resistance in streptococcal species has not been observed.

In NDA 22-110, the Applicant provided data from well-controlled studies to demonstrate a low potential for development of resistance to telavancin in bacterial species considered in the proposed indications. Although Van-A type vancomycin-resistant enterococcal species are not included in the proposed indications for telavancin (vancomycin-susceptible *E. faecalis* is listed in the proposed indications for the treatment of cSSSI), the data from resistance suggests a possible role for this resistance mechanism in staphylococcal species (e.g. vancomycin-resistant *S. aureus*). Surveillance, regarding the development and spread of this resistance mechanism is warranted. *S. aureus* heteroresistance to telavancin was not observed.

In addition to referencing studies of telavancin resistance submitted in support of NDA 22-110, the Applicant has provided data from four recent studies, as well as an overview of telavancin activity against *S. pneumoniae* (not included in the indications proposed in NDA 22110).

In an investigation of the ability of telavancin to induce expression of *vanA* and *vanB* operons in vancomycin-resistant enterococcus, isolates of *E. faecium* (*VanA*) and *E. faecalis* (*VanA* and *VanB*), listed in Table 15, were exposed to telavancin, vancomycin, or teicoplanin and harvested during the exponential growth phase. VanX dipeptidase activity and protein was assayed using D-Alanyl-(R)-phenylthioglycine as a substrate, to monitor the expression of VAN-resistance genes.

Table 15: *Enterococcus* spp. Isolates Used in the Study of Induction of VanX

Organism	Strain	Relevant Phenotype	MIC ($\mu\text{g/mL}$)			Source or Reference
			Telavancin	Vancomycin	Teicoplanin	
<i>E. faecalis</i>	BM4110 ^a	Vancomycin-susceptible	1	2	0.5	(16)
	BM4110/pIP816-1 ^b	VanA	8	1024	256	{2}
	ATCC 51575	VanB	1	256	0.5	ATCC ^c
	ATCC 51299	VanB	1	16	1	ATCC
<i>E. faecium</i>	ATCC 51599	VanA	8	1024	256-512	ATCC

^a Streptomycin-resistant derivative of JH2

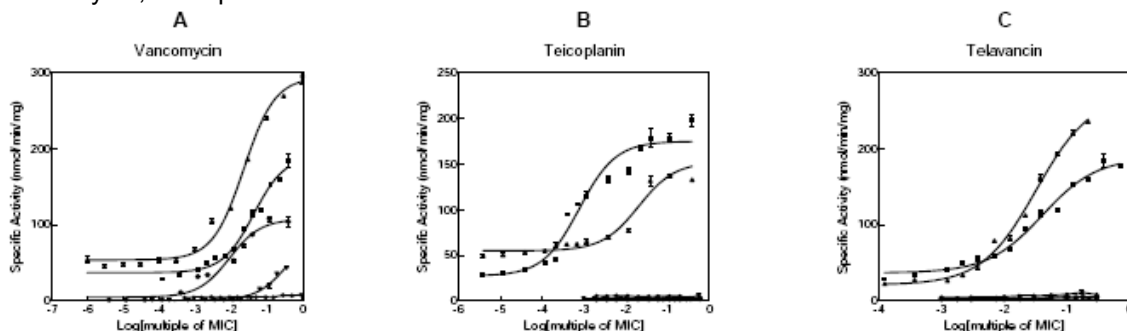
^b Natural plasmid pIP816-1 carrying Tn1546

^c ATCC, American Type Culture Collection

Source: This submission, Section 5.3.5.4.1.3.2.1

The results of the investigation are summarized in Figure 4. Vancomycin induced dipeptidase activity in VanA and VanB enterococci (A), but teicoplanin and telavancin induced VanX dipeptidase activity in VanA isolates but not in VanB isolates (B and C).

Figure 4: Specific Activity of VanX in VanA and VanB Enterococci Grown in the Presence of Vancomycin, Teicoplanin or Telavancin

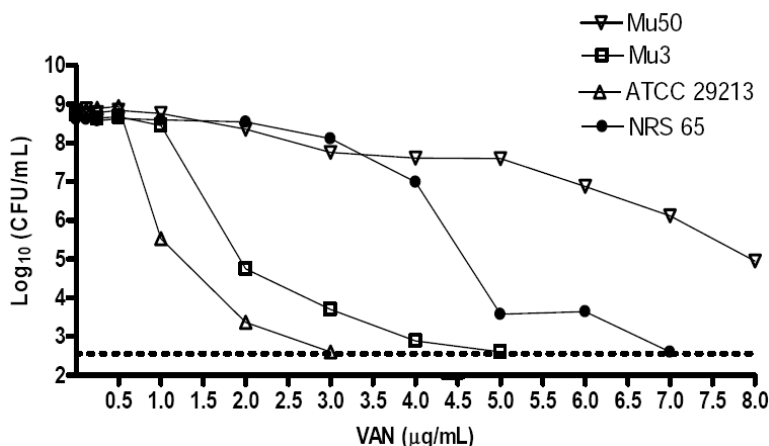


(A) Vancomycin induced dipeptidase activity in VanA and VanB enterococci. Higher levels of activity were observed in VanA strains at comparable MIC values. (B) Teicoplanin induced VanX activity in VanA enterococci but not in the VanB strains. (C) Telavancin induced VanX activity in VanA but not in VanB enterococci. (▲) ATCC 51559 (VanA), (■) BM4110/pIP816-1 (VanA), (●) ATCC 51575 (VanB), (▼) ATCC 51299 (VanB), (◆) BM4110 (vancomycin-susceptible).

Source: This submission, Section 5.3.5.4.1.3.2.1, Figure 1

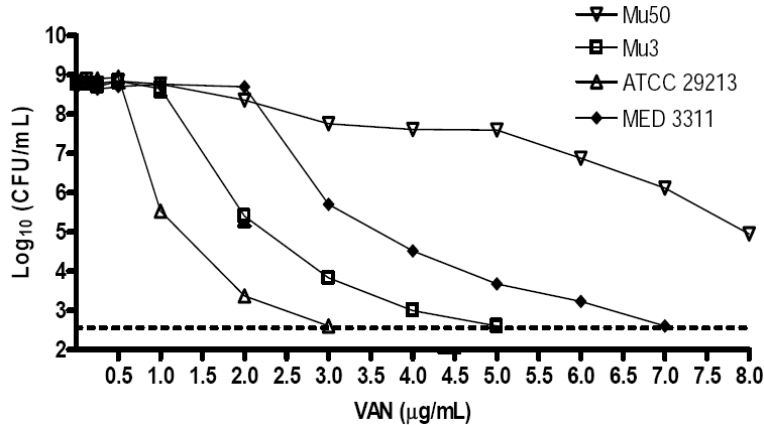
In a population analysis profile (PAP) study, submitted to support NDA 22110, *S. aureus* type strains ATCC 29213 (vancomycin-susceptible, ATCC 700698 (hVISA Mu3), and ATCC 700699 (VISA Mu3) were analyzed for heteroresistance to telavancin. In this study, no isolates were identified with an MIC greater than 1 mcg/ml (the proposed breakpoint for telavancin against *S. aureus*). The Applicant has submitted data from a second PAP study intended to further characterize the possibility of telavancin heteroresistance in isolates of *S. aureus*. The vancomycin PAP-AUC ratio was defined as: AUC of test isolate/AUC of hVISA Mu3. Analyzed isolates were characterized as VSSA, hVISA, and VISA, based on the determined ratio (<0.9, 0.9 – 1.3) and >1.3, respectively). The tested isolates included three recent clinical isolates (two, MED 3306 and MED 3314, identified as hVISA, and one, MED 3311, identified as VISA) and four reference isolates (Mu50 and NRS65, both identified as VISA, ATCC 29213, identified as VSSA, and Mu3, identified as hVISA). The results of the analysis are summarized in Figures 5 through 14. No subpopulations were identified, in this study, with reduced susceptibility to telavancin.

Figure 5: Vancomycin Population Analysis Profiles for *S. aureus* ATCC 29213, Mu3, Mu50, and NRS 65



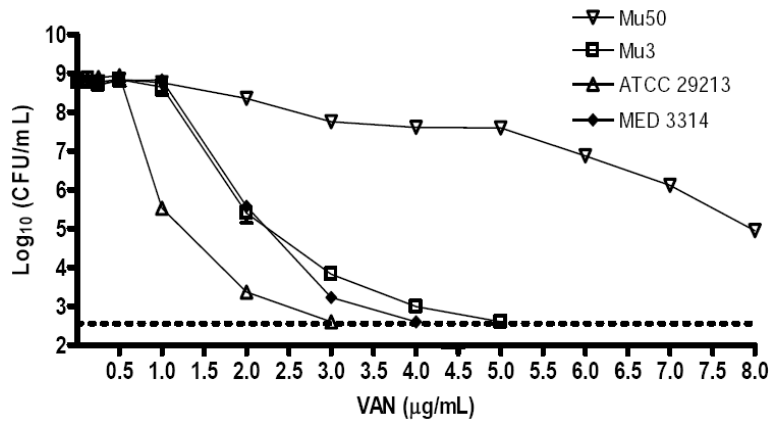
Source: This submission, Section 5.3.5.4.1.3.2.2, Figure 2

Figure 6: Vancomycin Population Analysis Profiles for *S. aureus* MED 3311



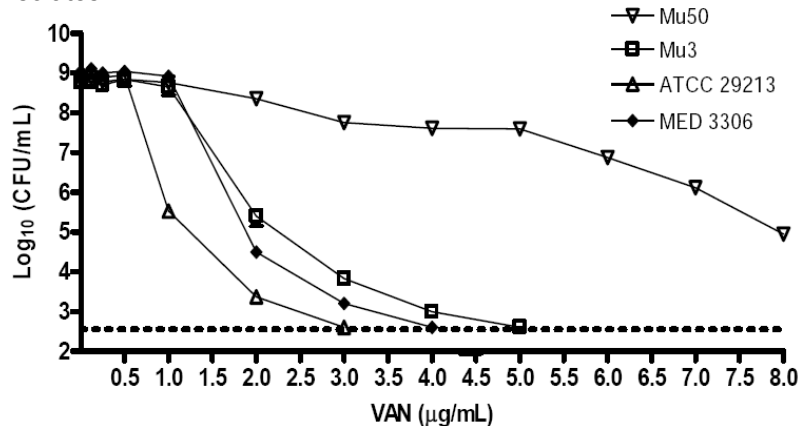
Source: This submission, Section 5.3.5.4.1.3.2.2, Figure 3

Figure 7: Vancomycin Population Analysis Profiles for *S. aureus* MED 3314 and Reference Isolates



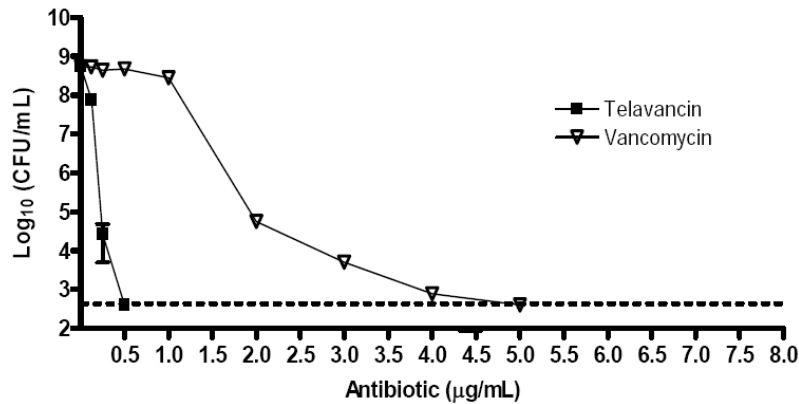
Source: This submission, Section 5.3.5.4.1.3.2.2, Figure 4

Figure 8: Vancomycin Population Analysis Profiles for *S. aureus* MED 3306 and Reference Isolates



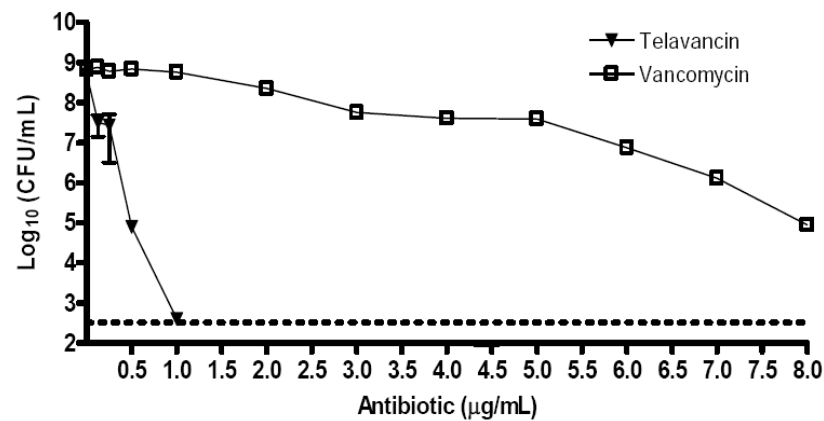
Source: This submission, Section 5.3.5.4.1.3.2.2, Figure 5

Figure 9: Telavancin and Vancomycin Population Analysis Profiles for *S. aureus* Mu3 (hVISA)



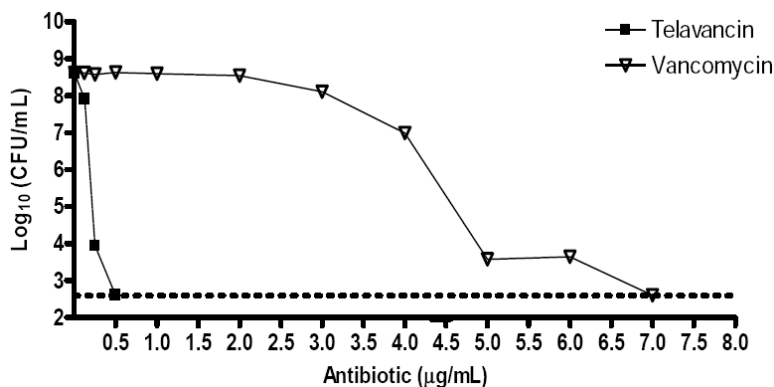
Source: This submission, Section 5.3.5.4.1.3.2.2, Figure 6

Figure 10: Telavancin and Vancomycin Population Analysis Profiles for *S. aureus* Mu50 (VISA)



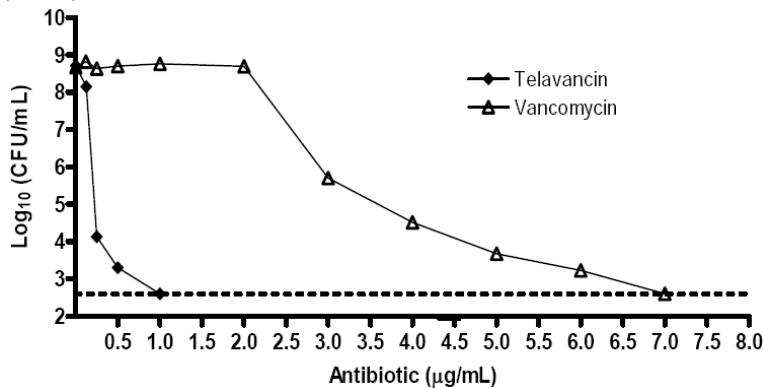
Source: This submission, Section 5.3.5.4.1.3.2.2, Figure 7

Figure 11: Telavancin and Vancomycin Population Analysis Profiles for *S. aureus* NRS65 (VISA)



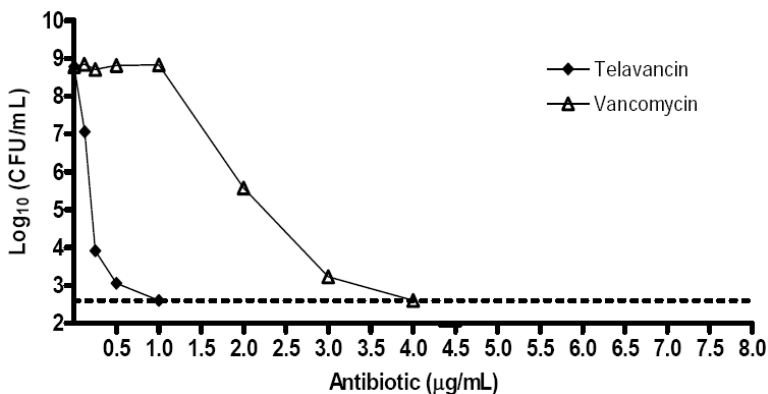
Source: This submission, Section 5.3.5.4.1.3.2.2, Figure 8

Figure 12: Telavancin and Vancomycin Population Analysis Profiles for *S. aureus* MED 3311 (VISA)



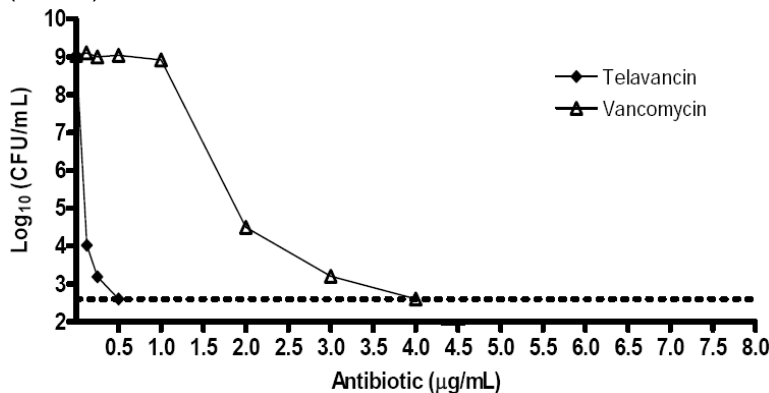
Source: This submission, Section 5.3.5.4.1.3.2.2, Figure 9

Figure 13: Telavancin and Vancomycin Population Analysis Profiles for *S. aureus* MED 3314 (hVISA)



Source: This submission, Section 5.3.5.4.1.3.2.2, Figure 10

Figure 14: Telavancin and Vancomycin Population Analysis Profiles for *S. aureus* MED 3306 (hVISA)



Source: This submission, Section 5.3.5.4.1.3.2.2, Figure 10

The Applicant has provided a preliminary report from a study designed to investigate the ability of telavancin to select resistant mutants from populations of vancomycin-susceptible and – nonsusceptible MRSA and vancomycin-susceptible enterococci [Clark 2008]. Recent clinical isolates were tested, including 10 MRSA isolates (4 vancomycin-susceptible (VSSA), 4

vancomycin-intermediate(VISA), and 2 heterogeneous-VISA (hVISA)), 1 vancomycin-susceptible *E. faecalis*, and 1 vancomycin-susceptible *E. faecium*. Susceptibility testing was performed using CLSI-approved broth macrodilution techniques. Serial passages were performed using the dilution 1-2 dilutions below the MIC for the particular organism and drug, with daily passage until a >4 fold increase in MIC was found (50 passages maximum, 14 passages minimum). Resistant clones, if isolated, were subcultured 10 times in drug-free medium to establish stability of resistance. The relatedness of parental isolates and resistant clones was tested by pulse-field gel electrophoresis. The results of this investigation are summarized in Table 16. Telavancin yielded an elevated MIC clone in one VSSA isolate after 43 days (with no subsequent elevation afterwards, through Day 50). In comparison, daptomycin yielded resistant clones in 4 of 10 MRSA isolates and both enterococcal isolates.

Table 16: Multistep Resistance Selection Results

Species	Strain		MIC (µg/mL)				
			Telavancin	Vancomycin	Teicoplanin	Daptomycin	Linezolid
<i>S. aureus</i>	SA525 (VSSA)	Initial MIC	0.5	2	1	1	4
		Final (Pass. No.)	1 (50)	8 (50)	8 (21)	8 (20)	16 (50)
		Post Subculture	-	-	4	2	-
	SA 547 (VSSA)	Initial MIC	0.5	2	2	1	4
		Final (Pass. No.)	2 (50)	8 (50)	16 (35)	8 (21)	32 (48)
		Post Subculture	-	-	4	4	32
	SA262 (VSSA)	Initial MIC	0.5	4	1	1	4
		Final (Pass. No.)	4 (34)	4 (50)	4 (50)	8 (16)	>32 (22)
		Post Subculture	1	-	-	4	32
	SA248 (VSSA)	Initial MIC	0.25	1	0.5	0.5	4
		Final (Pass. No.)	2 (43)	2 (50)	4 (32)	4 (41)	16 (50)
		Post Subculture	2	-	1	0.5	-
<i>S. aureus</i>	SA618 (hVISA)	Initial MIC	0.5	2	4	2	4
		Final (Pass. No.)	2 (50)	8 (50)	16 (50)	16 (14)	16 (50)
		Post Subculture	-	-	-	8	-
	SA873 (hVISA)	Initial MIC	0.5	2	2	1	2
		Final (Pass. No.)	2 (50)	4 (50)	16 (27)	2 (50)	8 (50)
		Post Subculture	-	-	4	-	-
	SA555 (VISA)	Initial MIC	1	8	16	16	2
		Final (Pass. No.)	2 (50)	8 (50)	32 (50)	32 (50)	4 (50)
		Post Subculture	-	-	-	-	-
	SA1287 (VISA)	Initial MIC	0.5	4	4	4	4
		Final (Pass. No.)	2 (50)	8 (50)	16 (50)	8 (50)	16 (50)
		Post Subculture	-	-	-	-	-
<i>S. aureus</i>	SA1948 (VISA)	Initial MIC	0.5	4	2	4	4
		Final (Pass. No.)	2 (50)	16 (50)	32 (14)	8 (50)	8 (50)
		Post Subculture	-	-	16	-	-
	SA770 (VISA)	Initial MIC	0.5	4	4	1	4
		Final (Pass. No.)	2 (50)	8 (50)	16 (50)	8 (35)	8 (50)
		Post Subculture	-	-	-	4	-
<i>E. faecalis</i>	<i>E. faecalis</i> HMC568 (Van-S)	Initial MIC	1	2	1	2	2
		Final (Pass. No.)	1 (50)	2 (50)	2 (50)	16 (21)	32 (35)
		Post Subculture	-	-	-	16	32
<i>E. faecium</i>	<i>E. faecium</i> HMC651 (Van-S)	Initial MIC	0.25	1	1	4	2
		Final (Pass. No.)	1 (50)	1 (50)	2 (50)	32 (24)	2 (50)
		Post Subculture	-	-	-	16	-

Source: This submission, Section 5.3.5.4.1.3.2.3, Table 2

The Applicant has provided a brief summary of telavancin activity against resistant isolates of *S. pneumoniae* from data collected and analyzed in the 2007 International Surveillance Program (JMI, North Liberty, Iowa), (b) (4). In this study, the telavancin MIC₉₀ (984 recent clinical isolates, including 64 with an MIC > 2 mcg/ml) was 0.03 mcg/ml.

Resistance Studies ~ Conclusions:

The Applicant has provided, as reference to NDA 22-110 and in information from investigations undertaken since that submission, sufficient data to demonstrate a low potential for development of resistance to bacterial species considered in the proposed indications. Data presented in this Application suggest that telavancin is an inducer of the VanA operon, but does not induce activity of the VanB operon. Population analysis profiles have not detected heteroresistance to telavancin in isolates of *S. aureus*. No resistance to telavancin was noted in isolates collected in clinical trials.

ANTIMICROBIAL INTERACTION STUDIES

In NDA 22-110, the applicant presented data from two independent investigations, employing both checkerboard microdilution studies and time-kill studies, to describe interactions of telavancin with other antimicrobials commonly used to treat complicated skin and skin structure infections. Modest synergy was observed in the checkerboard microdilution studies against staphylococci, enterococci, and streptococci (including *S. pneumoniae*), but no synergy between either telavancin and imipenem, or telavancin and cefepime, was observed against strains of MRSA and MSSA (ATCC 33591 and ATCC 29213, respectively), in the time-kill studies. No antagonism was noted in any of the drug interaction investigations.

The Applicant has submitted preliminary data from an ongoing investigation of synergistic interactions between telavancin and rifampin, gentamicin, cefepime, ceftriaxone, oxacillin, meropenem, and ciprofloxacin [Lin 2008]. In the study, telavancin was studied alone and in combination with rifampin, gentamicin, cefepime, ceftriaxone, oxacillin, meropenem, and ciprofloxacin against 22 MRSA isolates, including 6 identified as "community acquired", 2 hVISA, 8 VISA, and 3 VRSA. Standard broth microdilution techniques were used to determine MICs, with viability counts performed at 0, 3, 6, and 12 hours. The investigators defined synergy as "≥ 2 log₁₀ reduction in CFU/ml between the antimicrobial combination and its more active agent at each time point compared to time 0 h." The preliminary results of this study are summarized in Table 17. Telavancin was active against all tested isolates, including hVISA and VISA, at concentrations ≤ 1 mcg/ml, and displayed synergy against all tested isolates, at sub-MIC concentrations, in combination with β-lactams, gentamicin, rifampin, and ciprofloxacin.

Table 17: In Vitro Antimicrobial Interactions Studied by Time-Kill

Isolate/ phenotype	N ^a	Number of Strain at 24 hrs Showing Interaction for Telavancin Tested in Combination with													
		Gentamicin		Rifampin		Cefepime		Ceftriaxone		Oxacillin		Meropenem		Ciprofloxacin	
		A ^b	S ^c	A	S	A	S	A	S	A	S	A	S	A	S
All	22	2	20	7	15	3	19	1	21	6	16	1	21	5	17
VSSA	9	0	9	2	7	1	8	0	9	5	4	0	9	1	8
hVISA	2	0	2	0	2	0	2	0	2	0	2	0	2	1	1
VISA	8	1	7	3	5	1	7	1	7	0	8	1	7	2	6
VRSA	3	1	2	2	1	1	2	0	3	1	2	0	3	1	2

^a Number of isolates tested

^b Additive effect

^c Synergistic effect

Source: This submission, Section 5.3.5.4.1.7.3.1, Table 1

Antimicrobial Interaction Studies ~ Conclusions:

In data presented in this Application as well as in NDA 22-110, the Applicant has demonstrated modest synergy of telavancin with β-lactams, rifampin, ciprofloxacin, and gentamicin, against isolates of *S. aureus*, including methicillin-resistant and vancomycin-non-susceptible phenotypes. Telavancin activity is additive with other studied drug combinations. No antagonism has been demonstrated with telavancin and any tested antimicrobial.

EFFECTS OF MISCELLANEOUS FACTORS ON ACTIVITY

I. PROTEIN BINDING

Telavancin is highly protein-bound (~90%) in human serum, principally to serum albumin. Over a range of studied concentrations (1 to 500 µg/ml), the drug was approximately 88 to 92% bound. Studies in skin blister fluid demonstrated similar protein binding (85.5% at a concentration of 100 mcg/ml). Hepatic or renal insufficiency did not markedly alter levels of serum protein binding.

In NDA 22110, the Applicant submitted data from the three studies of protein binding on telavancin activity indicate that while activity is diminished in the presence of human serum or specific serum proteins (e.g. HSA), bactericidal activity consistently remains, at telavancin concentrations exceeding 4x MIC, against tested strains of gram-positive pathogens (*S. aureus*

and *E. faecalis* strains).

The Applicant has provided additional information regarding the effect of human serum albumin, human serum, and mouse serum on the in vitro activity of telavancin against isolates of *S. aureus*.

In one study [Tsuji 2008], investigators evaluated the effect of protein binding on the MIC values of telavancin, daptomycin, vancomycin, and teicoplanin against five clinical isolates of *S. aureus* (4 MRSA and 1 MSSA). MICs were determined using microbroth dilution techniques approved by CLSI. Evaluations included incubation in Mueller-Hinton broth (MHB, cation adjusted) without supplementation and in MHB with 4 g/dl human albumin, 100% mouse serum, and 50% human serum. The results of the investigation are summarized in Table 18. The investigators concluded that the calculated extent of protein binding, based on MIC changes for telavancin and daptomycin (62-70% and 58-66%, respectively) suggest that the impact of protein binding on the activity of these glycopeptides may be less than that predicted by studies analyzing on free fraction concentrations.

Table 18: Effect of Human Serum Albumin, Human Serum and Mouse Serum on MIC Values Obtained for Telavancin When Tested Against Clinical Isolates of *S. aureus*

Phenotype ^a	Strain ID	SCCmec Type	MIC (µg/mL)			
			CAMHB ^b	40 g/dL HSA ^b	50% HS ^b	100% MS ^b
HA-MRSA	494	Type II	0.25	1	1	0.5
HA-MRSA	67	Type II	0.125	0.5	1	2
CA-MRSA	IE	Type IV	0.125	1	1	1
CA-MRSA	MW2	Not Reported	0.25	1	1	1
MSSA	1199	Not Reported	0.125	0.5	0.25	1

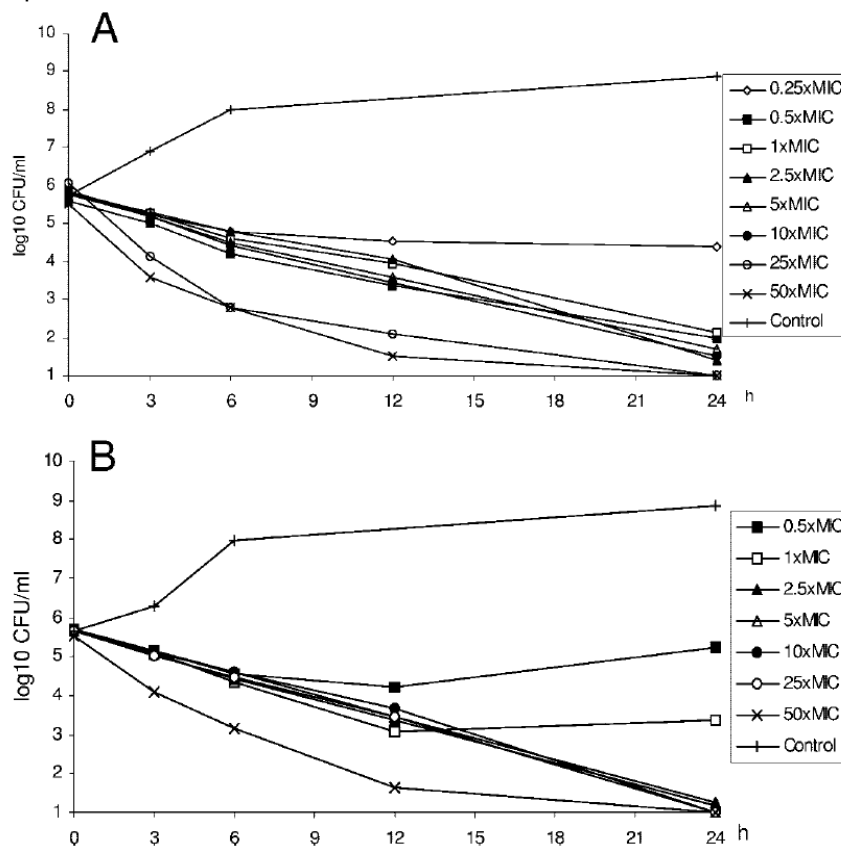
^a HA-MRSA, hospital-associated methicillin-resistant *S. aureus*; CA-MRSA, community-associated methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*

^b CAMHB, cation adjusted Mueller-Hinton Broth; HSA, human serum albumin; HS, human serum; MS, mouse serum

Source: This submission, Section 5.3.5.4.1.6.2.2, Table 2

In a second study [Odenholt 2007], researchers investigated the rate and extent of killing by telavancin in the presence and absence of human serum (4 g/dl) or human albumin (50%). Two *S. aureus* isolates were tested (methicillin susceptible *S. aureus* ATCC 13709 and methicillin-resistant *S. aureus* ATCC 33591). The investigators noted a minimal effect of human serum or human albumin on the killing activity of telavancin. Figure 15 illustrates the killing curves for telavancin against the methicillin-resistant *S. aureus* isolate in broth and in 40 g/liter human albumin.

Figure 15: Killing curves for telavancin against *S. aureus* 33591 (MRSA) in broth (static experiments) (A) and in 40-g/liter human albumin (B). Values shown are means of two experiments



Source: Oldenholt 2007

II. INTRACELLULAR ACTIVITY

In NDA 22-110 the applicant provided data to support the claim of intracellular activity of telavancin against strains of *S. aureus*. The activity appears to be localized in lysosomes and is concentration-dependent, which further supports a claim for enhanced efficacy of the antimicrobial, since phagocytosis of gram-positive cocci (and concomitant intracellular killing) represents a significant strategy in the limitation of the infectious process.

No additional information was provided in the current submission, regarding the intracellular activity of telavancin.

III. ACTIVITY AGAINST BIOFILMS

In NDA 22-110, the Applicant presented data from an investigation of a biofilm model, designed to demonstrate the activity of telavancin against non-planktonic bacterial communities. Data from that investigation supported the claim that telavancin is active in penetrating biofilms, is capable of reducing bacterial counts in in vitro biofilms models, and exceeds the activity of both glycopeptide and some non-glycopeptide comparators in both respects.

In this submission, the Applicant has provided a report from a recent study of the in vitro activity of telavancin and vancomycin against biofilm-producing staphylococcal and enterococcal isolates [LaPlante 2009]. The investigators used the minimal biofilm eradication concentration (MBEC)

assay activity of the two glycopeptides against biofilm-embedded bacteria. Conventional MIC testing was performed using broth microdilution techniques approved by CLSI. All assays were performed in quadruplicate. MBEC was defined as the minimal concentration of antibiotic required to eradicate growth in the 24-hour biofilms. Minimum biofilm inhibitory concentration (MBIC) was also assayed, and was defined as the lowest microbroth dilution with visible growth after incubation in biofilms and antibiotic for 24 hours. Tested bacteria included *S. aureus* ATCC 35556, *S. epidermidis* ATCC 35984, *E. faecalis* ATCC 29212, and three clinical *S. aureus* isolates. In this study, the investigators demonstrated no activity of vancomycin against any of the biofilm-embedded bacteria, with an assayed MBEC of ≥ 512 mcg/ml. The MBEC of telavancin ranged from 0.125 to 2 mcg/ml, with biofilm inhibition demonstrated at concentrations lower than the MIC.

IV. POSTANTIBIOTIC EFFECT

In the NDA 22-110 submission, the applicant supplied data from in vitro investigations that support a 2 – 6 hour postantibiotic effect (PAE) of telavancin against strains of *S. aureus*, including MSSA, MRSA, and VISA. A prolonged PAE was demonstrated against *S. pyogenes* and *S. agalactiae*. PAE against isolates of enterococcus was diminished, compared to the other tested pathogens, but vancomycin-susceptible *E. faecalis* demonstrated notable PAE (1.1 hours).

In this submission, the Applicant has provided a study report from a recent investigation [Pankuch 2009] of the post-antibiotic effect (PAE), the post-antibiotic subMIC effect (PA-SME), and the subMIC effect (SME) of telavancin against a panel of gram-positive pathogens. The tested isolates included 2 hVISA, 4 VISA, 1 VRSA, 1 *S. pyogenes*, 1 *S. agalactiae*, 2 *E. faecalis* (vancomycin-susceptible) and 1 *E. faecium* (vancomycin-susceptible).

PAE was as defined as the time required for counts of an antibiotic exposed culture (initial inoculum 5×10^6 CFU/ml) to increase by 1 log₁₀ after removal of antibiotic by dilution (minus growth control). For PA-SME determination, telavancin was added after dilution to produce sub-inhibitory concentrations of 0.2, 0.3 and 0.4 x MIC. SME determinations included the same addition of telavancin to culture tubes, but did not include the initial exposure to the drug (and no dilution step). The results of the study are summarized in Table 19. The PAE ranges for telavancin against staphylococci, streptococci, and enterococci were 0.9 – 3.9 hours, 0.4 - 6.7 hours, and 0.3 – 2.2 hours, respectively. The PA-SME ranges (at 0.4 x MIC) were 6.7 - >10.7 hours for staphylococci, >10.7 - >11.0 hours for streptococci, and >10 - >10.8 hours for enterococci. The SME ranges (at 0.4 x MIC) were 0.8 – 10.6 hours, 0.4 - >11.0 hours, and 3.6 – 10.0 hours, for staphylococci, streptococci, and enterococci, respectively.

Table 19: PAE, SME and PA-SME of Telavancin against Eleven Staphylococci, Two Streptococci, and Three Enterococci

Organism	MIC (µg/mL)	PAE	Effect (hr)					
			0.2X MIC		0.3X MIC		0.4X MIC	
			SME	PA-SME	SME	PA-SME	SME	PA-SME
MRSA								
ATCC 33591	0.25	1.5, 2.0	0.3, 0.3	7.7, 8.0	1.4, 1.4	>10.0, >10.3	2.3, 3.5	>10.0, >10.3
SA 1130	0.12	1.4, 1.6	0, 0.4	5.4, 5.8	2.0, 4.4	10.0, >10.5	6.5, 6.9	>10.0, >10.5
SA 1307	0.12	1.1, 1.6	1.1, 1.0	6.0, 6.4	2.6, 3.1	>10.5, >10.6	6.3, 6.5	>10.5, >10.6
SA 1316	0.12	1.8, 2.0	0.7, 1.1	2.9, 3.1	5.1, 5.2	5.4, 5.6	6.0, 6.1	>10.7, >10.6
hVISA								
SA618	0.12	1.7, 2.4	0.3, 0.8	5.7, 6.5	1.5, 1.6	8.3, 9.8	2.3, 4.3	10.3, >10.3
SA873	0.12	1.2, 1.6	0, 0.3	3.6, 4.0	0.5, 0.8	4.8, 6.0	1.0, 1.8	6.7, 7.0
VISA								
SA555	0.5	3.4, 3.9	0.3, 0.3	5.9, 6.0	1.7, 2.3	10.3, >10.6	4.3, 5.4	>10.3, >10.6
SA770	0.25	1.6, 2.3	0.7, 0.8	3.8, 5.0	0.8, 1.8	6.3, 8.3	0.8, 1.9	9.6, >10.7
SA1287	0.5	1.2, 1.8	0, 0.3	5.1, 5.2	0.4, 0.7	8.6, 10.0	0.8, 1.2	>10.3, >10.0
SA1984	0.25	0.9, 1.4	1.0, 1.0	6.8, 8.6	2.6, 3.0	>10.0, >10.6	10, 10.6	>10.0, >10.6
VRSA								
SA510	0.5	1.3, 2.0	1.9, 2.5	5.6, 5.8	2.3, 3.1	6.0, 6.6	3.6, 5.0	8.1, 8.8
<i>S. pyogenes</i>	0.06	6.1, 6.7	0, 0	8.7, 10.7	0, 0.4	>10.7, >10.7	0.4, 0.7	>10.7, >10.7
<i>S. agalactiae</i>	0.12	0.4, 1.0	0.2, 0.4	0.8, 2.1	2.1, 2.7	4.7, 6.2	>10.7, >11.0	>10.7, >11.0
<i>E. faecalis</i>	0.25	0.3, 0.7	0.8, 0.7	5.3, 5.8	2.0, 2.8	>10.7, >10.8	3.6, 4.0	>10.7, >10.8
	0.25	1.5, 2.2	0.1, 0.6	3.9, 5.1	2.6, 3.2	7.2, 7.6	9.6, 10.0	>10.6, >10.8
<i>E. faecium</i>	0.12	1.2, 1.6	1.2, 1.8	1.9, 2.2	7.2, 7.7	8.9, 9.3	8.8, 9.9	>10.0, >10.5

Source: This submission, Section 5.3.5.4.1.6.2.4, Table 3

V. EFFECT OF PULMONARY SURFACTANT

In NDA 22-110, the Applicant provided data regarding the activity of the effect of commercially available pulmonary surfactant (Survanta™) on the antimicrobial activity of telavancin (Report 05-6424-MB-03). In an investigation using standard checkerboard methodology, no antagonism of telavancin activity was observed at concentrations up to 1 mg/ml pulmonary surfactant. Of the other glycopeptide antimicrobials tested, vancomycin and teicoplanin also demonstrated no antagonism, while daptomycin was inhibited up to 32-fold against *S. aureus* isolates and 128-fold against *S. pneumoniae* isolates.

VI. ANTIMICROBIAL ACTIVITY OF PRIMARY HUMAN METABOLITES

The Applicant has provided the study report (Report 07-6424-MCB-01) from an investigation designed to describe the in vitro antimicrobial activity of the primary human metabolites of telavancin; AMI-11352, AMI-11353, and AMI-11355. CLSI broth microdilution techniques were used to determine the MICs of a panel of gram-positive pathogens that included reference strains and recent clinical isolates. The results of the investigation are summarized in Table 20. The in vitro activity of the primary telavancin metabolites were similar, and were each ≥ 8-fold higher than that of telavancin.

Table 20: MIC Values of Telavancin, AMI-11352, AMI-11353, AMI-11355, and Vancomycin

Organism	Isolate	MIC (µg/mL)				
		Telavancin	AMI-11352	AMI-11353	AMI-11355	Vancomycin
<i>S. aureus</i>	ATCC 29213	0.5	4	4	8	1
<i>S. aureus</i>	ATCC 33591	0.5	8	8	8	2
<i>E. faecalis</i>	ATCC 29212	0.5	16	16	16	4
<i>S. pneumoniae</i>	ATCC 49619	≤0.03	1	2	2	0.5
<i>S. agalactiae</i>	MED 2038	0.25	4	4	4	1
<i>S. pyogenes</i>	MED 2040	0.125	1	2	2	0.5

Source: This submission, Section 5.3.5.4.1.6.2.1, Table 1

Miscellaneous Studies ~ Conclusions:

Telavancin is approximately 90% protein bound, primarily by albumin. Studies presented in this Application and in NDA 22-110 indicate that telavancin retains in vitro activity against the principle respiratory pathogens sought in the proposed indication, in the presence of albumin or human serum. Recent studies also suggest that telavancin activity is not inhibited by pulmonary surfactant. Telavancin is active against isolates of *S. aureus* in stationary growth phase, and has demonstrated activity against isolates of *S. aureus*, *S. epidermidis*, and *E. faecalis* in a biofilm model. The postantibiotic effect of telavancin, against isolates of *S. aureus* (including methicillin-susceptible and –resistant isolates, as well as vancomycin-non-susceptible isolates) ranges from one to six hours. The antimicrobial activity of the three primary telavancin metabolites (AMI-11352, AMI-11353, and AMI-11355) is ≥ 8-fold higher than that of telavancin.

BACTERICIDAL ACTIVITY

I. Minimum Bactericidal Concentration Studies



The Applicant has provided no new data in this submission from studies using the MBC method to describe the bactericidal activity of telavancin.

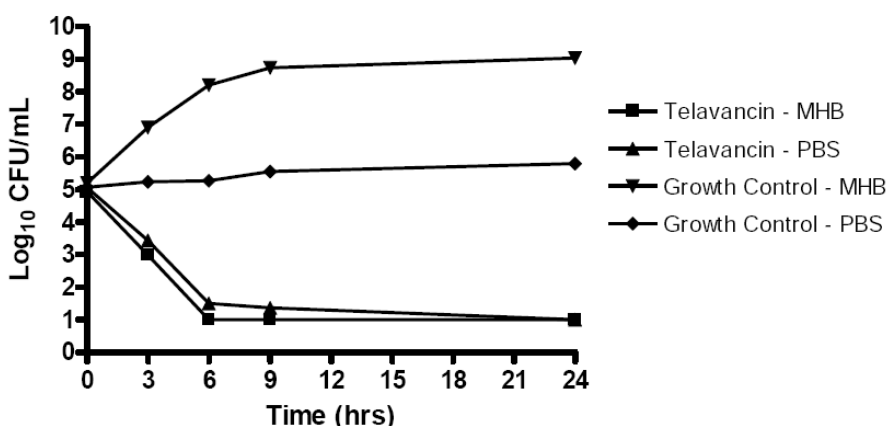
II. Time-kill Studies

In NDA 22-110, the applicant submitted data from time-kill kinetic studies to support a claim of bactericidal activity of telavancin against a variety of *S. aureus* isolates, including isolates susceptible and non-susceptible to methicillin, and isolates non-susceptible to vancomycin. This activity generally occurs at low multiples of the MIC and at concentrations consistent with therapeutic levels, even at trough concentrations. Bactericidal activity against tested isolates of *S. pneumoniae* (bactericidal at ≤ 2 x MIC, or up to 0.06 mcg/ml), and β-hemolytic streptococci (*S. pyogenes* and *S. agalactiae*) was also demonstrated. At low fixed concentrations activity against the β-hemolytic streptococci was variable (i.e. concentrations representing C_{min} for vancomycin in healthy adults dosed at 10 mg/kg). Telavancin demonstrated modest bactericidal activity against isolates of enterococcus, with killing occurring only at high drug concentrations. Telavancin bactericidal activity against enterococci was superior to comparators, though, in most cases.

The Applicant has provided study reports from two investigations of the bactericidal activity of telavancin against *S. aureus* isolates in a stationary growth phase.

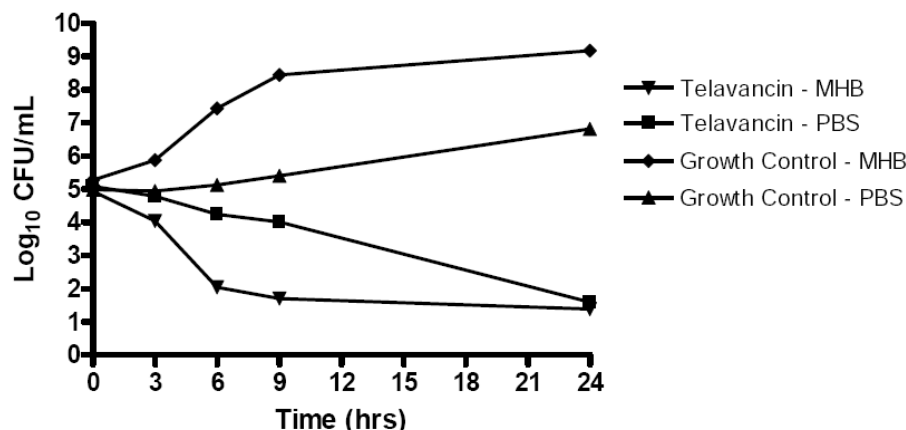
In the first study [Odenholt 2007], investigators tested the bactericidal activity of telavancin against *S. aureus* isolates in both exponential and stationary growth phases by testing isolates in either nutrient-rich or –depleted media. Tested isolates included a methicillin-resistant strain (ATCC 33591) and a methicillin-susceptible strain (ATCC 13709). The results of the investigation are summarized in Figures 15 and 16. For the methicillin-susceptible isolate, complete killing was demonstrated in both types of media within 6 hours (Fig 16). For the methicillin-resistant isolate (Fig 17), the initial killing rate against the isolate grown in nutrient broth was higher than that grown in saline, but complete killing was observed against both isolates within 24 hours.

Figure 16: Time-kill Plots Comparing the Activity of 10x MIC (10 µg/mL) Telavancin against Exponential and Stationary Phase of Methicillin-susceptible *S. aureus* ATCC 13709



Source: This submission, Section 5.3.5.4.1.5.3.1, Figure 1

Figure 17: Time-kill Plots Comparing the Activity of 10x MIC (10 µg/mL) Telavancin against Exponential and Stationary Phase of Methicillin-resistant *S. aureus* ATCC 33591

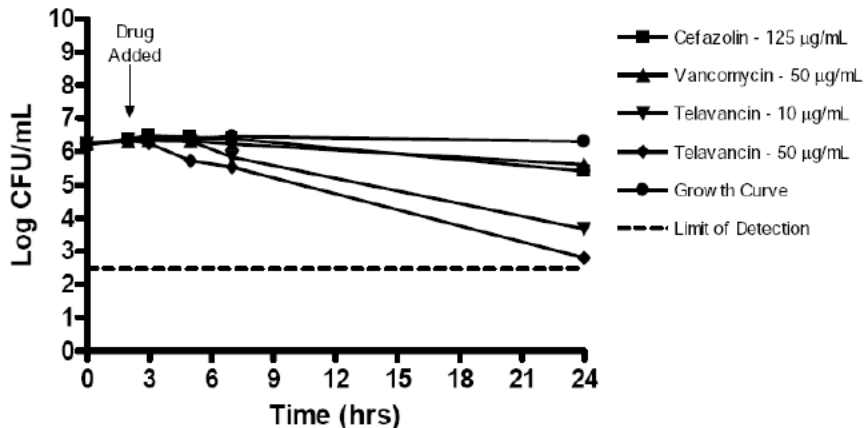


Source: This submission, Section 5.3.5.4.1.5.3.1, Figure 2

In the second study [Clouse 2007], investigators described the bactericidal activity of telavancin and comparators against isolates of methicillin-susceptible and –resistant *S. aureus* in peritoneal dialysate fluid (PDF), a nutrient-poor medium with bacteriostatic activity. Sixteen duplicate concentration-time-kill experiments were conducted in commercially obtained PDF, to compare killing rates of the antimicrobials. The results of the investigation are summarized in Figures 18

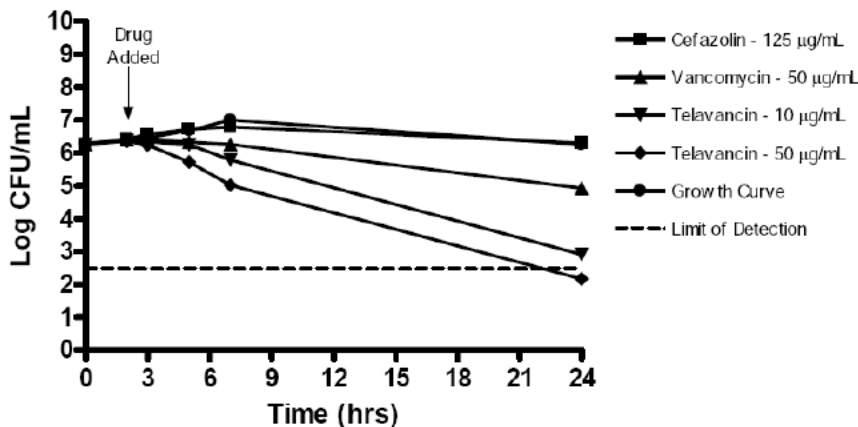
and 19. Telavancin, at both 10 mcg/ml and 50 mcg/ml exhibited statistically better kill ($P < 0.05$) than cefazolin and vancomycin against both staphylococcal isolates, with more rapid killing observed in the 50 mcg/ml telavancin determination (compared to the 10 mcg/ml concentration).

Figure 18: Time-kill Plots Comparing the Activity of Telavancin, Vancomycin and Cefazolin in Peritoneal Dialysis Fluid against Methicillin-susceptible *S. aureus* (ATCC 29213)



Source: This submission, Section 5.3.5.4.1.5.3.1, Figure 3

Figure 19: Time-kill Plots Comparing the Activity of Telavancin, Vancomycin and Cefazolin in Peritoneal Dialysis Fluid against Methicillin-resistant *S. aureus* (ATCC 33592)



Source: This submission, Section 5.3.5.4.1.5.3.1, Figure 4

Bactericidal Activity ~ Conclusions:

The Applicant has submitted data, in NDA 22110 and this Application, from time-kill kinetic studies to support a claim of bactericidal activity of telavancin against a variety of strains of *S. aureus*, including methicillin-susceptible and -resistant phenotypes, as well as isolates non-susceptible to vancomycin, and against isolates of *S. pneumoniae*. This activity generally occurs at low multiples of the MIC and at concentrations consistent with therapeutic levels, even at trough concentrations.

(b) (4)

HUMAN AND ANIMAL STUDIES

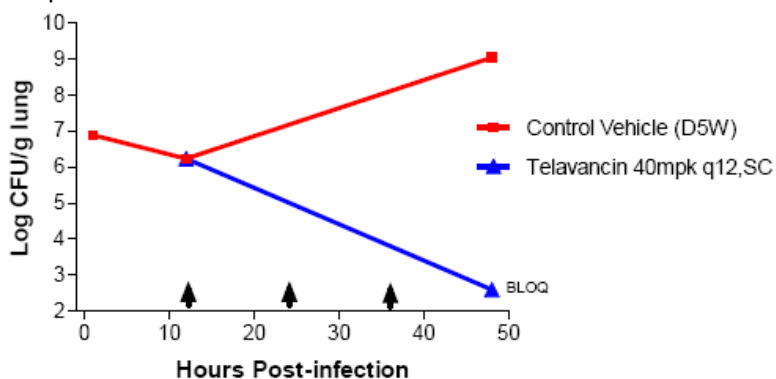
ANIMAL DISEASE MODELS

In NDA 22-110, the Applicant submitted data from a variety of animal models, including the mouse neutropenic thigh (MNT) model, murine subcutaneous infection (MSI) model, endocarditis infection model, pneumonia infection model, bacteremic infection model, and meningitis infection model. Data from animal in vivo studies supported the use of $AUC_{(0-24)}/MIC$ as the best PK/PD predictor of antimicrobial efficacy for unbound (free) telavancin. Comparison of data from the MNT and MSI models suggested that immune status may play a minor role in telavancin efficacy.

In this submission, the Applicant has provided study reports from four additional studies, including a neutropenic mouse pneumonia model, a neutropenic mouse bacteremia model, a rabbit chronic osteomyelitis model, and a mouse acute suppurative osteomyelitis model.

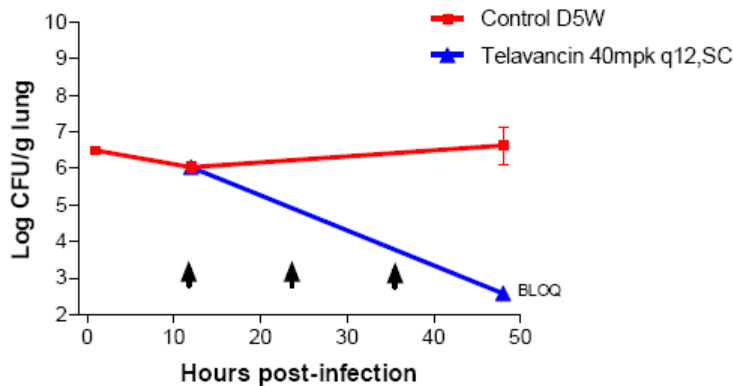
In a neutropenic mouse pneumonia model (Report 08-6424-PH-03), female BALB/c mice were rendered neutropenic, and inoculated nasally with 50 μ l (log 6.7-6.9 CFU/mL) of either *Streptococcus pneumoniae* MED 45 (penicillin-nonsusceptible) or *S. pneumoniae* MED 306 (penicillin-susceptible). Mice were dosed three times, subcutaneously (40 mg/kg q 12 hr), starting 12 hours after inoculation. The mice were euthanized at 48 hours, and lung titers were determined. The results of the study are summarized in Figures 19 and 20. The telavancin MIC against both isolates was 0.12 mcg/ml. Against *S. pneumoniae* MED 45, telavancin produced a 3.65 log CFU/g reduction in lung bacteria, with no deaths in the telavancin-treated group (1/6 mice in the control group died). Against *S. pneumoniae* MED 306, telavancin produced a 3.45 log CFU/g reduction in lung bacteria (there were no deaths in either the telavancin or control treatment group).

Figure 20: Efficacy of Telavancin (TLV) Against *S. pneumoniae* Strain MED 45 in the Neutropenic Murine Pneumonia Model



Arrows denote the time of dosing
Source: This Submission; Report 08-6424-PH-03, Figure 1

Figure 21: Efficacy of Telavancin (TLV) Against *S. pneumoniae* Strain MED 306 in the Neutropenic Murine Pneumonia Model



Arrows denote the time of dosing

Source: This Submission; Report 08-6424-PH-03, Figure 2

The in vivo efficacy of telavancin against *S. aureus* isolates with reduced susceptibility to vancomycin was studied in a neutropenic mouse bacteremia model (Report 08-6424-PH-01). In this study, female NSA mice were rendered neutropenic and inoculated with bacteria intraperitoneally. Test isolates included VISA HIP5836, VISA Mu50, and hVISA Mu3. Animals were dosed twice (at 4 and 16 hours post-infection) with either telavancin (40 mg/kg, SC, q 12 hours) or vancomycin (110 mg/kg, SC, q 12 hours). Control animals were dosed once, 4 hours post-infection, with vehicle. Designated test animals were euthanized at 12, 24, and 48 hours post-treatment. Control animals were euthanized at 0, 4, and 16 hours post-treatment. Bacterial counts were performed on blood and spleen tissue. The results of the study are summarized in Table 21. In this investigation, telavancin was more active than vancomycin in reducing the blood and spleen titers of all three vancomycin-nonsusceptible *S. aureus* isolates.

Table 21: Minimum Inhibitory Concentrations (MIC) and Blood/Spleen Counts

<i>S. aureus</i> Isolate	MIC (µg/mL)	Blood (log CFU/mL)*	Spleen (log CFU/g)*
HIP5836			
Pre-treatment titre	—	5.5 ± 0.41	8.0 ± 0.24
Vancomycin	8	3.6 ± 0.69	7.7 ± 0.49
Telavancin	1	1.0 ± 0.0 [†]	3.8 ± 0.16 [†]
Untreated	—	6.5 ± 0.21	9.4 ± 0.13
Mu50			
Pre-treatment titre	—	3.6 ± 0.20	7.2 ± 0.13
Vancomycin	8	2.6 ± 0.99	6.1 ± 0.73
Telavancin	0.5	1.0 ± 0.0 [†]	3.2 ± 0.33 [†]
Untreated	—	5.5 ± 0.69	8.4 ± 0.38
Mu3			
Pre-treatment titre	—	4.4 ± 0.28	7.3 ± 0.20
Vancomycin	2	4.5 ± 0.79	7.5 ± 0.33
Telavancin	0.25	1.0 ± 0.0 ^{††}	3.1 ± 0.14 ^{††}
Untreated	—	5.9 ± 0.54	8.9 ± 0.19

CFU, colony-forming units; MIC, minimum inhibitory concentration

*Titre at the onset of treatment (pre-treatment titre); at 48 h after treatment initiation (for telavancin- or vancomycin-treated animals), or at 12 h after the initiation of treatment (for untreated animals; no untreated animals survived beyond this time point)

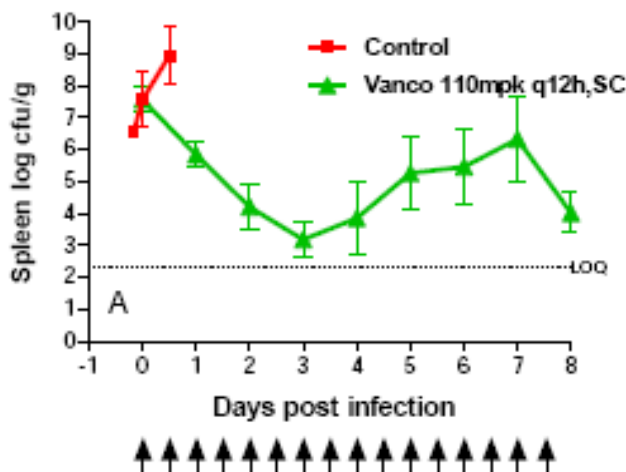
[†]P<0.05 vs. pre-treatment titre and vancomycin

^{††}P<0.05 vs. pre-treatment titre

Source: this Submission; Reports 08-6424-PH-01, Table 1

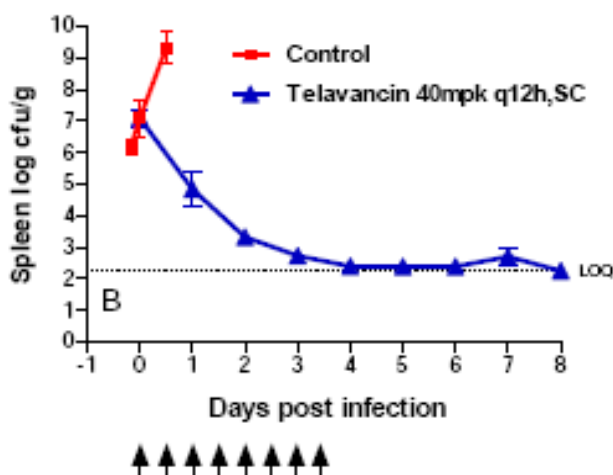
In a second study using the neutropenic mouse bacteremia model, investigators compared the efficacy of sub-chronic treatment with telavancin and vancomycin (Report 08-6424-PH-02). Female NSA mice were rendered neutropenic and inoculated intraperitoneally with *S. aureus* Mu3 (hVISA). Mice were treated (4 hours post-inoculation) with either telavancin (40 mg/kg, q 12 hr, SC for 4 days) or vancomycin (110 mg/kg, q 12 hr, SC for 8 day). A third group received no treatment. Animals (groups of 5) were euthanized at pre-treatment and at 24 hour intervals for 8 days. Figures 22 and 23 summarize spleen titer results for the two treatment protocols. Telavancin reduced titers by Day 3, with sustained reduction for the test period. Vancomycin initially reduced titers, but an upsurge was noted between Days 3 and 7. Vancomycin-treated mice remained bacteremic throughout the test period, while no telavancin-treated animals were bacteremic after Day 1.

Figure 22: Efficacy of 8-day Treatment with Vancomycin on Spleen titres in the Neutropenic Murine Bacteremia Model of *S. aureus* Mu3 (hVISA) infection



Source: This submission, Section 5.3.5.4.1.9.2.2, Figure 2

Figure 23: Efficacy of 8-day Treatment with Telavancin on Spleen titres in the Neutropenic Murine Bacteremia Model of *S. aureus* Mu3 (hVISA) infection



Source: This submission, Section 5.3.5.4.1.9.2.2, Figure 2

Animal Disease Models ~ Conclusions:

The applicant has submitted data from animal in vivo studies that supports the use of $AUC_{(0-24)}/MIC$ as the best PK/PD predictor of antimicrobial efficacy for unbound (free) telavancin. Data from neutropenic mouse thigh models suggest that a $AUC_{(0-24)}/MIC$ ratio of 219 results in a one log₁₀ reduction in CFU/g against methicillin-resistant *S. aureus* with an MIC of 1 mcg/ml. Animal models of infection suggest that immune status may play a minor role in telavancin efficacy.

PHARMACOKINETIC / PHARMACODYNAMIC STUDIES

The pharmacokinetics of telavancin was investigated in eleven clinical pharmacology studies (data and summaries submitted in NDA 22-110). Telavancin pharmacokinetics was approximately linear up to a dose of 12.5 mg/kg in healthy volunteers. Peak and trough concentrations, following a single 10 mg/kg dose, were 105 ± 12 mcg/ml and 8.02 ± 1.84 mcg/ml, respectively. Following repeated doses (10 mg/kg every 25 hours for 3 days) the mean plasma C_{max} was 116 ± 30 mcg/ml (trough concentrations were 8.11 ± 2.28 mcg/ml). The primary elimination route for telavancin is by renal clearance.

Studies included the antibacterial activity of primary metabolites. Additional studies, describing the activity of the three primary human metabolites of telavancin were submitted in this application and are reviewed above.

In NDA 22-110, the Applicant provided data from a variety of studies to support the proposed pharmacokinetic parameters. Monte Carlo simulation, based on the proposed dosage (10 mg/kg) support a susceptible breakpoint as high as 2 µg/ml (based on > 99% target attainment at that concentration).

Since submission of NDA 22-100, the Applicant conducted a Phase 1 study to determine the steady-state concentrations of telavancin in alveolar macrophages, epithelial lining fluid (ELF), and plasma. The study enrolled 20 healthy volunteers, each of who received 3 daily 10mg/kg doses. Specimens were collected by bronchoscopy on Day 3 at 4, 8, 12 or 24 hours post-infusion (five subjects sampled at each collection time). The mean concentrations in ELF were 3.73 mcg/ml at 8 hours, 1.77 mcg/ml at 12 hours, and 0.89 mcg/ml at 24 hours. The concentration in alveolar macrophages exceeded 10 mcg/ml at all time points.

In another investigation of telavancin PK in human epithelial lining fluid [Lodise 2008], population modeling and Monte Carlo simulation were employed to estimate the penetration of telavancin into the ELF. Plasma and ELF PK data were obtained from 20 healthy volunteers. Concentration-time profiles were modeled using a three-compartment model. Monte Carlo simulation of 9,999 subjects was used to estimate the AUC_{ELF} and free drug in plasma AUC_{plasma} and to calculate an ELF/plasma penetration ratio. The investigators determined that in uninfected lung tissue, the median AUC_{ELF} is approximately 75% of the free AUC_{plasma} . While these data suggest that telavancin penetrates into ELF in non-infected lung tissue, it is unclear whether these levels are comparable in diseased tissue, or whether the observed concentration is sufficient for inhibition of the target pathogens.

Pharmacokinetic / Pharmacodynamic Studies ~ Conclusions:

In NDA 22-110, the Applicant provided data from a variety of studies to support the proposed pharmacokinetic parameters. Monte Carlo simulation, based on the proposed dosage (10 mg/kg) supports a susceptible breakpoint as high as 2 µg/ml (based on > 99% target attainment at that concentration). Additional information, provided in this Application, suggests that telavancin is concentrated in human alveolar macrophages (exceeding 10 mcg/ml) and that the AUC of the antimicrobial in epithelial lining fluid (in uninfected lung tissue) is approximately 75% that of

AUC_{plasma}

CLINICAL TRIALS

Previous Complicated Skin and Skin Structure Infection Studies

NDA 22-110 included data from pivotal clinical trials (Studies 202a, 202b, 0017, and 0018). Each of the studies was a double-blind, randomized, active-controlled comparison of telavancin with standard therapy. Exclusions included infections with vancomycin-resistant enterococcal species (VRE). Phase 2 comparators included an anti-staphylococcal penicillin or vancomycin. Vancomycin was the sole comparator in Phase 3 trials. Initial dosing in the clinical trials was set at 7.5 mg/kg IV. Based on pharmacokinetic/pharmacodynamic data and Monte Carlo simulation, the dosage was increased to 10 mg/kg IV. The 202b (Post Amendment) study, and the two Phase 3 trials studied telavancin at the 10 mg/kg dose. The clinical microbiology review of that application was based on the Post Amendment Study 202b and the two ATLAS studies (0017 and 0018). Data from post-amendment clinical trials indicated that telavancin is efficacious in infections involving pathogens in the proposed indication [complicated skin and skin structure infections caused by *S. aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group, and vancomycin-susceptible *Enterococcus faecalis*]. Isolates analyzed from the ME population were primarily gram-positive pathogens, and were recovered mainly from major abscesses, deep/extensive cellulitis, and wound infections. Similar eradication rates, for organisms in the proposed indication, were seen in the telavancin-treated population and the vancomycin-treated population. Telavancin was active against certain specific resistant phenotypes (e.g. methicillin-resistant *S. aureus*), but study design prohibited the observation of activity against vancomycin-resistant phenotypes (e.g. vancomycin-resistant *S. aureus*, vancomycin-resistant enterococcus species). Incidence of superinfection and colonization, developed in the course of those clinical trials, was low.

Hospital Associated Pneumonia Studies

In the current submission, the Applicant has submitted data from two Phase 3 studies that were designed to compare the safety and efficacy of telavancin and vancomycin in the treatment of hospital associated pneumonia (HAP) due to a confirmed gram-positive pathogen. The study was enriched for methicillin-resistant *S. aureus*-associated HAP by enrollment of subjects with known risk factors (including nursing home admissions, hospitalization within the previous 6 months, prior MRSA infection, antibiotic treatment within the previous 3 months, and geographic prevalence).

The two Phase 3 trials, Study 0015 and Study 0019, were given the acronym ATTAIN. The studies were double-blind, randomized, active controlled, noninferiority trials, comparing telavancin 10 mg/kg IV q 24 hours with standard therapy (vancomycin 1 g IV q 12 hours) (Table 21). Subjects were treated for a minimum of 7 days and a maximum of 21 days. The initial noninferiority margin was 20% for the primary endpoint of clinical responses at Test of Cure (TOC). Post hoc analysis included determination of a mortality endpoint and a post hoc clinical noninferiority margin of 14%. The two studies were analyzed separately and as pooled data. Other efficacy parameters included by-patient microbiological response at the Follow-up Visit (TOC), by pathogen microbiological response at TOC, and clinical response at the End-of-Therapy (EOT) visit. The criteria for efficacy evaluations are summarized in Table 23. The criteria for evaluating microbiologic response are summarized in Table 24. Inclusion criteria included "identification of an organism consistent with a respiratory pathogen isolated from cultures of respiratory tract, sputum, or blood samples."

Aztreonam and/or metronidazole could be added for treatment of gram-negative aerobes and facultative pathogens, and for anaerobic bacteria. Nafcillin could be substituted for vancomycin in cases where *S. aureus* was identified as the principle pathogen and was found susceptible to

oxacillin. Subjects were considered to have received adequate therapy if antibiotics with in vitro activity against all gram-negative isolates recovered at the baseline visit, was administered from Study Day 1 through end of therapy. Subjects with no baseline pathogens were considered to have received inadequate gram-negative therapy if they 1) never received at least one antibiotic with in vitro gram-negative activity, or 2) did not receive at least one antibiotic with in vitro gram-negative activity until Study Day 3 or later.

The study population analysis definitions are summarized in Table 22. The All Treated (AT) population included 1503 subjects (749 randomized to telavancin, 754 randomized to vancomycin). The Modified All-Treated (MAT) population included 1089 subjects (560 randomized to telavancin, 529 randomized to vancomycin). The Clinically Evaluable (CE) population included 44% of the subjects in the AT population (654 subjects, with 312 randomized to telavancin, 342 randomized to vancomycin). The Microbiologically Evaluable (ME) population included 480 subjects (243 randomized to telavancin, 237 randomized to vancomycin). Demographics were well balanced in compared analysis populations. The majority of subjects were 65 years of age or older, and the majority (58%) were in the ICU at Baseline. Comorbidities, including congestive heart failure, diabetes, and hypertension, were common in all analysis populations.

Table 21: Completed Efficacy and Safety Studies of Telavancin in Hospital-acquired Pneumonia

Type	ID	Title	Objective	Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Treated Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Tx	Study Status
Efficacy	0015	A Phase 3, Randomized, Double Blind, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Hospital-acquired Pneumonia with a Focus on Patients with Infections Due to Methicillin-Resistant <i>Staphylococcus aureus</i>	Efficacy and Safety	Double blind, randomized active-controlled	Telavancin for injection, 10 mg/kg IV q 24h	372	Gram-positive pneumonia acquired while residing in a health care facility	7 to 21 days	Complete
					Vancomycin 1 g IV q 12hr	374			
Efficacy	0019	A Phase 3, Randomized, Double Blind, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Hospital-acquired Pneumonia with a Focus on Patients with Infections Due to Methicillin-Resistant <i>Staphylococcus aureus</i>	Efficacy and Safety	Double blind, randomized active-controlled	Telavancin for injection, 10 mg/kg IV q 24h	377	Gram-positive pneumonia acquired while residing in a health care facility	7 to 21 days	Complete
					Vancomycin 1 g IV q 12hr	380			

Source: This submission, Section 5.3.5.4.1.10.3, Table 8

Table 22: Definition of Analysis Populations in Studies 0015 and 0019

Analysis Population	– Definition
All-treated (AT)	– All patients who receive any amount of study medication.
Modified All-treated (MAT)	– All patients in the AT Population who also have a baseline pathogen identified, defined as an organism known to cause pneumonia identified from baseline respiratory cultures from sputum, endotracheal aspirate (ETA), blind bronchial suctioning (BBS), bronchoalveolar lavage (BAL), mini-BAL, or protected specimen brush (PSB). If baseline respiratory cultures did not identify a respiratory pathogen (or if baseline respiratory cultures were not available), then an organism known to cause pneumonia that was identified from baseline blood cultures would qualify a patient for the MAT Population..
Clinically Evaluable (CE)	All patients in the AT Population (1) whose adherence to protocol expectations makes it reasonable to infer that his/her clinical outcome reflects the effect of study medication, or (2) who died on or after Study Day 3, where the death is attributable to the HAP episode under study. To be deemed to have adhered to protocol expectations, and on that basis be included in the CE Population, a patient must meet the following criteria: - o Patient complied with the following <u>inclusion criteria</u>: • #2, which requires certain clinical signs and symptoms consistent with pneumonia • #3, which requires a chest radiograph consistent with the diagnosis of pneumonia • #4, which requires the availability of appropriate specimens for Gram stain and culture, and venous access for dosing. - o Patient did not violate the following <u>exclusion criteria</u> (or was approved for enrollment by the Medical Monitor): • #1, which excludes patients who have received more than a specified amount of potentially effective systemic antibiotic therapy for Gram-positive pneumonia immediately prior to randomization. • #2, which excludes patients with respiratory tract specimens or sputum with only Gram-negative bacteria. • #3, which excludes patients with MSSA or <i>S. pneumoniae</i> who also require more than a specified amount of concomitant antibiotic therapy for Gram-negative coverage that has activity versus MSSA or <i>S. pneumoniae</i>. • #4, which excludes patients with known or suspected pulmonary disease that precludes evaluation of therapeutic response, cystic fibrosis, or active tuberculosis. • #5, which excludes patients with known or suspected <i>Legionella pneumophila</i> pneumonia. • #6, which excludes patients who are known or suspected to be infected with an organism that is not susceptible to medications permitted by the protocol. • #7, which excludes patients with documented or suspected meningitis, endocarditis, or osteomyelitis. - o Patient did not have pneumonia due to <i>Stenotrophomonas maltophilia</i> or <i>Burkholderia cepacia</i> at Baseline. - o Patient did not have a persistent <i>S. aureus</i> bacteremia. - o If the patient received prior (i.e., pre-study) treatment with vancomycin or teicoplanin, the patient was not a treatment failure to that treatment. - o The patient was treated with the study medication assigned by the randomization.
Analysis Population	– Definition
	- o The patient received at least 80% of intended doses of active study medication. - o The patient did not receive potentially effective concomitant systemic antibiotic therapy for more than 2 calendar days. - o Patient was a "failure" at EOT, or else was either a "cure" or a "failure" at TOC. - o If the patient was a "failure" at EOT, then the EOT assessment was made between Study Day 0P and Study Day 5P inclusive. Otherwise, the TOC assessment was made between Study Day 6P and Study Day 28P inclusive. - o If the patient was a "cure," the patient received study medication daily through Study Day 5. - o If the patient was a "failure," the patient received study medication daily through Study Day 3."
Microbiologically evaluable	All patients in the CE Population who also had a baseline Gram-positive pathogen recovered from respiratory specimens or blood cultures. Note that the ME Population is a subset of both the MAT and CE Populations.

Source: This submission, Section 5.3.5.4.1.10.3, Table 9

Table 23: Criteria for Efficacy Evaluation in Studies 0015 and 0019

Response ¹	Criteria
Clinical Response at End-of-Therapy	
Failure:	At least one of the following: - Persistence or progression of signs and symptoms of pneumonia that still require antibiotic therapy - Termination of study medication due to "lack of efficacy" and initiation within 2 calendar days of therapy with a potentially effective anti-staphylococcal medication - Death on or after Day 3 attributable to primary infection
Cure:	- Investigator determined that signs and symptoms of pneumonia improved to the point that no further antibiotics for pneumonia are required, and - Baseline radiographic findings improved or did not progress
Indeterminate:	Inability to determine outcome
Clinical Response at Test-of-cure evaluation (unless a failure at End of Therapy)	
Failure:	At least one of the following: - Relapsed pneumonia with the same Gram-positive organism after termination of study medication - Death after the end of study medication therapy attributable to primary infection (i.e., pneumonia)
Cure:	- Signs and symptoms of pneumonia resolved, and - Baseline radiographic findings improved or did not progress
Indeterminate:	Inability to determine outcome

¹ Protocol outcome designation

Source: This submission, Section 5.3.5.4.1.10.3, Table 10

Table 24: Microbiological Response By-Patient and By-Pathogen in Studies 0015 and 0019

Response ¹	Criteria
Microbiological Response By-Patient	
Patients with one or more pathogens isolated at Baseline were assigned a By-Patient Microbiological Response at the Follow-up visit.	
The following preliminary categorizations were made for each culture within the specified evaluation's analysis window:	
Eradicated	All baseline respiratory pathogens were eradicated (confirmed or presumed), no superinfection, and no new infection; colonization may be present and a Clinical Response of "Success".
Persisted ²	At least one baseline respiratory pathogen was present (confirmed or presumed), and a Clinical Response of "Failure".
Indeterminate:	No culture data were available, and Clinical Response of "Indeterminate".
Missing	No culture data were available, and Clinical Response was "Missing".
Microbiological Response By-Pathogen	
By-Pathogen Microbiological Response was to be determined at the Follow-up visit only for Gram-positive pathogens isolated at the baseline evaluation from an appropriate source.	
Preliminary categorization of each culture within the specified evaluation's analysis window was to be done as follows:	
Confirmed Eradicated	The absence of the given baseline pathogen from the culture, or "No Growth" was recorded on the CRF. (Blood cultures were either negative or not available)
Presumed Eradicated ⁴	No respiratory tract culture data were available, and a Clinical Response of "Cure".
Confirmed Persisted ³	At least one baseline pathogen was documented as present from either the respiratory tract cultures or blood cultures.
Presumed Persisted ³	No respiratory tract culture data were available, and a Clinical Response of "Failure".
Indeterminate:	No respiratory tract culture data were available, and a Clinical Response of "Indeterminate".
Missing	No respiratory tract culture data were available, and Clinical Response was "Missing".
Potential Superinfection	Respiratory pathogen was isolated from respiratory tract cultures during the course of treatment. ³

¹ Microbiological response correlated to clinical response: Eradicated = Cure; Persisted = Failed

² For analysis, Eradicated or Presumed Eradicated was considered "Eradicated".

³ For analysis, Persisted or Presumed Persisted was considered "Persisted". Baseline pathogens were also categorized by susceptibility to study medication (i.e., development of resistance).

⁴ "Colonization" was not distinguished from "Infection" for pathogens identified post-baseline in these studies.

Source: This submission, Section 5.3.5.4.1.10.3, Table 11

Microbiological evaluation included pre-treatment baseline collection of respiratory specimens (BAL, mini-BAL, protected specimen brush (PSB), blind bronchial suction (BBS), or endotracheal aspirate (ETA) for culture and Gram stain, blood culture (x2), and urinary antigen testing for *Legionella pneumophila*. Respiratory specimens were graded for adequacy based on the presence of > 25 polymorphonuclear leukocytes and < 10 epithelial cells per high power field (100 x magnification). Collection of respiratory specimens was repeated on Day 4, if clinically indicated. Blood cultures were repeated if the initial cultures were positive or if clinically indicated. Initial processing and culture of specimens, as well as Gram stain interpretation, was performed by the local laboratory. The studies focused on "respiratory pathogens", including all species sought in the proposed indication, including isolates collected by respiratory and blood culture, and bacteria identified by urinary antigen testing. Any isolate recovered from blood culture was considered a "pathogen." If blood culture isolates differed from respiratory isolates, the respiratory isolate was considered the baseline pathogen. If no respiratory pathogens were isolated at baseline, but blood cultures were positive, the blood culture isolate was considered the baseline pathogen. Multiple baseline pathogens were allowed for analysis purposes. If more than one resistance phenotype of a particular species was identified at baseline, all were tracked separately for eradication analysis.

Isolates recovered in culture were sub-cultured and sent to (b) (4) for identification to species level and susceptibility testing (by both MIC and disk diffusion methods). Isolates collected in South Africa, Europe and Russia were tested in the (b) (4) laboratory in (b) (4). Isolates collected in all other countries were tested in the (b) (4) laboratory in (b) (4). Staphylococcus aureus isolates (methicillin-susceptible and -resistant) were shipped to (b) (4) for Panton-Valentine Leukocidin (PVL) screening.

Isolates were identified at (b) (4) primarily by automated methods, employing the Vitek System (bioMerieux, Durham, NC). Susceptibility testing was performed by both the MIC and disk diffusion methods.

Three different MIC panel formats were utilized, using methods approved by CLSI for broth microdilution testing. All isolates were subcultured to trypticase-soy agar + 5% sheep blood, 18-24 hours before testing. Isolates were suspended in cation adjusted Mueller-Hinton broth (without polysorbate 80), and adjusted to a concentration of approximately 5×10^4 CFU/ml. Panels were incubated at 35°C in ambient atmospheric conditions, and read at 16-20 hours (streptococcal susceptibility panels were incubated for 20-24 hours).

For disk diffusion susceptibility determinations, the Kirby-Bauer method was employed, according to methods approved by CLSI. Mueller-Hinton agar plates were swabbed with approximately 10^8 CFU/ml of the isolate (5% sheep blood was added to the Mueller-Hinton agar, for testing of streptococcal isolates). Plates were incubated in ambient atmospheric conditions at 35°C for 16-18 hours (streptococcal isolates were incubated in 5-7% CO₂ for 20-24 hours).

All bacterial isolates were cryo-preserved by the central testing laboratory.

STUDY 0015

Study 0015 enrolled the first subject on 8 February 2005 and the last visit was completed on 11 July 2007. There were 761 subjects randomized at 201 centers (381 in the telavancin arm and 380 in the vancomycin arm), and 746 subjects treated. The original protocol for Study 0015 allowed imipenem for gram-negative coverage, as well as aztreonam and/or metronidazole. In order to limit potential bias, possibly resulting from the synergistic activity of linezolid with the glycopeptides, use of linezolid was removed in Protocol Amendment 1.

Acute renal failure was more prevalent in subjects randomized to the telavancin group (9% vs. 5% in the vancomycin group). Approximately 27% of subjects enrolled in Study 0015 met the definition of having ventilator-associated pneumonia. Demographics were generally balanced between the two arms of the study.

Table 25 summarizes the number of Study 0015 subjects analyzed by treatment group.

Table 25: Summary of patients included in each Study 0015 analysis population by treatment group

	Telavancin 10 mg/kg Number (%) of Patients [1]	Vancomycin
Randomized	381	380
Safety (As-treated)	372	374
Efficacy Populations (As-randomized)		
All-treated (AT)	372 (100%)	374 (100%)
Modified All-treated (MAT)	257 (69%)	247 (66%)
Clinically Evaluable (CE)	141 (38%)	172 (46%)
Microbiologically Evaluable (ME)	108 (29%)	113 (30%)
ME as Percent of CE	77%	66%

[1] Percentages are calculated relative to the number of patients treated (AT)

AT – all patients who received at least one dose of study medication.

MAT – those AT patients who had a respiratory pathogen isolated at Baseline.

CE – those AT patients whose adherence to the protocol made it reasonable to infer that their clinical response reflected the effect of the study medication

ME – those CE patients who had at least one Gram-positive pathogen that was associated with pneumonia

Source: This submission; Module 2.7.6.3, page 10

STUDY 0019

Study 0019 enrolled the first subject on 23 January 2005 and the last visit was completed on 2 May 2007. There were 771 subjects randomized at 250 centers (386 in the telavancin arm and 385 in the vancomycin arm), and 757 subjects treated. As in Study 0015, the original protocol for Study 0019 allowed imipenem for gram-negative coverage, as well as aztreonam and/or metronidazole. In order to limit potential bias, possibly resulting from the synergistic activity of linezolid with the glycopeptides, use of linezolid was removed in Protocol Amendment 1.

Approximately 30% of the subjects enrolled in Study 0019 met the definition for ventilator-associated pneumonia.

Table 26 summarizes the number of Study 0019 subjects analyzed by treatment group.

Table 26: Summary of patients included in each Study 0019 analysis population by treatment group

	Telavancin 10 mg/kg Number (%) of Patients [1]	Vancomycin
Randomized	386	385
Safety (As-treated)	379	378
Efficacy Populations (As-randomized)		
All Treated (AT)	377 (100%)	380 (100%)
Modified All-treated (MAT)	303 (80%)	282 (74%)
Clinically Evaluable (CE)	171 (45%)	170 (45%)
Microbiologically Evaluable (ME)	135 (36%)	124 (33%)
ME as Percent of CE	79%	73%

[1] Percentages are calculated relative to the number of patients treated (AT)

AT – all patients who received at least one dose of study medication.

MAT – those AT patients who had a respiratory pathogen isolated at Baseline.

CE – those AT patients whose adherence to the protocol made it reasonable to infer that their clinical response reflected the effect of the study medication

ME – those CE patients who had at least one Gram-positive pathogen that was associated with pneumonia

Source: This submission; Module 2.7.6.3, page 28

SUMMARY OF CLINICAL STUDIES

Table 27 summarizes the numbers of subjects included in each analysis population for Studies 0015 and 0019 (and combined). The most common reason for exclusion from the Microbiologically Evaluable (ME) population was "no gram-positive pathogen at baseline" (noted in 45% of exclusions in the telavancin arms, and in 48% of exclusions in the vancomycin arms).

Table 27: Data Sets Analyzed – Studies 0015 and 0019, Individually and Combined – AT Population

	0015		Number of Patients 0019		Total	
	Telavancin 10 mg/kg (N=372)	Vancomycin (N=374)	Telavancin 10 mg/kg (N=377)	Vancomycin (N=380)	Telavancin 10 mg/kg (N=749)	Vancomycin (N=754)
All-treated (AT)	372 (100%)	374 (100%)	377 (100%)	380 (100%)	749 (100%)	754 (100%)
Modified All-treated (MAT)	257 (69%)	247 (66%)	303 (80%)	282 (74%)	560 (75%)	529 (70%)
Respiratory Pathogens	249 (97%)	245 (99%)	297 (98%)	279 (99%)	546 (98%)	524 (99%)
Blood Pathogens Only	8 (3%)	2 (<1%)	6 (2%)	3 (1%)	14 (3%)	5 (<1%)
Clinically Evaluable (CE)	141 (38%)	172 (46%)	171 (45%)	170 (45%)	312 (42%)	342 (45%)
Microbiologically Evaluable (ME)	108 (29%)	113 (30%)	135 (36%)	124 (33%)	243 (32%)	237 (31%)
Respiratory Pathogens	105 (97%)	113 (100%)	134 (99%)	123 (99%)	239 (98%)	236 (100%)
Blood Pathogens Only	3 (3%)	0	1 (<1%)	1 (<1%)	4 (2%)	1 (<1%)
ME as % of CE Population	77%	66%	79%	73%	78%	69%

Note: MAT, CE, and ME percentages are calculated relative to the number in the AT population.

Output file: ISE_t_analpop_at_01.rtf

Source: Dataset(s): ADSL Program: \SCE\LOCAL\SANDBOX_2393719\Biostat\td-6424\hap\ISE\src\programs\it_analpop.sas Run Date: 29JUL08/10:46 by wabanadmin on NET_ASRV SASv9.1

Source: This submission, Section 5.3.5.4.1.10.3, Table 12

Table 28 summarizes the type and location of respiratory specimens sampled for bacterial culture, from the All Treated (AT) population. The specimen types were generally well balanced between the vancomycin and telavancin arms in both clinical trials, with sputum, endotracheal aspirate, and BAL representing 90% of the collected respiratory specimens. Endotracheal aspiration produced the highest number of positive cultures. Invasive methods were culture positive 77% of the time in the telavancin arm, and 80% of the time in the vancomycin arm.

Table 28: Type and Location of Respiratory Tract Specimen Collection – Studies 0015 and 0019 Individually and Combined – AT Population

	Number of Patients[4]					
	0015		0019		Total	
	Telavancin 10 mg/kg (N=372)	Vancomycin (N=374)	Telavancin 10 mg/kg (N=377)	Vancomycin (N=380)	Telavancin 10 mg/kg (N=749)	Vancomycin (N=754)
Sputum	169 (45%)	174 (47%)	151 (40%)	164 (43%)	320 (43%)	338 (45%)
Culture Positive [1]	104 (62%)	105 (60%)	104 (69%)	111 (68%)	208 (65%)	216 (64%)
Culture Negative	65 (38%)	69 (40%)	47 (31%)	53 (32%)	112 (35%)	122 (36%)
Endotracheal Aspirate	132 (35%)	134 (36%)	171 (45%)	180 (47%)	303 (40%)	314 (42%)
Culture Positive [1]	100 (76%)	97 (72%)	147 (86%)	140 (78%)	247 (82%)	237 (75%)
Culture Negative	32 (24%)	37 (28%)	24 (14%)	40 (22%)	56 (18%)	77 (25%)
Bronchoalveolar Lavage	20 (5%)	22 (6%)	34 (9%)	27 (7%)	54 (7%)	49 (6%)
Culture Positive [1]	15 (75%)	17 (77%)	27 (79%)	22 (81%)	42 (78%)	39 (80%)
< 10 ⁴ CFU/mL	1 (7%)	4 (24%)	3 (11%)	2 (9%)	4 (10%)	6 (15%)
>= 10 ⁴ CFU/mL	6 (40%)	8 (47%)	16 (59%)	10 (45%)	22 (52%)	18 (46%)
Quantitation not done	8 (53%)	5 (29%)	8 (30%)	10 (45%)	16 (38%)	15 (38%)
Culture Negative	5 (25%)	5 (23%)	7 (21%)	5 (19%)	12 (22%)	10 (20%)
Mini-bronchoalveolar Lavage	27 (7%)	21 (6%)	19 (5%)	10 (3%)	46 (6%)	31 (4%)
Culture Positive [1]	18 (67%)	14 (67%)	17 (89%)	9 (90%)	35 (76%)	23 (74%)
< 10 ⁴ CFU/mL	6 (33%)	2 (14%)	3 (18%)	1 (11%)	9 (26%)	3 (13%)
>= 10 ⁴ CFU/mL	7 (39%)	7 (50%)	11 (65%)	5 (56%)	18 (51%)	12 (52%)
Quantitation not done	5 (28%)	5 (36%)	3 (18%)	3 (33%)	8 (23%)	8 (35%)
Culture Negative	9 (33%)	7 (33%)	2 (11%)	1 (10%)	11 (24%)	8 (26%)
Protected Specimen Brush	2 (<1%)	2 (<1%)	0	1 (<1%)	2 (<1%)	3 (<1%)
Culture Positive [1]	1 (50%)	2 (100%)	0	1 (100%)	1 (50%)	3 (100%)
>= 10 ³ CFU/mL	1 (100%)	1 (50%)	0	1 (100%)	1 (100%)	2 (67%)
Quantitation not done	0	1 (50%)	0	0	0	1 (33%)
Culture Negative	1 (50%)	0	0	0	1 (50%)	0
Blinded Bronchial Suction	12 (3%)	9 (2%)	6 (2%)	2 (<1%)	18 (2%)	11 (1%)
Culture Positive [1]	10 (83%)	7 (78%)	4 (67%)	2 (100%)	14 (78%)	9 (82%)
Culture Negative	2 (17%)	2 (22%)	2 (33%)	0	4 (22%)	2 (18%)
Other [2]	7 (2%)	9 (2%)	2 (<1%)	2 (<1%)	9 (1%)	11 (1%)
Culture Positive [1]	6 (86%)	9 (100%)	1 (50%)	1 (50%)	7 (78%)	10 (91%)
Culture Negative	1 (14%)	0	1 (50%)	1 (50%)	2 (22%)	1 (9%)
All Invasive Methodologies [3]	68 (18%)	62 (17%)	61 (16%)	42 (11%)	129 (17%)	104 (14%)
Culture Positive [1]	50 (74%)	48 (77%)	49 (80%)	35 (83%)	99 (77%)	83 (80%)
Culture Negative	18 (26%)	14 (23%)	12 (20%)	7 (17%)	30 (23%)	21 (20%)

[1] A positive culture is defined as identification of at least one respiratory tract pathogen.

[2] Other methods: Nares, Protected Endotracheal Specimen, and Quantitative Tracheal Lavage.

[3] Bronchoalveolar lavage, mini-bronchoalveolar lavage, protected specimen brush, or blinded bronchial washing and other.

[4] If more than one specimen type was taken at baseline, then the patient will be counted under each specimen type taken. If a patient has more than one specimen of the same type, then the patient is counted only once and the culture is deemed positive if any specimen is positive. For quantitative cultures, if multiple pathogens are identified, the patient will be counted only once for each specimen type taken under the highest quantification parameter.

Source: This submission, Section 5.3.5.4.1.10.3, Table 16

Table 29 summarizes the species of bacterial pathogens collected from telavancin-treated subjects in the two clinical trials. The numbers and percentages of bacterial species, particularly with regard to the principle pathogens (respiratory pathogens sought in the proposed indications) were similar in the vancomycin arm (e.g. there were 130 *S. aureus* isolates collected from sputum in the telavancin arm, compared to 134 *S. aureus* isolates collected from sputum in the vancomycin arm). *Staphylococcus aureus* was the most common pathogen isolated from any source, with methicillin-resistant phenotypes dominant. Most subjects had only one or two respiratory pathogens. gram-negative respiratory pathogens were isolated from < 25% of specimens (with *Pseudomonas aeruginosa*, *Acinetobacter calcoaceticus*, *A. baumannii*, and *Klebsiella pneumonia* isolated most frequently).

Table 29: Respiratory Pathogens Isolated at Baseline by Method of Specimen Collection from Telavancin Patients MAT Population

	Number of Patients [1]					
	Sputum (N=208)	Endo- tracheal Aspiration (N=247)	Broncho- alveolar Lavage (N=42)	Mini- broncho- alveolar Lavage (N=35)	Blind Bronchial Suctioning (N=14)	Other [2] (N=8)
Gram-positive Pathogens						
STAPHYLOCOCCUS AUREUS	130 (63%)	174 (70%)	29 (69%)	27 (77%)	8 (57%)	5 (63%)
- MRSA	82 (39%)	113 (46%)	15 (36%)	10 (29%)	7 (50%)	4 (50%)
- MSSA	52 (25%)	61 (25%)	14 (33%)	17 (49%)	1 (7%)	1 (13%)
STREPTOCOCCUS PNEUMONIAE	12 (6%)	9 (4%)	5 (12%)	3 (9%)	2 (14%)	0
ENTEROCOCCUS FAECALIS	6 (3%)	5 (2%)	1 (2%)	0	0	1 (13%)
ENTEROCOCCUS FAECIUM	2 (<1%)	1 (<1%)	1 (2%)	0	0	0
Gram-negative Pathogens						
PSEUDOMONAS AERUGINOSA	37 (17.8%)	60 (24.3%)	10 (23.8%)	2 (5.7%)	1 (7.1%)	0
ACINETOBACTER CALCOACETICUS	16 (7.7%)	32 (13.0%)	2 (4.8%)	2 (5.7%)	1 (7.1%)	0
KLEBSIELLA PNEUMONIAE	14 (6.7%)	20 (8.1%)	5 (11.9%)	1 (2.9%)	1 (7.1%)	0
ESCHERICHIA COLI	13 (6.3%)	14 (5.7%)	6 (14.3%)	2 (5.7%)	1 (7.1%)	2 (25.0%)
STENOTROPOMONAS MALTOPHILIA	12 (5.8%)	12 (4.9%)	2 (4.8%)	2 (5.7%)	0	0
HAEMOPHILUS INFLUENZAE	11 (5.3%)	10 (4.0%)	2 (4.8%)	2 (5.7%)	0	0
ENTEROBACTER CLOACAE	8 (3.8%)	7 (2.8%)	2 (4.8%)	1 (2.9%)	0	0
PROTEUS MIRABILIS	3 (1.4%)	7 (2.8%)	0	1 (2.9%)	0	0
ACINETOBACTER BAUMANNII	1 (0.5%)	6 (2.4%)	0	0	0	0
SERRATIA MARCESCENS	4 (1.9%)	6 (2.4%)	0	2 (5.7%)	0	0
CITROBACTER KOSERI	0	2 (0.8%)	0	0	0	0
ENTEROBACTER AEROGENES	3 (1.4%)	2 (0.8%)	0	0	0	1 (12.5%)
ENTEROBACTER SPP	0	2 (0.8%)	0	1 (2.9%)	0	0
KLEBSIELLA OXYTOCA	3 (1.4%)	2 (0.8%)	0	0	0	0
PROTEUS VULGARIS	0	2 (0.8%)	0	0	0	0
ACHROMOBACTER XYLOSOXIDANS	1 (0.5%)	1 (0.4%)	0	0	0	0
ACINETOBACTER LWOFFII	0	1 (0.4%)	0	0	0	0
BURKHOLDERIA CEPACIA	0	1 (0.4%)	0	0	0	0
CHRYSEOBACTERIUM MENINGOSEPTICUM	0	1 (0.4%)	0	0	0	0
CITROBACTER FREUNDII COMPLEX	1 (0.5%)	1 (0.4%)	1 (2.4%)	0	1 (7.1%)	0
SERRATIA LIQUEFACIENS	0	1 (0.4%)	0	0	0	0
EMPEDOBACTER BREVIS	1 (0.5%)	0	0	0	0	0
ENTEROBACTER HORMAECHAEI	0	0	0	0	0	1 (12.5%)
HAEMOPHILUS PARAHAEOLYTICUS	1 (0.5%)	0	0	0	0	0
PROVIDENCIA STUARTII	1 (0.5%)	0	0	0	0	0
PSEUDOMONAS PUTIDA	2 (1.0%)	0	0	0	1 (7.1%)	0
Pathogens by Gram Stain						
Single Gram-positive Pathogen Only	96 (46%)	95 (38%)	17 (40%)	21 (60%)	7 (50%)	5 (63%)
Multiple Gram-positive Pathogens Only	6 (3%)	8 (3%)	3 (7%)	2 (6%)	0	0
Single Gram-negative Pathogen Only	50 (24%)	48 (19%)	3 (7%)	6 (17%)	4 (29%)	1 (13%)
Multiple Gram-negative Pathogens Only	12 (6%)	15 (6%)	4 (10%)	0	0	1 (13%)
Mixed Gram-positive and Gram-negative Pathogens	44 (21%)	81 (33%)	15 (36%)	6 (17%)	3 (21%)	1 (13%)
Number of Pathogens						
1 Pathogen	146 (70%)	143 (58%)	20 (48%)	27 (77%)	11 (79%)	6 (75%)
2 Pathogens	44 (21%)	71 (29%)	16 (38%)	4 (11%)	3 (21%)	2 (25%)
3 Pathogens	14 (7%)	21 (9%)	4 (10%)	2 (6%)	0 (0%)	0 (0%)
4 or More Pathogens	4 (2%)	12 (5%)	2 (5%)	2 (6%)	0 (0%)	0 (0%)

[1] Sample size in the column headings represents the number of patients with positive cultures from that source.

[2] Other methods: Bronchial Suction via Fibrobronch, Pleural Effusion, Pleural Fluid, Pleural Tissue, and Tracheostomy Aspirate.

Source: This submission, Section 5.3.5.4.1.10.3, Table 17

Table 30 compares the study populations in the telavancin and vancomycin arms of the two studies (and combined) as subpopulations based on categorization of methicillin-resistant *S. aureus*. The number of MRSA isolates was comparable between the two arms, and in the analysis groups.

Table 30: Population Presented as Subpopulations Based on MRSA Categorization

	0015		0019		Total	
	Telavancin 10 mg/kg	Vancomycin	Telavancin 10 mg/kg	Vancomycin	Telavancin 10 mg/kg	Vancomycin
All Treated	372 (100%)	374 (100%)	377 (100%)	380 (100%)	749 (100%)	754 (100%)
AT(MRSA)	115 (31%)	114 (30%)	118 (31%)	117 (31%)	233 (31%)	231 (31%)
CE(MRSA)	70 (19%)	84 (22%)	69 (18%)	70 (18%)	139 (19%)	154 (20%)
AT(MRSA-C)	257 (69%)	260 (70%)	259 (69%)	263 (69%)	516 (69%)	523 (69%)
AT - CE(MRSA)	302 (81%)	290 (78%)	308 (82%)	310 (82%)	610 (81%)	600 (80%)

Note: AT(MRSA) = AT patients with MRSA at baseline; CE(MRSA) = CE patients with MRSA at baseline.

AT(MRSA-C) = AT patients in whom MRSA was not identified at baseline.

AT - CE(MRSA) = AT patients who are not in the CE(MRSA) subpopulation.

Source: This submission, Section 5.3.5.4.1.10.3, Table 19

Table 31 lists the respiratory pathogens cultured at baseline from subjects in each arm of both studies (MAT population). The principle gram-positive respiratory pathogens (*Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Enterococcus faecalis*) were well balanced between the two arms in both studies. In 43% of the telavancin-treatment group subjects and 46% of the vancomycin-treatment group subjects, a single gram-positive pathogen was the only organism cultured at baseline. Study 0019 had a larger percentage of mixed gram-positive/gram-negative cultures at baseline, compared to Study 0015. Approximately 25% of baseline respiratory cultures yielded only gram-negative isolates. The majority of bacterial isolates were cultured only from respiratory specimens (91% for the telavancin arm, 92% for the vancomycin arm). Respiratory pathogens were isolated from blood and respiratory baseline cultures in 6% of telavancin-treated subjects and 7% of vancomycin-treated subjects. Respiratory pathogens were isolated from baseline blood cultures-only in 3% of telavancin-treated subjects and < 1% of vancomycin-treated subjects. Of the respiratory pathogens isolated from blood, the majority were *S. aureus* (32 of 48 in the telavancin-treated subjects, 29 of 44 in the vancomycin-treated subjects).

Table 31: Respiratory Pathogens from Baseline Cultures – MAT Population

	Number of Patients					
	0015		0019		Total	
	Telavancin 10 mg/kg (N=257)	Vancomycin (N=247)	Telavancin 10 mg/kg (N=303)	Vancomycin (N=282)	Telavancin 10 mg/kg (N=560)	Vancomycin (N=529)
Any Respiratory Tract Pathogen	249 (96.9%)	245 (99.2%)	297 (98.0%)	279 (98.9%)	546 (97.5%)	524 (99.1%)
Pathogen Isolated from Respiratory Tract Only	229 (89%)	228 (92%)	283 (93%)	257 (91%)	512 (91%)	485 (92%)
Pathogen Isolated from Both Respiratory Tract and Blood	20 (8%)	17 (7%)	14 (5%)	22 (8%)	34 (6%)	39 (7%)
Gram-positive Pathogens	181 (70%)	178 (72%)	220 (73%)	205 (73%)	401 (72%)	383 (72%)
STAPHYLOCOCCUS AUREUS	168 (65.4%)	170 (68.8%)	199 (65.7%)	178 (63.1%)	367 (65.5%)	348 (65.8%)
- MRSA	111 (43.2%)	113 (45.7%)	117 (38.6%)	117 (41.5%)	228 (40.7%)	230 (43.5%)
- MSSA	61 (23.7%)	57 (23.1%)	83 (27.4%)	63 (22.3%)	144 (25.7%)	120 (22.7%)
STREPTOCOCCUS PNEUMONIAE	15 (5.8%)	7 (2.8%)	14 (4.6%)	23 (8.2%)	29 (5.2%)	30 (5.7%)
ENTEROCOCCUS FAECALIS	3 (1.2%)	6 (2.4%)	10 (3.3%)	13 (4.6%)	13 (2.3%)	19 (3.6%)
ENTEROCOCCUS FAECIUM	1 (0.4%)	0	3 (1.0%)	1 (0.4%)	4 (0.7%)	1 (0.2%)
Gram-negative Pathogens	118 (46%)	111 (45%)	171 (56%)	155 (55%)	289 (52%)	266 (50%)
PSEUDOMONAS AERUGINOSA	43 (16.7%)	36 (14.6%)	67 (22.1%)	56 (19.9%)	110 (19.6%)	92 (17.4%)
ACINETOBACTER CALCOACETICUS	15 (5.8%)	18 (7.3%)	41 (13.5%)	34 (12.1%)	56 (10.0%)	52 (9.8%)
KLEBSIELLA PNEUMONIAE	14 (5.4%)	19 (7.7%)	26 (8.6%)	34 (12.1%)	40 (7.1%)	53 (10.0%)
ESCHERICHIA COLI	18 (7.0%)	7 (2.8%)	18 (5.9%)	11 (3.9%)	36 (6.4%)	18 (3.4%)
HAEMOPHILUS INFLUENZAE	15 (5.8%)	9 (3.6%)	10 (3.3%)	8 (2.8%)	25 (4.5%)	17 (3.2%)
STENOTROPHOMONAS MALTOPHILIA	8 (3.1%)	8 (3.2%)	18 (5.9%)	6 (2.1%)	26 (4.6%)	14 (2.6%)
ENTEROBACTER CLOACAE	6 (2.3%)	9 (3.6%)	12 (4.0%)	9 (3.2%)	18 (3.2%)	18 (3.4%)
PROTEUS MIRABILIS	5 (1.9%)	9 (3.6%)	5 (1.7%)	6 (2.1%)	10 (1.8%)	15 (2.8%)
SERRATIA MARCESCENS	7 (2.7%)	3 (1.2%)	4 (1.3%)	4 (1.4%)	11 (2.0%)	7 (1.3%)
ACINETOBACTER BAUMANNII	3 (1.2%)	2 (0.8%)	4 (1.3%)	4 (1.4%)	7 (1.3%)	6 (1.1%)
KLEBSIELLA OXYTOCA	2 (0.8%)	2 (0.8%)	3 (1.0%)	6 (2.1%)	5 (0.9%)	8 (1.5%)
ENTEROBACTER AEROGENES	3 (1.2%)	2 (0.8%)	3 (1.0%)	2 (0.7%)	6 (1.1%)	4 (0.8%)
CITROBACTER FREUNDII COMPLEX	1 (0.4%)	1 (0.4%)	3 (1.0%)	1 (0.4%)	4 (0.7%)	2 (0.4%)
ACHROMOBACTER XYLOXIDANS	1 (0.4%)	2 (0.8%)	1 (0.3%)	1 (0.4%)	2 (0.4%)	3 (0.6%)
CITROBACTER KOSERI	0	0	2 (0.7%)	2 (0.7%)	2 (0.4%)	2 (0.4%)
CHRYSEOBACTERIUM MENINGOSEPTICUM	1 (0.4%)	1 (0.4%)	0	1 (0.4%)	1 (0.2%)	2 (0.4%)
ENTEROBACTER SPP	1 (0.4%)	0	2 (0.7%)	0	3 (0.5%)	0
PROVIDENCIA STUARTII	1 (0.4%)	1 (0.4%)	0	1 (0.4%)	1 (0.2%)	2 (0.4%)
PSEUDOMONAS PUTIDA	3 (1.2%)	0	0	0	3 (0.5%)	0
BURKHOLDERIA CEPACIA	0	0	1 (0.3%)	1 (0.4%)	1 (0.2%)	1 (0.2%)
PROTEUS VULGARIS	0	0	2 (0.7%)	0	2 (0.4%)	0
SERRATIA LIQUEFACIENS	0	1 (0.4%)	1 (0.3%)	0	1 (0.2%)	1 (0.2%)
ACINETOBACTER LWOFFII	0	0	1 (0.3%)	0	1 (0.2%)	0
BURKHOLDERIA PSEUDOMALLEI	0	0	0	1 (0.4%)	0	1 (0.2%)
CITROBACTER AMALONATICUS	0	1 (0.4%)	0	0	0	1 (0.2%)
CITROBACTER FREUNDII	0	0	0	1 (0.4%)	0	1 (0.2%)
EMPEDOBACTER BREVIS	0	0	1 (0.3%)	0	1 (0.2%)	0
ENTEROBACTER ASBURIAE	0	1 (0.4%)	0	0	0	1 (0.2%)
ENTEROBACTER HORMAECHAEI	1 (0.4%)	0	0	0	1 (0.2%)	0
FUSOBACTERIUM NUCLEATUM	0	0	1 (0.3%)	0	1 (0.2%)	0
HAEMOPHILUS PARAHAEOMOLYTICUS	1 (0.4%)	0	0	0	1 (0.2%)	0
HAFNIA ALVEI	0	1 (0.4%)	0	0	0	1 (0.2%)
PROVIDENCIA ALCALIFACIENS	0	1 (0.4%)	0	0	0	1 (0.2%)
PROVIDENCIA RETTGERI	0	1 (0.4%)	0	0	0	1 (0.2%)
Pathogens by Gram Type						
Gram-positive Pathogens Only	131 (51%)	134 (54%)	126 (42%)	124 (44%)	257 (46%)	258 (49%)
Single Pathogen	121 (47%)	127 (51%)	120 (40%)	115 (41%)	241 (43%)	242 (46%)
Multiple Pathogens	10 (4%)	7 (3%)	6 (2%)	9 (3%)	16 (3%)	16 (3%)
Gram-negative Pathogens Only	68 (26%)	67 (27%)	77 (25%)	74 (26%)	145 (26%)	141 (27%)
Single Pathogen	56 (22%)	53 (21%)	57 (19%)	56 (20%)	113 (20%)	109 (21%)
Multiple Pathogens	12 (5%)	14 (6%)	20 (7%)	18 (6%)	32 (6%)	32 (6%)
Mixed Gram-positive/Gram-negative Infection	50 (19%)	44 (18%)	94 (31%)	81 (29%)	144 (26%)	125 (24%)
Number of Pathogens						
1 Pathogen	177 (71%)	180 (73%)	177 (60%)	171 (61%)	354 (65%)	351 (67%)
2 Pathogens	48 (19%)	50 (20%)	89 (30%)	85 (30%)	137 (25%)	135 (26%)
3 Pathogens	19 (8%)	11 (4%)	20 (7%)	19 (7%)	39 (7%)	30 (6%)
4 or More Pathogens	5 (2%)	4 (2%)	11 (4%)	4 (1%)	16 (3%)	8 (2%)

Note: More than one pathogen may have been present in any patient
Source: This submission, Section 5.3.5.4.1.10.3, Table 21

Table 32 summarizes the telavancin MIC ranges for the key respiratory pathogens isolated from baseline cultures in the MAT population. The table includes one isolate of *E. faecalis* where the initial susceptibility test indicated an MIC value of 2 mcg/ml. Re-testing in duplicate resulted in an MIC of 1 mcg/ml for this isolate. All MIC₉₀ values were lower than the achievable serum and epithelial lining fluid levels for telavancin (discussed elsewhere in this review).

Table 32: Telavancin MIC Population Distributions for Key Species Isolated from Patients in Studies 0015 and 0019 – MAT Population

Organism	Study	N	No. of Isolates Inhibited at Telavancin Concentration (ug/mL) [1]										MIC (ug/mL)		
			0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2		Range	50%	90%
ENTEROCOCCUS FAECALIS	US	8							5	3			0.5 - 1	0.5	-
	NON-US	26						3	12	10	1		0.25 - 2	0.5	1
	GLOBAL	34						3	17	13	1		0.25 - 2	0.5	1
STAPHYLOCOCCUS AUREUS, ALL	US	143					3	93	46	1			0.12 - 1	0.25	0.5
	NON-US	507				2	10	257	214	24			0.06 - 1	0.25	0.5
	GLOBAL	650				2	13	350	260	25			0.06 - 1	0.25	0.5
STAPHYLOCOCCUS AUREUS, MRSA	US	94					2	61	30	1			0.12 - 1	0.25	0.5
	NON-US	315				2	1	110	179	23			0.06 - 1	0.5	0.5
	GLOBAL	409				2	3	171	209	24			0.06 - 1	0.5	0.5
STAPHYLOCOCCUS AUREUS, MSSA	US	49					1	32	16				0.12 - 0.5	0.25	0.5
	NON-US	192					9	147	35	1			0.12 - 1	0.25	0.5
	GLOBAL	241					10	179	51	1			0.12 - 1	0.25	0.5
STREPTOCOCCUS PNEUMONIAE	US	8	1	1	6								0.008 - 0.03	0.03	-
	NON-US	46	4	29	12	1							0.008 - 0.06	0.015	0.03
	GLOBAL	54	5	30	18	1							0.008 - 0.06	0.015	0.03

Source: This submission, Section 5.3.5.4.1.10.3, Table 23

The MIC₅₀, MIC₉₀ and MIC_{range} values for isolates collected from respiratory specimens, in the clinical trials (MAT population) for both telavancin and vancomycin, are compared in Table 33. MIC₉₀ values for each species (and phenotype) is one doubling dilution less for telavancin, compared to vancomycin, with the exception of isolates of *E. faecalis* collected from vancomycin-treated subjects. Table 34 provides the same information for isolates collected from baseline blood cultures.

Table 33: Susceptibility of Gram-Positive Pathogens Isolated from Baseline Respiratory in Studies 0015 and 0019 to Telavancin and Vancomycin – MAT Population

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

Source: This submission, Section 5.3.5.4.1.10.3, Table 24

Table 34: Susceptibility of Gram-Positive Pathogens Isolated from Baseline Blood in Studies 0015 and 0019 to Telavancin and Vancomycin – MAT Population

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

Source: This submission, Section 5.3.5.4.1.10.3, Table 25

The by-pathogen eradication rates for the principle gram-positive respiratory pathogens collected in the clinical trials (ME Population), is summarized in Table 35. Eradication rates were notably higher in telavancin-treated subjects, compared to vancomycin-treated subjects, in Study 0015, which included substantially more patients with renal failure and other chronic comorbidities (including diabetes mellitus) than Study 0019. Microbiological eradication rates were similar, between the two treatment arms, against *S. aureus* (including MRSA) in the pooled results, but differed in the individual studies (e.g. eradication of MRSA by telavancin was approximately 5% higher than eradication by vancomycin, in Study 0015, and approximately 5% lower than eradication by vancomycin in Study 0019).

Table 35: By-pathogen Microbiological Eradication Rates at Test-of-cure – ME Population, Studies 0015 and 0019; Gram-Positive pathogens at Baseline

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

Source: This submission, Section 5.3.5.4.1.10.3, Table 26

Microbial eradication rates in the ME population were comparable in the telavancin-treated subjects and vancomycin subjects (Table 36). The majority of subjects had a single gram-positive respiratory pathogen isolated (164 in the telavancin arm, 165 in the vancomycin arm), and in this group, microbial eradication was higher in the telavancin treated subjects (82.9% for the telavancin-treated subjects and 75.8% for the vancomycin-treated subjects, in the pooled data, ME population). This difference was also observed in the individual studies.

Table 36: By-patient Microbiological Response at Test-of-cure – ME Population, Studies 0015 and 0019

	0015		Number of Patients 0019		Total	
	Telavancin 10 mg/kg	Vancomycin	Telavancin 10 mg/kg	Vancomycin	Telavancin 10 mg/kg	Vancomycin
By-patient Microbiological Response						
Eradicated	86 (79.6%)	85 (75.2%)	103 (76.3%)	96 (77.4%)	189 (77.8%)	181 (76.4%)
Persisted	22 (20.4%)	28 (24.8%)	32 (23.7%)	28 (22.6%)	54 (22.2%)	56 (23.6%)
- Total -	108 (100.0%)	113 (100.0%)	135 (100.0%)	124 (100.0%)	243 (100.0%)	237 (100.0%)
Difference (95% CI) [1]	4.4% (-6.6% , 15.4%)		-1.1% (-11.4% , 9.2%)		1.4% (-6.1% , 9.0%)	
Eradication Rate by Number of Pathogens						
Single Gram-positive Pathogen Only	67 / 82 (81.7%)	66 / 88 (75.0%)	69 / 82 (84.1%)	59 / 77 (76.6%)	136 / 164 (82.9%)	125 / 165 (75.8%)
Difference (95% CI) [1]	6.7% (-5.6% , 19.0%)		7.5% (-4.8% , 19.8%)		7.1% (-1.7% , 15.9%)	
Multiple Gram-positive Pathogens Only	5 / 6 (83.3%)	0 / 2 (0.0%)	3 / 5 (60.0%)	7 / 7 (100.0%)	8 / 11 (72.7%)	7 / 9 (77.8%)
Mixed Gram-positive and Gram-negative	14 / 20 (70.0%)	19 / 23 (82.6%)	31 / 48 (64.6%)	30 / 40 (75.0%)	45 / 68 (66.2%)	49 / 63 (77.8%)
Difference (95% CI) [1]	-12.6% (-36.8% , 13.2%)^A		-10.4% (-29.5% , 8.6%)		-11.1% (-25.8% , 4.8%)^A	

[1] Difference in eradication rates (telavancin - vancomycin); two-sided 95% confidence interval
^A = Confidence interval uses Agresti-Caffo adjustment. Pooled analysis is stratified by study.

Source: This submission, Section 5.3.5.4.1.10.3, Table 27

Tables 37 through 40 summarize the MIC and zone diameter results versus microbiological eradication rates for isolates of *S. aureus* (MRSA and MSSA) recovered in the combined clinical trials (global and US results, ME population). No *S. aureus* isolate was recovered with an MIC greater than 1 mcg/ml. The disk diffusion results indicated a relatively narrow range (16 – 21 mm) for *S. aureus* zone diameters.

Table 37: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin MIC Value: Global (ME Population)

				Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
				Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV mic (ug/mL)											
S. aureus	OX:R[1]	0.12	1 (100%)					1 (100%)			
		0.25	43 (72%)	17 (28%)				41 (68%)	19 (32%)		
		0.5	44 (79%)	12 (21%)				44 (79%)	12 (21%)		
		1	4 (80%)	1 (20%)				4 (80%)	1 (20%)		
		Missing	13 (65%)	7 (35%)				13 (65%)	7 (35%)		
		- Total -	105	37	0	0		103	39		
	OX:S[1]	0.12	3 (100%)					3 (100%)			
		0.25	46 (79%)	12 (21%)				45 (78%)	13 (22%)		
		0.5	14 (93%)	1 (7%)				14 (93%)	1 (7%)		
		Missing	8 (89%)	1 (11%)				8 (89%)	1 (11%)		
		- Total -	71	14	0	0		70	15		

[1] S = Susceptible, R = Resistant. A patient can have multiple mic values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_GLOBAL_ALL_MIC_SAUR_115 Program: ltd-6424haplmicro_analysis\programs\it_micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASRV SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 115

Table 38: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin MIC Value: US Patients (ME Population)

				Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
				Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV mic (ug/mL)											
S. aureus	OX:R[1]	0.12	1 (100%)					1 (100%)			
		0.25	13 (68%)	6 (32%)				13 (68%)	6 (32%)		
		0.5	5 (83%)	1 (17%)				5 (83%)	1 (17%)		
		Missing	4 (57%)	3 (43%)				4 (57%)	3 (43%)		
		- Total -	23	10	0	0		23	10		
	OX:S[1]	0.12	1 (100%)					1 (100%)			
		0.25	5 (83%)	1 (17%)				5 (83%)	1 (17%)		
		0.5	6 (86%)	1 (14%)				6 (86%)	1 (14%)		
		- Total -	12	2	0	0		12	2		

[1] S = Susceptible, R = Resistant. A patient can have multiple mic values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_US_ALL_MIC_SAUR_117 Program: \td-6424\hap\micro_analysis\programs\t_micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASRV SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 117

Table 39: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin Zone Diameter Value: Global (ME Population)

				Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
				Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV Zone Diameter (mm)											
S. aureus	OX:R[1]	16	7 (78%)	2 (22%)				7 (78%)	2 (22%)		
		17	27 (71%)	11 (29%)				26 (68%)	12 (32%)		
		18	32 (74%)	11 (26%)				32 (74%)	11 (26%)		
		19	17 (81%)	4 (19%)				17 (81%)	4 (19%)		
		20	8 (80%)	2 (20%)				8 (80%)	2 (20%)		
		21	1 (100%)						1 (100%)		
		Missing	13 (65%)	7 (35%)				13 (65%)	7 (35%)		
		- Total -	105	37	0	0		103	39		
	OX:S[1]	16	6 (100%)					6 (100%)			
		17	25 (83%)	5 (17%)				24 (80%)	6 (20%)		
		18	18 (75%)	6 (25%)				18 (75%)	6 (25%)		
		19	11 (85%)	2 (15%)				11 (85%)	2 (15%)		
		20	2 (100%)					2 (100%)			
		21	1 (100%)					1 (100%)			
		Missing	8 (89%)	1 (11%)				8 (89%)	1 (11%)		
		- Total -	71	14	0	0		70	15		

[1] S = Susceptible, R = Resistant. A patient can have multiple Zone Diameter values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_GLOBAL_ALL_ZONE_SAUR_121 Program: \td-6424\hap\micro_analysis\programs\t_micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASRV SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 121

Table 40: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin Zone Diameter Value: US Patients (ME Population)

				Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
				Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV Zone Diameter (mm)											
S. aureus	OX:R[1]	16	6 (75%)	2 (25%)				6 (75%)	2 (25%)		
		17	6 (60%)	4 (40%)				6 (60%)	4 (40%)		
		18	6 (86%)	1 (14%)				6 (86%)	1 (14%)		
		19	1 (100%)					1 (100%)			
		Missing	4 (57%)	3 (43%)				4 (57%)	3 (43%)		
		- Total -	23	10	0	0		23	10		
	OX:S[1]	16	2 (100%)					2 (100%)			
		17	7 (78%)	2 (22%)				7 (78%)	2 (22%)		
		18	2 (100%)					2 (100%)			
		19	1 (100%)					1 (100%)			
		- Total -	12	2	0	0		12	2		

[1] S = Susceptible, R = Resistant. A patient can have multiple Zone Diameter values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_US_ALL_ZONE_SAUR_122 Program: 'td-6424\hap\micro_analysis\programs\t_micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASrv SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 122

Tables 41 through 44 summarize the MIC and zone diameter results versus microbiological eradication rates for isolates of *S. pneumoniae* recovered in the combined clinical trials (global and US results, ME population). No *S. pneumoniae* isolate was recovered with an MIC greater than 0.03 mcg/ml. The disk diffusion range for isolates of *S. pneumoniae* recovered in the combined clinical trials was 18 – 23 mm.

Table 41: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin MIC Value Value: Global (ME Population)

			Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
			Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV mic (ug/mL)										
S. PNEUMONIAE	0.008		2 (100%)				2 (100%)			
	0.015		9 (90%)	1 (10%)			10 (100%)			
	0.03		5 (100%)				5 (100%)			
	Missing		2 (67%)	1 (33%)			2 (67%)	1 (33%)		
	- Total -		18	2	0	0	19	1		

[1] S = Susceptible, R = Resistant. A patient can have multiple mic values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_GLOBAL_ALL_MIC_SPHE_133 Program: 'td-6424\hap\micro_analysis\programs\t_micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASrv SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 133

Table 42: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin MIC Value: US Patients (ME Population)

			Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
			Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV mic (ug/mL)										
S.	PNEUMONIAE	0.03	1 (100%)				1 (100%)			
		Missing	1 (100%)				1 (100%)			
		- Total -	2	0	0	0	2			

[1] S = Susceptible, R = Resistant. A patient can have multiple mic values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_US_ALL_MIC_SPHE_135 Program: \td-6424\hap\micro_analysis\programs\micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASRV SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 135

Table 43: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin Zone Diameter Value: Global (ME Population)

			Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
			Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV Zone Diameter (mm)										
S.	PNEUMONIAE	18	2 (100%)				2 (100%)			
		19	4 (100%)				4 (100%)			
		20	3 (100%)				3 (100%)			
		21	6 (100%)				6 (100%)			
		22		1 (100%)			1 (100%)			
		23	1 (100%)				1 (100%)			
		Missing	2 (67%)	1 (33%)			2 (67%)	1 (33%)		
		- Total -	18	2	0	0	19	1		

[1] S = Susceptible, R = Resistant. A patient can have multiple Zone Diameter values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_GLOBAL_ALL_ZONE_SPHE_139 Program: \td-6424\hap\micro_analysis\programs\micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASRV SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 139

Table 44: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin Zone Diameter Value: US Patients (ME Population)

			Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
			Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV Zone Diameter (mm)										
S.	PNEUMONIAE	21	1 (100%)				1 (100%)			
		Missing	1 (100%)				1 (100%)			
		- Total -	2	0	0	0	2			

[1] S = Susceptible, R = Resistant. A patient can have multiple Zone Diameter values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_US_ALL_ZONE_SPHE_140 Program: \td-6424\hapi\micro_analysis\programs\it_micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASrv SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 140

Tables 45 through 48 summarize the MIC and zone diameter results versus microbiological eradication rates for isolates of *E. faecalis* recovered in the combined clinical trials (global results and US results, ME population). One isolate of *E. faecalis* initially displayed an MIC result of 2 mcg/ml, but on re-testing (in duplicate), an MIC result of 1 mcg/ml was determined. The disk diffusion results for all isolates of *E. faecalis* recovered in the clinical trials were with a narrow range, 16-18mm.

Table 45: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin MIC Value: Global (ME Population)

			Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
			Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV mic (ug/mL)										
E.	FAECALIS	0.25	1 (100%)				1 (100%)			
		0.5	1 (25%)	3 (75%)			1 (25%)	3 (75%)		
		1	3 (100%)				3 (100%)			
		- Total -	5	3	0	0	5	3		

[1] S = Susceptible, R = Resistant. A patient can have multiple mic values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_GLOBAL_ALL_MIC_EFAE_151 Program: \td-6424\hapi\micro_analysis\programs\it_micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASrv SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 151

Table 46: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin MIC Value: US Patients (ME Population)

		Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
		Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV mic (ug/mL)									
E. FAECALIS	1	1 (100%)				1 (100%)			
	- Total -	1	0	0	0	1			

[1] S = Susceptible, R = Resistant. A patient can have multiple mic values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_US_ALL_MIC_EFAE_153 Program: \td-6424\hap\micro_analysis\programs\t_micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASrv SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 153

Table 47: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin Zone Diameter Value: Global (ME Population)

		Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
		Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV Zone Diameter (mm)									
E. FAECALIS	16	1 (100%)				1 (100%)			
	17	3 (60%)	2 (40%)			3 (60%)	2 (40%)		
	18	1 (50%)	1 (50%)			1 (50%)	1 (50%)		
	- Total -	5	3	0	0	5	3		

[1] S = Susceptible, R = Resistant. A patient can have multiple Zone Diameter values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_GLOBAL_ALL_ZONE_EFAE_157 Program: \td-6424\hap\micro_analysis\programs\t_micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASrv SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 157

Table 47: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin Zone Diameter Value: US Patients (ME Population)

		Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
		Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV Zone Diameter (mm)									
E. FAECALIS	16	1 (100%)				1 (100%)			
	- Total -	1	0	0	0	1			

[1] S = Susceptible, R = Resistant. A patient can have multiple Zone Diameter values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_US_ALL_ZONE_EFAE_158 Program: \td-6424\hap\micro_analysis\programs\t_micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASrv SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 158

Using the proposed telavancin breakpoints for *S. aureus* (including methicillin-resistant isolates), streptococcal species (including *S. pneumoniae*), and *E. faecalis* (vancomycin-susceptible isolates), no non-susceptible isolates of the principle gram-positive respiratory pathogens (sought in the proposed indications) were recovered in the two Phase 3 clinical trials

With the exception of *S. aureus* isolates resistant to oxacillin (MRSA), there were no gram-positive respiratory pathogens identified in the clinical trials with phenotypes commonly considered "drug-resistant" or "multi-drug resistant", i.e. no isolates of *S. pneumoniae* were identified as penicillin-resistant and no isolates of *S. aureus* were identified as vancomycin non-susceptible. Vancomycin-resistant enterococci were excluded from the trial by design.

Development of resistance during the trials was defined as an increase of 2 or more doubling dilutions in the MIC values of isolates obtained at EOT or TOC, compared to the MIC at Baseline. No isolates collected from subjects in the telavancin-treatment arm met this criteria. Molecular methods (e.g. pulsed field gel electrophoresis) were not employed to characterize and compare isolates obtained at various time-points in the trial. This resulted in the inability of the Applicant to adequately characterize one *S. aureus* isolate, collected from a subject in the vancomycin arm, which may have displayed a 4-fold (2 doubling dilutions) increase in MIC to telavancin. Two *S. aureus* isolates were collected from the subject at baseline, one from respiratory secretions (telavancin MIC = 0.25 mcg/ml), and the other from blood (telavancin MIC = 1 mcg/ml). The isolate recovered at EOT had an MIC of 1 mcg/ml.

"Potential superinfection" was defined by the Applicant as "isolation from post-treatment cultures of a pathogen that was not present at Baseline", with the term "potential" used to indicate the inability to distinguish colonization versus infection. The predominant isolate identified as a causative agent of potential superinfection was *Pseudomonas aeruginosa*, with incidence rates of 9% and 7% in the telavancin-treated subjects and vancomycin-treated subjects, respectively (ME population). Overall rates of potential superinfection were notably higher in the telavancin arm, with 33% incidence, compared to 22% incidence in the vancomycin arm.

QUALITY CONTROL PROCEDURES DURING CLINICAL STUDIES

All bacterial isolates collected in the Phase 3 clinical trials were shipped to (b) (4) for confirmation of identification and for susceptibility testing. Isolates originating in Europe, Russia, and South Africa were tested at the (b) (4) facility in (b) (4). All other isolates were tested at the (b) (4) facility in (b) (4).

MIC susceptibility testing was performed using frozen microbroth dilution panels supplied by (b) (4), according to procedures approved by CLSI. The Applicant has provided plate lot numbers and complete plate configurations in the study report, "Telavancin MIC and Disk Diffusion Quality Control Results for Phase 3 Clinical Studies 0015 and 0019" (Report 08-6424-MCB-03) and are summarized in Table 43. Isolates were subcultured to trypticase-soy agar + 5% sheep blood 12-24 hours prior to testing. Isolates were suspended in demineralized water or cation adjusted Mueller-Hinton broth to an approximate concentration of 10^8 CFU/ml. This suspension was diluted with demineralized water (without Tween), to a concentration of 5×10^4 CFU/ml, which was delivered to the microtiter wells. Plates were incubated in ambient air at 35°C for 16-20 hours (streptococcal isolates were incubated for 20-24 hours) and read manually.

Disk diffusion susceptibility testing was performed using the Kirby-Bauer method approved by CLSI. Mueller-Hinton agar plates were swabbed with a bacterial suspension of approximately 10^8 CFU/ml (5% sheep blood was added to the Mueller-Hinton agar when streptococci were tested). Streptococcal isolates were incubated at 35°C in 5-7% CO₂ for 20-24 hours. Staphylococci and enterococci were incubated at 35°C in ambient air for 16-18 hours. Telavancin disk diffusion was performed using a 30 mcg disk manufactured by BBL (Becton Dickinson, Sparks, MD).

Quality control was performed on each day of testing. Quality control ranges (reviewed in the NDA 22110 submission) were based on CLSI M23 studies, and approved by CLSI for testing of telavancin. Results were reported only when all QC results were within ranges approved by CLSI. The quality control organisms tested are listed in Table 44.

Table 43: MIC Frozen Panel Summary

Panel (part number)	Concentration Range (µg/mL)		Growth Media	Lot Numbers Used at Study Site	
	Telavancin	Vancomycin		(b) (4)	
CML1FSTA	0.015-16	0.25-32	CAMHB ¹	5484, 6351 and 7141	5484, 6351 and 7141
CML3FENC	0.015-32	0.5-512	CAMHB ¹	4433 and 4452	4452
CML2FSRP	0.001-2	0.06-1	CAMHB +2.5% LHB ²	4431 and 7021	4454 and 7021

¹Cation Adjusted Mueller-Hinton Broth prepared according to CLSI M7-A7 (2)

²Lysed Horse Blood

Source: This submission; Report 08-6424-MCB-03, Table 1

Table 44: Quality Control Strains and CLSI Approved Ranges

Strain	CLSI Approved MIC range (µg/mL) ¹	
	Telavancin	Vancomycin
<i>Staphylococcus aureus</i> ATCC 29213	0.12-1	0.5-2
<i>Enterococcus faecalis</i> ATCC 29212	0.12-0.5	1-4
<i>Streptococcus pneumoniae</i> ATCC 49619	0.004-0.03 ²	0.12-0.5
Strain	CLSI Approved Telavancin Disk range (mm) ¹	
<i>Staphylococcus aureus</i> ATCC 25923	16-20	
<i>Streptococcus pneumoniae</i> ATCC 49619	17-24	

¹From CLSI M100-S17 (1)

²From CLSI M100-S17 (tentative) (1)

Source: This submission; Report 08-6424-MCB-03, Table 2

Quality control results for MIC tests are summarized in Table 45 through 47. There was no noted site-to-site or frozen panel lot-to-lot variation.

For *S. aureus*, all vancomycin tests were within established control range. Telavancin results were within the tentative range on 172 of 173 tests (99.4%).

Table 45: *S. aureus* ATCC 29213 – Number of Results at Each MIC from HAP Clinical Studies 0015 and 0019

Telavancin				Vancomycin			
MIC (µg/mL)	(b) (4)		Both Sites	MIC (µg/mL)	(b) (4)		Both Sites
0.12	1	1	2	≤ 0.5	15	36	51
0.25	51	58	109	0.5	32	48	80
0.5	21	36	57	1	26	16	42
1		4	4	2			
2		1	1				
- Total -	73	100	173	- Total -	73	100	173

Shaded area indicates CLSI approved ranges

Source: This submission, Section 5.3.5.4.1.10.2, Table 1

For *E. faecalis*, all vancomycin tests were within established control range. Telavancin results were within the tentative range on 167 of 171 tests (98.2%).

Table 46: *E. faecalis* ATCC 29212 – Number of Results at Each MIC from HAP Clinical Studies 0015 and 0019

Telavancin				Vancomycin			
MIC (µg/mL)	(b) (4)		Both Sites	MIC (µg/mL)	(b) (4)		Both Sites
0.06		1	1				
0.12	2		2	1	1	3	4
0.25	64	62	126	2	70	94	164
0.5	7	32	39	4	2	1	3
1		3	3				
- Total -	73	98	171	- Total -	73	98	171

Shaded area indicates CLSI approved ranges

Source: This submission, Section 5.3.5.4.1.10.2, Table 2

For *S. pneumoniae*, all vancomycin tests were within established control range. All telavancin results were within the tentative range.

Table 47: *S. pneumoniae* ATCC 49619 – Number of Results at Each MIC from HAP Clinical Studies 0015 and 0019

Telavancin				Vancomycin			
MIC (µg/mL)	(b) (4)		Both Sites	MIC (µg/mL)	(b) (4)		Both Sites
0.004				0.12	21	1	22
0.008	5		5	0.25	11	11	22
0.015	22	14	36	0.5	1	2	3
0.03	6		6				
- Total -	33	14	47	- Total -	33	14	47

Shaded area indicates CLSI approved ranges

Source: This submission, Section 5.3.5.4.1.10.2, Table 3

Quality control results for disk diffusion susceptibility testing are summarized in Table 48. All vancomycin and telavancin results were within ranges approved by CLSI.

Table 48: Telavancin Disk Diffusion Results for *S. aureus* ATCC 25923 and *S. pneumoniae* ATCC 49619 – Number of Results at Each Inhibition Zone from HAP Clinical Study 0015 and Study 0019 Combined

Zone (mm)	<i>S. aureus</i> ATCC 25923			Zone (mm)	<i>S. pneumoniae</i> ATCC 49619		
	(b) (4)		Both Sites		(b) (4)		Both Sites
16	9	8	17	16			
17	20	30	50	17			
18	24	22	46	18	3	2	5
19	7	5	12	19	4	5	9
20	4		4	20	16	3	19
21				21	22	3	25
22				22	14	1	15
23				23	4		4
24				24	1		1
- Total -	64	65	129	- Total -	64	14	78

Shaded area indicates CLSI approved ranges

Source: This submission, Section 5.3.5.4.1.10.2. Table 6

Clinical Studies ~ Conclusions:

Data from the two Phase 3 clinical trials indicate that telavancin is effective against the pathogens in the proposed indications. Specimen types, subject demographics, subject co-morbidities, and bacterial isolates were similar between the telavancin and vancomycin arms of the trials. The majority of principle pathogens were recovered from non-invasive specimens (sputum and endotracheal aspiration), and a majority of specimens yielded a single gram-positive pathogen. Methicillin-resistant *S. aureus* was the predominant pathogen isolated. Using breakpoints proposed in this Application, no telavancin-nonsusceptible isolates were recovered in the clinical trials. No development of telavancin resistance was observed during the trials.

SUSCEPTIBILITY TEST METHODS

VALIDATION STUDIES

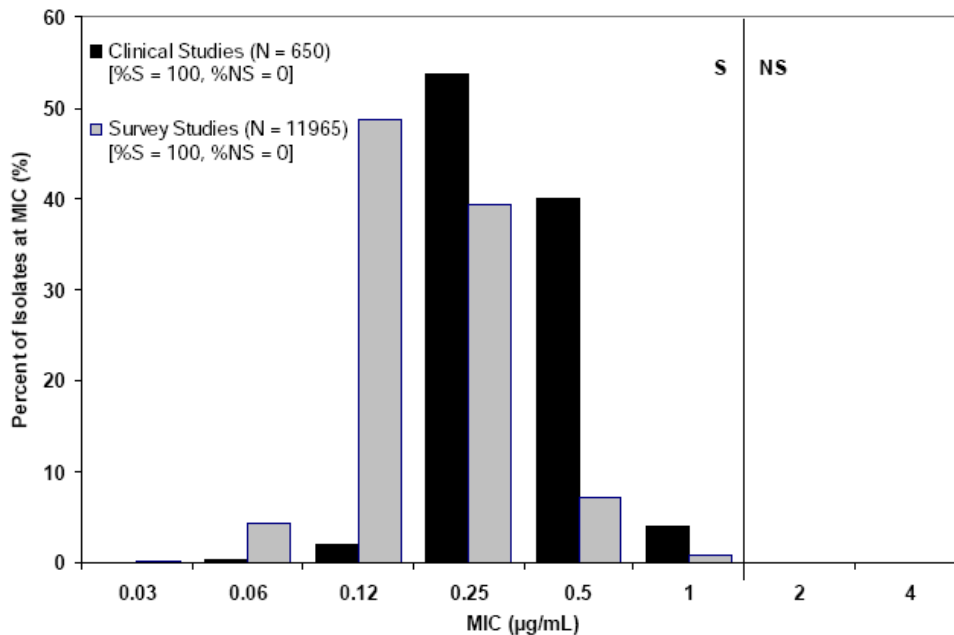
In NDA 22-110, the Applicant provided data from studies designed to investigate the effect of altered conditions (temperature, pH, incubation time, calcium ion concentration, incubation atmosphere, and inoculum size) in the susceptibility testing of telavancin against isolates of *S. aureus*, *E. faecalis*, *E. faecium*, and *S. pneumoniae*. While most parameters had little or no effect on outcome (MIC values within 1 doubling dilution, compared to testing under standard conditions), isolates of *S. pneumoniae* demonstrated dramatic differences in MIC values with changes in pH and inoculum size. Disk diffusion results for isolates of *S. pneumoniae*, *E. faecium*, and *S. epidermidis* were affected by differences in solid media lots and manufacturers. No additional studies of this type have been submitted in this Application.

The NDA 22-110 submission also included data from studies comparing broth dilution to agar dilution for the determination of telavancin MIC values. These studies generally demonstrated equivalence between the two methods, when testing staphylococcal and enterococcal isolates. Significant disparities were noted, however, when streptococcal isolates (including *S. pneumoniae*) were tested, with notably higher results obtained by the agar dilution method (> 1 doubling dilution). No additional studies, comparing agar dilution to broth dilution techniques have been submitted in this Application.

BROTH DILUTION METHODS

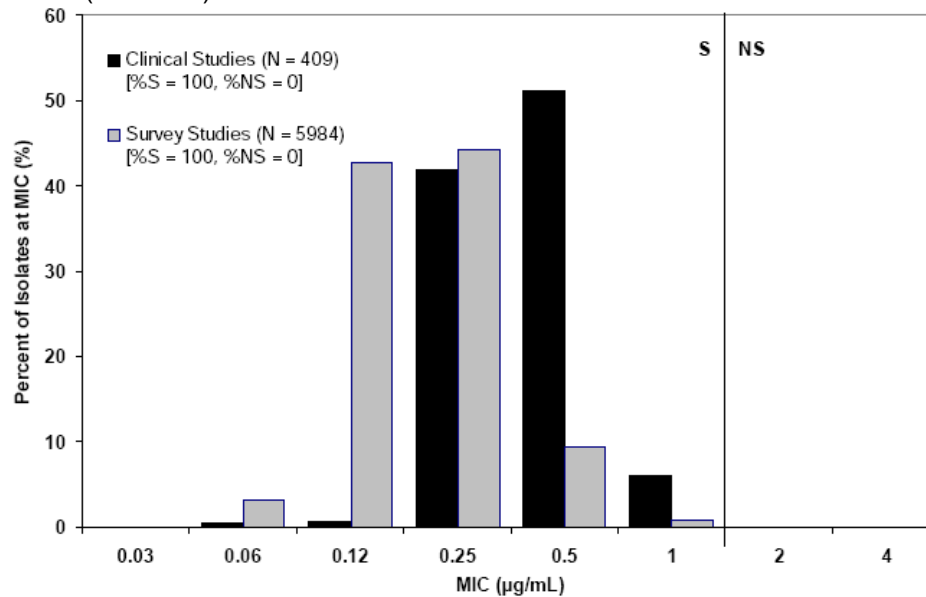
MIC data from all *S. aureus* isolates tested in studies submitted in support of this Application is summarized in Figure 24. The distribution of all tested isolates is unimodal, ranging from 0.03 mcg/ml to 1 mcg/ml (0.03 – 1 mcg/ml for the 11965 isolates tested in the survey studies, 0.06 – 1 mcg/ml for the 650 isolates tested in the clinical studies). The MIC₉₀ for the isolates tested in the clinical studies was 0.5 mcg/ml, and 0.25 mcg/ml for isolates tested in the survey studies. The MIC_{range} and MIC₉₀ values for methicillin-resistant *S. aureus* (Figure 25) were identical to those of methicillin-susceptible *S. aureus* (0.06 – 1 mcg/ml and 0.5 mcg/ml, respectively, for isolates collected in the clinical trials). With a breakpoint of 1 mcg/ml (proposed for both NDA 22110 and this Application), 100% of *S. aureus* isolates analyzed in both the survey studies and clinical studies are susceptible. No vancomycin non-susceptible *S. aureus* isolates were recovered in the clinical trials. The highest telavancin MIC against *S. aureus*, at which clinical efficacy was demonstrated in the HAP clinical studies was 1 mcg/ml.

Figure 24: Frequency Distribution of Telavancin MIC Values for *Staphylococcus aureus* from HAP Clinical Studies (N = 650, all baseline isolates) and Survey Studies (N = 11,965)



Vertical line on graph indicates proposed MIC breakpoint
4% of clinical trial and 0.4% of survey isolates tested at the proposed MIC breakpoint
Source: This submission, Section 5.3.5.4.1; Figure 1

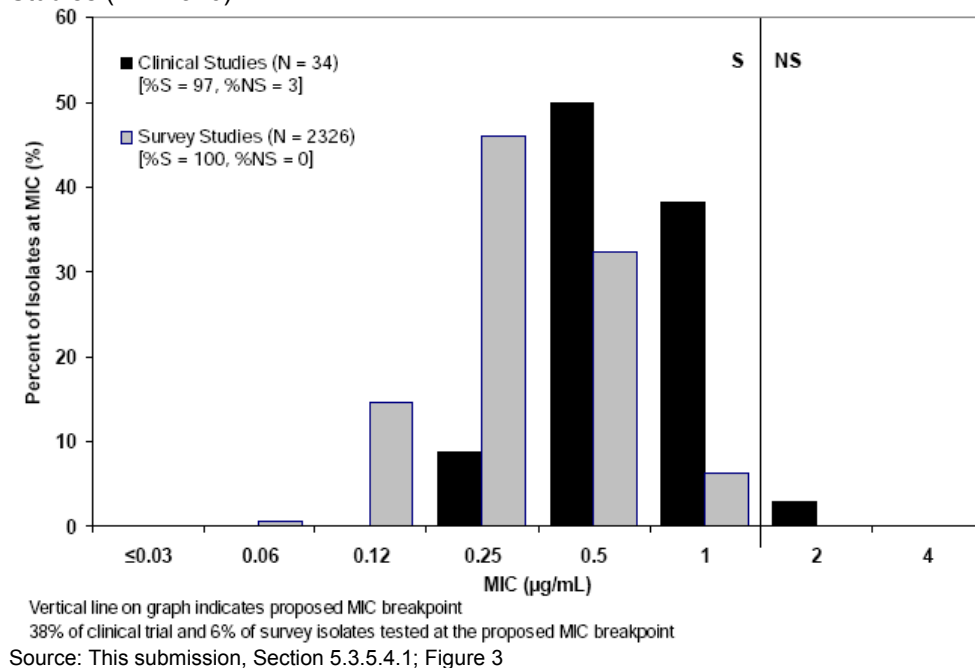
Figure 25: Frequency Distribution of Telavancin MIC Values for Methicillin-Resistant *Staphylococcus aureus* from HAP Clinical Studies (N = 409, all baseline isolates) and Survey Studies (N = 5984)



Vertical line on graph indicates proposed MIC breakpoint
6% of clinical trial and 0.6% of survey isolates tested at the proposed MIC breakpoint
Source: This submission, Section 5.3.5.4.1; Figure 2

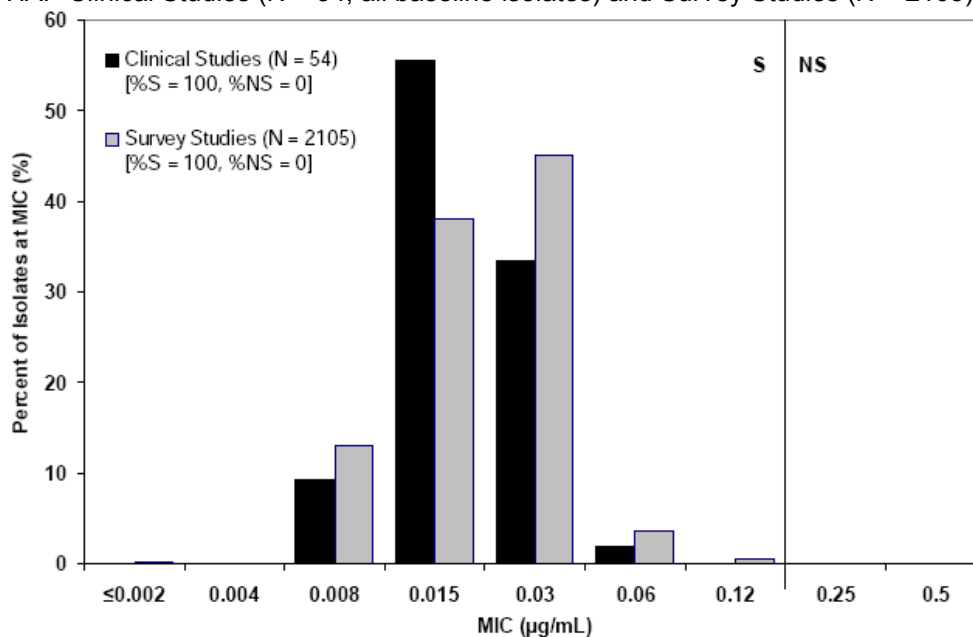
The distribution of all *Enterococcus faecalis* isolates tested in support of this Application (34 from clinical trials, 2325 from survey studies) is unimodal, ranging from ≤ 0.03 – 2 mcg/ml (Figure 26). The MIC_{range} and MIC₉₀ for the isolates recovered in clinical trials were 0.25 – 2 mcg/ml and 1 mcg/ml, respectively (compared to ≤ 0.03 – 1 mcg/ml and 1 mcg/ml for isolates tested in survey studies). At the proposed breakpoint of 1 mcg/ml, 100% of survey isolates and 97% (33 of 34) clinical trial isolates were susceptible to telavancin. The one clinical trial isolate with an MIC value of 2 mcg/ml was retested, with a value of 1 mcg/ml reported from duplicate analyses. The highest telavancin MIC against *E. faecalis*, at which clinical efficacy was demonstrated in the HAP clinical studies was 1 mcg/ml.

Figure 26: Frequency Distribution of Telavancin MIC Values for Vancomycin-susceptible *Enterococcus faecalis* from HAP Clinical Studies (N = 34, all baseline isolates) and Survey Studies (N = 2326)



The distribution of all *Streptococcus pneumoniae* isolates tested in support of this Application (54 from clinical trials, 2105 from survey studies) is unimodal, ranging from ≤ 0.002 – 0.12 mcg/ml (Figure 27). The MIC_{range} and MIC₉₀ for the isolates recovered in clinical trials were 0.008 – 0.06 mcg/ml and 0.03 mcg/ml, respectively (compared to ≤ 0.002 – 0.12 mcg/ml and 0.03 mcg/ml for isolates tested in survey studies). At the proposed breakpoint of 0.12 mcg/ml, 100% of survey isolates and clinical trial isolates were susceptible to telavancin. The highest telavancin MIC for *S. pneumoniae*, at which clinical efficacy was demonstrated in the HAP clinical studies was 0.03 mcg/ml.

Figure 27: Frequency Distribution of Telavancin MIC Values for *Streptococcus pneumoniae* from HAP Clinical Studies (N = 54, all baseline isolates) and Survey Studies (N = 2105)



Vertical line on graph indicates proposed MIC breakpoint
0% of clinical trial and 0.1% of survey isolates tested at the proposed MIC breakpoint
Source: This submission, Section 5.3.5.4.1; Figure 3

Table 49 summarizes clinical cure rates versus MIC values for isolates collected in the combined HAP clinical trials. Table 50 summarizes microbial eradication rates versus MIC values for the same set of organisms. The *E. faecalis* row includes the one isolate initially reported with an MIC value of 2 mcg/ml (re-tested twice, and reported here as 1 mcg/ml).

Table 49: Global Results for the Combined HAP Clinical Studies, ME Population, Telavancin Treatment Arm, Telavancin MIC versus Clinical Cure, n/N (%)

MIC (µg/mL)	<i>S. aureus</i> (All)	MRSA	MSSA	<i>S. pneumoniae</i>	<i>E. faecalis</i>
0.008	-- ^a	--	--	2/2 (100)	--
0.015	--	--	--	9/10 (90)	--
0.03	--	--	--	5/5 (100)	--
0.06	--	--	--	--	--
0.12	4/4 (100)	1/1 (100)	3/3 (100)	--	--
0.25	89/118 (75)	43/60 (72)	46/58 (79)	--	1/1 (100)
0.5	58/71 (82)	44/ 56 (79)	14/15 (93)	--	1/4 (25)
1	4/5 (80)	4/5 (80)	--	--	3/3 (100)
- Total -	155/198 (78)	92/122 (75)	63/76 (83)	16/17 (94)	5/8 (63)

^a Data not available

Source: This submission, Section 5.3.5.4.1.11; Table 3

Table 50: Global Results for the Combined HAP Clinical Studies, ME Population, Telavancin Treatment Arm, Telavancin MIC versus Microbiological Eradication, n/N (%)

MIC (µg/mL)	<i>S. aureus</i> (All)	MRSA	MSSA	<i>S. pneumoniae</i>	<i>E. faecalis</i>
0.008	-- ^a	--	--	2/2 (100)	--
0.015	--	--	--	10/10 (100)	--
0.03	--	--	--	5/5 (100)	--
0.06	--	--	--	--	--
0.12	4/4 (100)	1/1 (100)	3/3 (100)	--	--
0.25	86/118 (73)	41/60 (68)	45/58 (78)	--	1/1 (100)
0.5	58/71 (82)	44/56 (79)	14/15 (93)	--	1/4 (25)
1	4/5 (80)	4/5 (80)	--	--	3/3 (100)
- Total -	152/198 (77)	90/122 (74)	62/76 (82)	17/17 (100)	5/8 (63)

^a Data not available

Source: This submission, Section 5.3.5.4.1.11; Figure 4

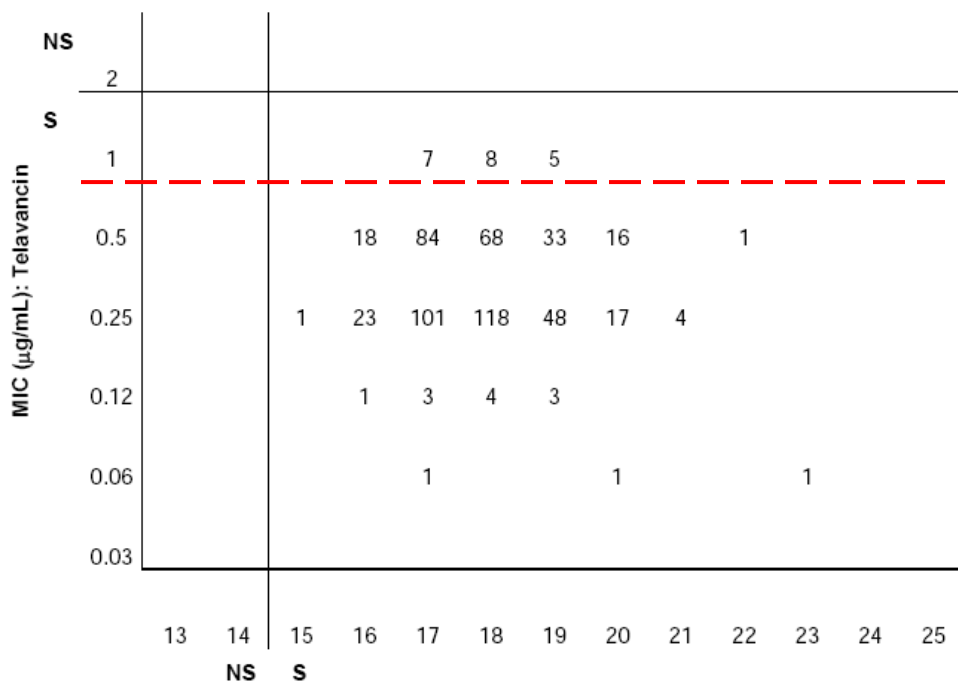
DISK DIFFUSION METHODS

Scatter plots, comparing MIC and disk diffusion results from isolates tested in the HAP clinical trials (ME population) are presented in Figures 29 through 32.

The scatter plot for *S. aureus* (n = 566), along with charted categorical errors, is presented in Figure 28. The scatter plot of methicillin-resistant isolates of *S. aureus* (n = 377), along with charted categorical errors, is presented in Figure 29.

Using data from the HAP clinical trials, and the Agency-proposed susceptible breakpoint of ≥ 0.05 µg/ml (susceptible zone size = 15mm), the very major error rate for *S. aureus* (methicillin-resistant and –susceptible) is 0%, as is the very major error rate for methicillin-resistant isolates, analyzed separately. The major error rates for both analysis groups (all *S. aureus* and MRSA) is also 0%. Breakpoints proposed by the Applicant are shown in non-hashed, black lines. Breakpoints proposed by the Agency are shown in hashed, red lines. Clinical outcome data, comparing cure rates during clinical trials to baseline telavancin susceptibility (disk diffusion method) is presented in Table 51.

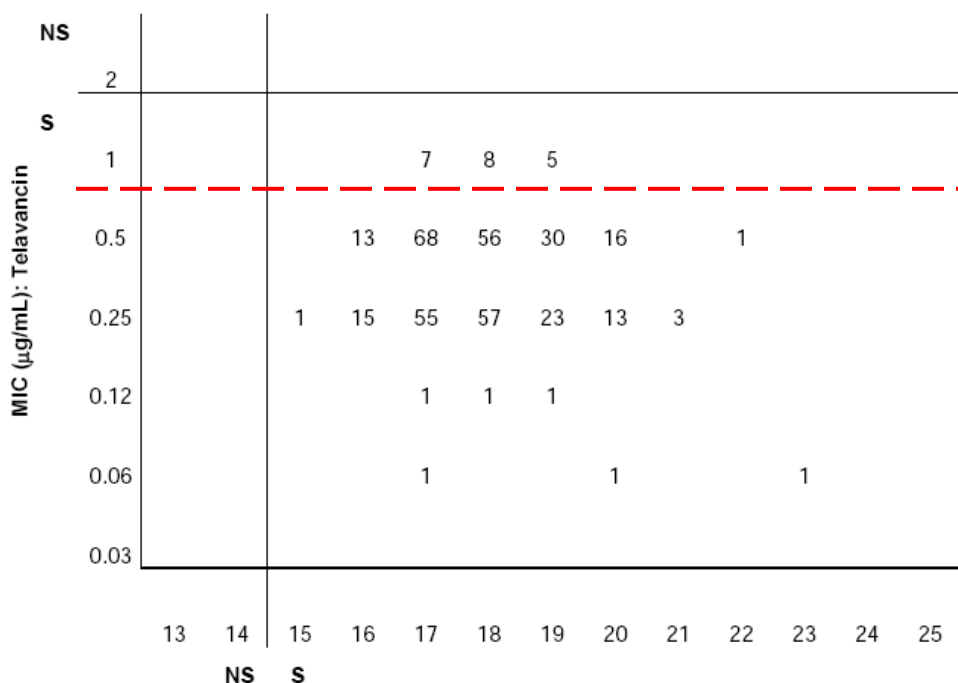
Figure 28: Telavancin Broth Microdilution MIC vs. Disk Diffusion Zone Diameter against *Staphylococcus aureus* from HAP Clinical Studies (Microbiologically Evaluable population, all treatment arms) (N = 566)



Zone Diameter (mm): Telavancin					
MIC Range	Total N	Very Major	% Very Major	Major	% Major
≥ R+1	0	0	0.0%	N/A	N/A
R+S	239	0	0.0%	0	0.0%
≤ S-1	327	N/A	N/A	0	0.0%
Total	566	0	0.0%	0	0.0%

Source: This submission, Section 5.3.5.4.1; Figure 5

Figure 29: Telavancin Broth Microdilution MIC vs. Disk Diffusion Zone Diameter against Methicillin-resistant *Staphylococcus aureus*, from HAP Clinical Studies (Microbiologically Evaluable population, all treatment arms) (N = 377)



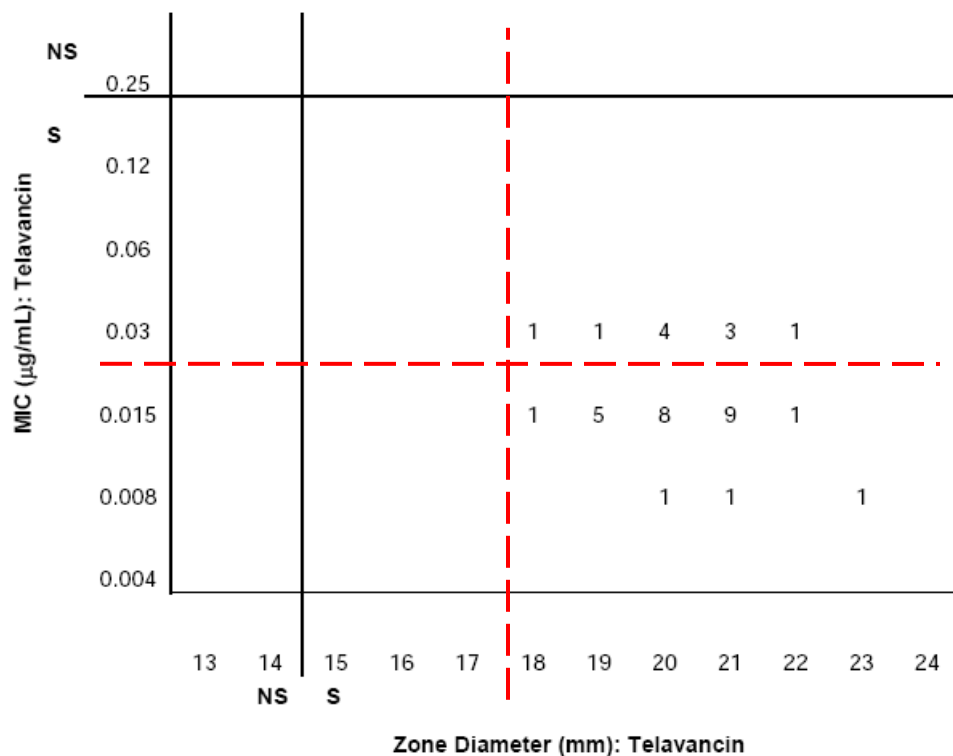
Zone Diameter (mm): Telavancin					
MIC Range	Total N	Very Major	% Very Major	Major	% Major
≥ R+1	0	0	0.0%	N/A	N/A
R+S	204	0	0.0%	0	0.0%
≤ S-1	173	N/A	N/A	0	0.0%
Total	377	0	0.0%	0	0.0%

Source: This submission, Section 5.3.5.4.1.11; Figure 6

The scatter plot for *S. pneumoniae* isolates collected in HAP clinical trials (n = 37), along with charted categorical errors, is presented in Figure 30. Since the number of isolates of *S. pneumoniae* that were collected in the clinical trials was relatively low, and since *S. pneumoniae* was not sought as an indication in NDA 22110 (and discussed in that review), a scatter plot of combined isolates of *S. pneumoniae* from clinical trials and survey studies (n = 137), along with charted categorical errors, is presented in Figure 31.

Using data from the HAP clinical trials only, the Agency-proposed susceptible breakpoint of ≥ 0.015 mcg/ml (susceptible zone size = 18 mm), the very major error rate and major error rate for *S. pneumoniae* is 0%. Breakpoints proposed by the Applicant are shown in non-hashed, black lines. Breakpoints proposed by the Agency are shown in hashed, red lines. Clinical outcome data, comparing cure rates during clinical trials to baseline telavancin susceptibility (disk diffusion method) is presented in Table 51.

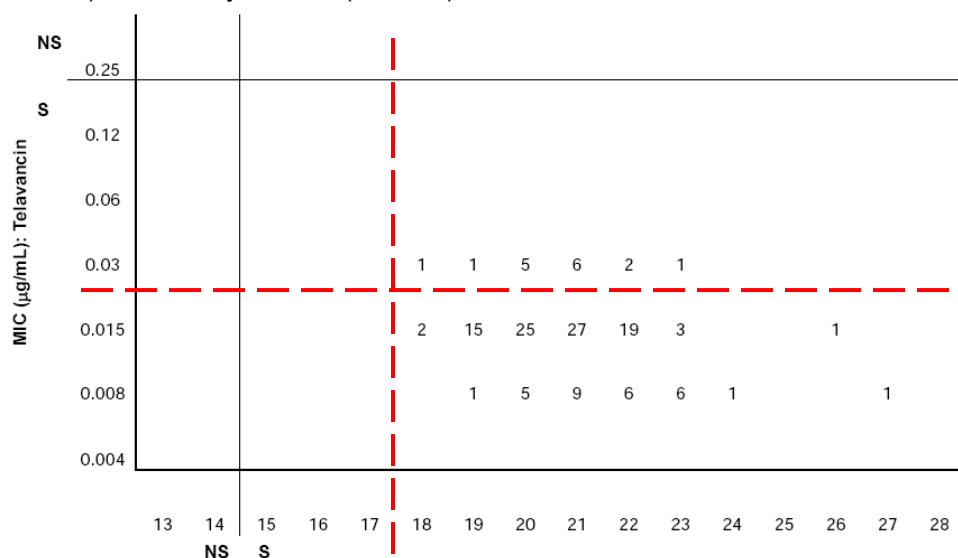
Figure 30: Telavancin Broth Microdilution MIC vs. Disk Diffusion Zone Diameter against *Streptococcus pneumoniae* from HAP Clinical Studies (Microbiologically Evaluable Population, N = 37)



MIC Range	Total N	Very Major	% Very Major	Major	% Major
≥ R+1	0	0	0.0%	N/A	N/A
R+S	34	0	0.0%	0	0.0%
≤ S-1	3	N/A	N/A	0	0.0%
Total	37	0	0.0%	0	0.0%

Source: This submission, Section 5.3.5.4.1.11; Figure 8

Figure 31: Telavancin Broth Microdilution MIC vs. Disk Diffusion Zone Diameter against *Streptococcus pneumoniae* from Combined HAP Clinical (Microbiologically Evaluable Population, N = 37) and Survey Studies (N = 100)



Zone Diameter (mm): Telavancin					
MIC Range	Total N	Very Major	% Very Major	Major	% Major
≥ R+1	0	0	0.0%	N/A	N/A
R+S	108	0	0.0%	0	0.0%
≤ S-1	29	N/A	N/A	0	0.0%
Total	137	0	0.0%	0	0.0%

Source: This submission, Section 5.3.5.4.1.11; Figure 7

Table 51: Global Results for the Combined HAP Clinical Studies, ME Population, Telavancin Treatment Arm, Zone Diameter versus Clinical Cure, n/N (%)

Zone (mm)	<i>S. aureus</i> (All)	MRSA	MSSA	<i>S. pneumoniae</i>	<i>E. faecalis</i>
23	-- ^a	--	--	1/1 (100)	--
22	--	--	--	0/1 (0)	--
21	2/2 (100)	1/1 (100)	1/1 (100)	6/6 (100)	--
20	10/12 (83)	8/10 (80)	2/2 (100)	3/3 (100)	--
19	28/34 (82)	17/21 (81)	11/13 (85)	4/4 (100)	--
18	50/67 (75)	32/43 (74)	18/24 (75)	2/2 (100)	1/2 (50)
17	52/68 (76)	27/38 (71)	25/30 (83)	--	3/5 (60)
16	13/15 (87)	7/9 (78)	6/6 (100)	--	1/1 (100)
15	--	--	--	--	--
- Total -	155/198 (78)	92/122 (75)	63/76 (83)	16/17 (94)	5/8 (63)

^a Data not available

Source: This submission, Section 5.3.5.4.1.11; Figure 5

Table 52: Global Results for the Combined HAP Clinical Studies, ME Population, Telavancin Treatment Arm, Zone Diameter versus Microbiological Eradication, n/N (%)

Zone (mm)	<i>S. aureus</i> (All)	MRSA	MSSA	<i>S. pneumoniae</i>	<i>E. faecalis</i>
23	-- ^b	--	--	1/1 (100)	--
22	--	--	--	1/1 (100)	--
21	1/2 (50)	0/1 (0)	1/1 (100)	6/6 (100)	--
20	10/12 (83)	8/10 (80)	2/2 (100)	3/3 (100)	--
19	28/34 (82)	17/21 (81)	11/13 (85)	4/4 (100)	--
18	50/67 (75)	32/43 (74)	18/24 (75)	2/2 (100)	1/2 (50)
17	50/68 (74)	26/39 (68)	24/30 (80)	--	3/5 (60)
16	13/15 (87)	7/9 (78)	6/6 (100)	--	1/1 (100)
15	--	--	--	--	--
- Total -	152/198 (77)	90/122 (74)	62/76 (82)	17/17 (100)	5/8 (63)

Data not available

Source: This submission, Section 5.3.5.4.1.11; Figure 6

Susceptibility Test Methods ~ Conclusions:

Telavancin MIC distributions from clinical trials and survey studies are unimodal for *S. aureus* (both methicillin-susceptible and methicillin-resistant strains), *E. faecalis*, and *S. pneumoniae*. Distributions derived from clinical studies, for these pathogens, are similar to those derived from survey studies, although the percentage of clinical isolates with higher telavancin MIC values appears to trend higher, for isolates of *S. aureus* and *E. faecalis*, compared to survey isolates, particularly at higher MIC values. Since this may imply developing resistance among these pathogens, continued surveillance is warranted.

Correlation studies comparing the disk diffusion method of susceptibility testing with the minimum inhibitory concentration method support the zone size recommendations of the Applicant.

Data from reference laboratory reports, reviewed in NDA 22110, suggest that susceptibility testing of telavancin, using solid media techniques, may result in values that are difficult to reproduce or vary from acceptable quality control ranges. This may be due to the size of the telavancin molecule and its diffusion properties. Susceptibility testing by the agar diffusion method is not recommended. Data presented in this Application suggests that modest alterations in the pH of test media and inoculum size may result in unreliable telavancin susceptibility results for *S. pneumoniae*.

Data from quality control studies do not support vancomycin as a class-representative surrogate for telavancin susceptibility testing.

APPLICANT'S PROPOSED SUSCEPTIBILITY INTERPRETIVE CRITERIA

Table 53: Applicant-proposed Telavancin Susceptibility Breakpoints

Pathogen	Susceptibility Interpretive Criteria ^a					
	MIC (µg/mL)			Zone Diameter (mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i> (including methicillin-resistant strains)	≤ 1	--	--	≥ 15	--	--
<i>Streptococcus agalactiae</i> <i>Streptococcus anginosus</i> group <i>Streptococcus pneumoniae</i> <i>Streptococcus pyogenes</i>	≤ 0.12	--	--	≥ 15	--	--
<i>Enterococcus faecalis</i> (vancomycin-susceptible only)	≤ 1	--	--	≥ 15	--	--

^a The current absence of data on resistant isolates precludes defining any categories other than Susceptible (S). Isolates yielding results other than susceptible should be submitted to a reference laboratory for further testing.

Based on data from the Phase 3 clinical trials, in addition to in vitro studies of telavancin activity against the pathogens sought in the proposed indications, the Agency proposes the following susceptibility breakpoints (Table 54) for pathogens investigated in studies of patients diagnosed with nosocomial pneumoniae (including VAP). Note that this table includes recommendations for susceptibility testing of isolates of *S. pneumoniae*, although the Agency is recommending removal of that bacterium from the list of pathogens in the proposed labeling.

Table 54: Agency-proposed Telavancin Susceptibility Breakpoints

Pathogen	Susceptibility Interpretive Criteria					
	MIC (mcg/ml)			Zone Diameter (mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i> (including methicillin-resistant isolates)	≤ 1	-	-	≥15	-	-
<i>Streptococcus pneumoniae</i>	≤0.03	-	-	≥18	-	-

APPLICANT'S PROPOSED SUBSECTION OF THE PACKAGE INSERT

Telavancin is a semisynthetic, lipoglycopeptide antibiotic. Telavancin exerts concentration-dependent, bactericidal activity against gram-positive organisms in vitro, as demonstrated by time-kill assays and MBC/MIC ratios (minimum bactericidal concentration/minimum inhibitory concentration) using broth dilution methodology. In vitro studies demonstrated a telavancin post-antibiotic effect ranging from 1 to 6 hours against *S. aureus* and other gram-positive pathogens.

Although telavancin is approximately 90% protein bound, the presence of human serum or human serum albumin has minimal impact on the *in vitro* activity of telavancin against staphylococci, streptococci, and vancomycin-susceptible enterococci.

Mechanism of Action:

Telavancin inhibits cell wall biosynthesis by binding to late-stage peptidoglycan precursors, including lipid II. Telavancin also binds to the bacterial membrane and disrupts membrane barrier

function.

Interactions with Other Antibiotics:

In vitro investigations demonstrated no antagonism between telavancin and amikacin, aztreonam, cefepime, ceftriaxone, ciprofloxacin, gentamicin, imipenem, meropenem, oxacillin, piperacillin/tazobactam, rifampin, and trimethoprim/sulfamethoxazole, (b) (4)

(b) (4)

Cross-Resistance:

Some vancomycin-resistant enterococci have reduced susceptibility to telavancin. There is no known cross-resistance between telavancin and other classes of (b) (4)

(b) (4)

Susceptibility Test Methods:

When available, the clinical microbiology laboratory should provide cumulative results of the *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution technique

Quantitative methods are used to determine antimicrobial MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure (b) (4). Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of telavancin powder. The MIC values should be interpreted according to the criteria provided in Table (b) (4)

Diffusion technique

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations (b) (4). This procedure uses paper disks impregnated with 30 µg of telavancin to test the susceptibility of microorganisms to telavancin. The disk diffusion interpretive criteria are provided in Table (b) (4)

Table (b) (4) Susceptibility Interpretive Criteria for Telavancin

	Susceptibility Interpretive Criteria ^a					
	Minimal Inhibitory Concentration (µg/mL)			Disk Diffusion Zone Diameter (mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i> (including methicillin-resistant isolates)	≤ 1	--	--	≥ 15	--	--
(b) (4) <i>Streptococcus pyogenes</i> <i>Streptococcus agalactiae</i> <i>Streptococcus anginosus</i> group	≤ 0.12	--	--	≥ 15	--	--
<i>Enterococcus faecalis</i> (vancomycin-susceptible isolates only)	≤ 1	--	--	≥ 15	--	--

a. The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding results other than susceptible should be subjected to additional testing.

A report of "Susceptible" indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to monitor the performance of the supplies and reagents used in the assay and the techniques of the individuals performing the test. Standard telavancin powder should provide the range of values noted in Table (b) (4).

Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains used for microbiological quality control are not clinically significant.

Table (b) (4) Acceptable Quality Control Ranges for Telavancin to be Used in Validation of Susceptibility Test Results

	Acceptable Quality Control Ranges	
	Minimal Inhibitory Concentration (µg/mL)	Disk Diffusion Zone Diameter (mm)
<i>Enterococcus faecalis</i> ATCC 29212	0.12-0.5	Not applicable
<i>Staphylococcus aureus</i> ATCC 29213	0.12-1	Not applicable
<i>Staphylococcus aureus</i> ATCC 25923	Not applicable	16-20
<i>Streptococcus pneumoniae</i> ATCC 49619 ^a	0.004-0.03	17-24

^a This organism may be used for validation of susceptibility test results when testing *Streptococcus* spp. other than *S. pneumoniae*.

CONCLUSIONS AND RECOMMENDATIONS

See page 3.

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Kerry Snow MS, MT(ASCP)
Clinical Microbiology Reviewer

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/s/

KERRY SNOW
12/23/2012

Division of Anti-Infective and Ophthalmology Products Clinical Microbiology Review

NDA: 22-407, Telavancin for injection

Date Company Submitted: 23 January 2009
Date received by CDER: 23 January 2009
Date Assigned: 3 February 2009
Date Completed: 4 September 2009
Reviewer: Kerry Snow MS

NAME AND ADDRESS OF APPLICANT:

Theravance, Inc.
901 Gateway Boulevard
South San Francisco, California USA

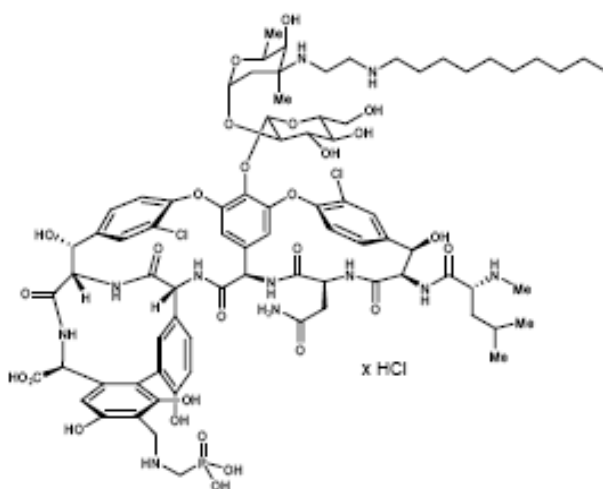
CONTACT PERSON:

Joseph Tsiakals, Vice President, Quality
Phone: 650-808-6167

DRUG PRODUCT NAMES:

Proprietary Name: Vibativ
Code Name: TD-6424
Established Name: Telavancin hydrochloride
Molecular Weight: 1755.6
Chemical Name: vancomycin, N3" [2 (decylamino) ethyl] 29 [[[phosphono-methyl) amino] methyl]
hydrochloride

STRUCTURAL FORMULA:



Telavancin hydrochloride

MOLECULAR FORMULA:

$C_{80}H_{106}Cl_2N_{11}O_{27}P \cdot xHCl$ (where $x = 1$ to 3)

MOLECULAR WEIGHT:

1755.6

DRUG CATEGORY:

Antibacterial

PROPOSED DOSAGE FORM AND STRENGTH:

Sterile, lyophilized powder for intravenous infusion in two dosage forms, 250 mg/vial and 750 mg/vial

ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT:

Proposed dosing is 10 mg/kg over a 60-minute period by intravenous infusion once every 24 hours for 7 to 14 days (in patients with normal renal clearance). For renally impaired patients, the following dosage adjustments are recommended by the Applicant:

Dosage Adjustment in Adult Patients with Renal Impairment

Creatinine Clearance* (mL/min)	Telavancin Dose and Dosage Interval
> 50	10 mg/kg every 24 hours
30-50	7.5 mg/kg every 24 hours
< 30 and hemodialysis	10 mg/kg every 48 hours

DISPENSED:

Rx

PROPOSED INDICATION:

Treatment of patients with nosocomial pneumonia caused by susceptible isolates of *Staphylococcus aureus* (including methicillin-susceptible and –resistant) isolates and *Streptococcus pneumoniae*.

RELATED DOCUMENTS:

IND 60,237
NDA 22-110

TYPE OF SUBMISSION:

New Drug Application

PURPOSE OF SUBMISSION:

This New Drug Application (NDA) is submitted to seek approval for the use of Telavancin (Vibativ) as an intravenous infusion (10mg/kg administered over 60 minutes) for the treatment of nosocomial pneumonia. This review addresses the development testing criteria and quality control parameters, proposed by the applicant for the in vitro testing of telavancin. Supportive data, reviewed here, include in vitro drug characteristics (including mechanism of action, drug interaction, and development of resistance), pharmacokinetic/pharmacodynamic analysis, and correlation of in vitro activity with clinical outcomes.

REMARKS:

The Applicant has referenced NDA 22-110, which was submitted on 6 December 2006. That Application was submitted to seek approval for the use of telavancin (Vibativ) as an intravenous infusion (10 mg/kg administered over 60 minutes) for the treatment of complicated skin and skin structure infections (cSSSI), and addressed the development of testing criteria and quality control parameters for susceptibility testing of telavancin. Subsequently this application for the use of telavancin for the treatment of cSSSI was approved by the Agency.

SUMMARY AND RECOMMENDATIONS:

Because the Agency has decided not to approve telavancin for HAP at this time due to issues of data integrity a final summary and conclusion can not be written. However, the clinical microbiology in vitro and clinical study data that was provided in this submission to support the use of telavancin for HAP suggests that telavancin may have clinical utility in treating HAP due to *S. pneumoniae* and *S. aureus*.

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EXECUTIVE SUMMARY

I. IN VITRO INFORMATION

MECHANISM OF ACTION

Investigations of telavancin generally support the claim for two distinct mechanisms of action, and for enhanced activity, compared to vancomycin and other comparators. Studies by the Applicant demonstrate substrate-dependent inhibition of PG biosynthesis, both with regard to formation of immature PG and to cross-linking of mature PG strands. Inhibition of PG biosynthesis appears to be enhanced, compared to vancomycin; an effect that may be attributable to a higher affinity of telavancin for cell membrane components. In investigations that linked mechanisms of action to antibacterial activity, MICs for telavancin-treated bacteria were lower than glycopeptide comparators (vancomycin and/or teicoplanin). In the current submission, the Applicant has provided data that supports the contention that the second mechanism of action, depolarization of the microbial cell membrane, occurs at attainable drug levels, in the absence of cell lysis, and is dependent on association of telavancin with Lipid II.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

Data submitted from large prospective surveillance studies and other investigations of in vitro activity, including investigations conducted in support of NDA 22110, support the applicant's claim of activity against the pathogens generally associated with hospital acquired pneumonia, including the organisms listed in the proposed indication for telavancin. MIC values for all tested strains of *S. aureus* and *S. pneumoniae* (including isolates resistant to other classes of antimicrobials, and stains with specific virulence profiles) were below attainable drug levels.

RESISTANCE STUDIES

The Applicant has provided, as reference to NDA 22110 and in information from investigations undertaken since that submission, sufficient data to demonstrate a low potential for development of resistance to bacterial species considered in the proposed indications. Data presented in this Application suggest that telavancin is an inducer of the VanA operon, but does not induce activity of the VanB operon. Population analysis profiles have not detected heteroresistance to telavancin in isolates of *S. aureus*. No resistance to telavancin was noted in isolates collected in clinical trials.

ANTIMICROBIAL INTERACTION STUDIES

In data presented in this Application as well as in NDA 22110, the Applicant has demonstrated modest synergy of telavancin with β -lactams, rifampin, ciprofloxacin, and gentamicin, against isolates of *S. aureus*, including methicillin-resistant and vancomycin-non-susceptible phenotypes. Telavancin activity is additive with other studied drug combinations. No antagonism has been demonstrated with telavancin and any tested antimicrobial.

EFFECTS OF MISCELLANEOUS FACTORS ON ACTIVITY

Telavancin is approximately 90% protein bound, primarily by albumin. Studies presented in this Application and in NDA 22110 indicate that telavancin retains in vitro activity against the principle respiratory pathogens sought in the proposed indication, in the presence of albumin or human serum. Recent studies also suggest that telavancin activity is not inhibited by pulmonary surfactant. Telavancin is active against isolates of *S. aureus* in stationary growth phase, and has

demonstrated activity against isolates of *S. aureus*, *S. epidermidis*, and *E. faecalis* in a biofilm model. The postantibiotic effect of telavancin, against isolates of *S. aureus* (including methicillin-susceptible and –resistant isolates, as well as vancomycin-non-susceptible isolates) ranges from one to six hours. The antimicrobial activity of the three primary telavancin metabolites (AMI-11352, AMI-11353, and AMI-11355) is ≥ 8 -fold higher than that of telavancin.

BACTERICIDAL ACTIVITY

The Applicant has submitted data, in NDA 22110 and this Application, from time-kill kinetic studies to support a claim of bactericidal activity of telavancin against a variety of strains of *S. aureus*, including methicillin-susceptible and –resistant phenotypes, as well as isolates non-susceptible to vancomycin, and against isolates of *S. pneumoniae*. This activity generally occurs at low multiples of the MIC and at concentrations consistent with therapeutic levels, even at trough concentrations. Telavancin demonstrated modest bactericidal activity against strains of enterococcus, with killing occurring only at high drug concentrations. Telavancin bactericidal activity against enterococci was superior to comparators, though, in most cases.

II. HUMAN AND ANIMAL STUDIES

ANIMAL DISEASE MODELS

The applicant has submitted data from animal in vivo studies that supports the use of $AUC_{(0-24)}/MIC$ as the best PK/PD predictor of antimicrobial efficacy for unbound (free) telavancin. Data from neutropenic mouse thigh models suggest that an $AUC_{(0-24)}/MIC$ ratio of 219 results in a one log₁₀ reduction in CFU/g against methicillin-resistant *S. aureus* with an MIC of 1 mcg/ml. Animal models of infection suggest that immune status may play a minor role in telavancin efficacy.

PHARMACOKINETIC / PHARMACODYNAMIC STUDIES

In NDA 22110, the applicant provided data from a variety of studies to support the proposed pharmacokinetic parameters. Monte Carlo simulation, based on the proposed dosage (10 mg/kg) supports a susceptible breakpoint as high as 2 µg/ml (based on > 99% target attainment at that concentration). Additional information, provided in this Application, suggests that telavancin is concentrated in human alveolar macrophages (exceeding 10 mcg/ml) and that the AUC of the antimicrobial in epithelial lining fluid (in uninfected lung tissue) is approximately 75% that of AUC_{plasma} .

III. CLINICAL TRIALS

Data from the two Phase 3 clinical trials indicate that telavancin is effective against the pathogens in the proposed indications. Specimen types, subject demographics, subject co-morbidities, and bacterial isolates were similar between the telavancin and vancomycin arms of the trials. The majority of principle pathogens were recovered from non-invasive specimens (sputum and endotracheal aspiration), and a majority of specimens yielded a single Gram-positive pathogen. Methicillin-resistant *S. aureus* was the predominant pathogen isolated. Using breakpoints proposed in this Application, no telavancin-nonsusceptible isolates were recovered in the clinical trials. No development of telavancin resistance was observed during the trials.

IV. SUSCEPTIBILITY TEST METHODS

Telavancin MIC distributions from clinical trials and survey studies are unimodal for *S. aureus* (both methicillin-susceptible and methicillin-resistant strains), *E. faecalis*, and *S. pneumoniae*. Distributions derived from clinical studies, for these pathogens, are similar to those derived from

survey studies, although the percentage of clinical isolates with higher telavancin MIC values appears to trend higher, for isolates of *S. aureus* and *E. faecalis*, compared to survey isolates, particularly at higher MIC values. Since this may imply developing resistance among these pathogens, continued surveillance is warranted.

Correlation studies comparing the disk diffusion method of susceptibility testing with the minimum inhibitory concentration method support the zone size recommendations of the Applicant.

Data from reference laboratory reports, reviewed in NDA 22110, suggest that susceptibility testing of telavancin, using solid media techniques, may result in values that are difficult to reproduce or vary from acceptable quality control ranges. This may be due to the size of the telavancin molecule and its diffusion properties. Susceptibility testing by the agar diffusion method is not recommended. Data presented in this Application suggests that modest alterations in the pH of test media and inoculum size may result in unreliable telavancin susceptibility results for *S. pneumoniae*.

Data from quality control studies do not support vancomycin as a class-representative surrogate for telavancin susceptibility testing.

V. AGENCY'S PROPOSED CLINICAL MICROBIOLOGY SUBSECTION OF THE PACKAGE INSERT

Because labeling will not be discussed with the Applicant at this time due to non-approval of the drug for treating HAP by the Agency labeling will not be included in this review.

INTRODUCTION

LIPOGLYCOPEPTIDE CLASS OF ANTIBIOTICS

The glycopeptides of the vancomycin class and teicoplanin class are naturally occurring products, derived from various species of soil actinomycetes (Kahne 2005). Glycopeptides are known to inhibit synthesis of the bacterial cell wall, by binding to the D-alanyl-D-alanine terminus of lipid II, the GlcNAc-MurNAc disaccharide (linked to an undecaprenyl pyrophosphate carrier) that is the peptidoglycan precursor for most bacterial species of clinical interest. The stable complex that is formed by the glycopeptide and the lipid II molecule results in steric hindrance of the glycosylase and transpeptidase enzymes that are necessary for cell wall synthesis (Perkins 1974). The glycopeptides are generally bactericidal.

Lipoglycopeptides include naturally occurring antibiotics (e.g. teicoplanin) and semi-synthetic derivatives (e.g. dalbavancin and oritavancin). Lipoglycopeptides share the basic mechanism of action of the glycopeptide class, described above.

The glycopeptides and lipoglycopeptides are large, complex molecules. Because of their considerable molecular mass (the molecular weight of vancomycin is 1485.73 and the molecular weight of telavancin is 1755.6), members of the class are unable to cross the outer membrane of Gram negative bacteria, limiting their activity to Gram positive pathogens. Both Vancomycin (the only glycopeptide approved for use in the United States) and Daptomycin (the only approved lipoglycopeptide) have broad-spectrum activity against Gram positive microorganisms, including most staphylococcal species, most streptococci (including all strains of *S. pyogenes*, *S. agalactiae*, and *S. pneumoniae*), *Bacillus* species (including *B. anthracis*), most *Corynebacterium* species (including *C. jeikeium*), and many anaerobic Gram positive pathogens (including *Clostridium difficile*) (Mandell 2005). The activity of vancomycin against some strains of enterococci has decreased in recent years, possibly as a result of more widespread use of the antimicrobial against methicillin-resistant *S. aureus* (MRSA). The gene cluster responsible for this increased resistance has been identified in rare instances of staphylococcal infection (VRSA). Reduced activity of vancomycin against *S. aureus* (GISA, hGISA) has been noted more frequently than VRSA, and may result from a mechanism other than that mediated by the VanA gene cluster. Daptomycin appears to retain activity against vancomycin-resistant strains of enterococci (VRE) and staphylococci (both GISA and VRSA), and exhibits rapid, bactericidal activity against these pathogens (Akins 2001).

The glycopeptides have poor bioavailability and are difficult to administer intramuscularly. They are approved for intravenous administration. The most predictive pharmacodynamic parameter for both vancomycin and daptomycin is the AUC/MIC ratio. Daptomycin exhibits a prolonged postantibiotic effect (PAE), where the PAE of vancomycin against staphylococcal and enterococcal species is relatively short.

The resurgence of interest in the glycopeptides, since the beginning of the 1980s, corresponds to the concurrent increases in nosocomial infections caused by Gram positive pathogens, the emergence and spread of resistant strains, and improvements in the purification and dosing of vancomycin (Bryskier 2005). Rising rates of vancomycin treatment failures (Moise 2000), the increasing spread of resistance in enterococci and staphylococci, and the emergence of heterogeneous vancomycin-intermediate *S. aureus* (hVISA) continue to spur research for improved glycopeptide antimicrobials.

Telavancin (formerly TD-6424; proposed proprietary name, Vibativ) is a semisynthetic derivative of vancomycin, substituted on the vancosamine sugar by a decylamino-ethyl hydrophobic side chain, and on the resorcinol moiety of the cyclic peptidic core by a phosphonomethyl aminomethyl side chain. The lipid side chain is credited with the increased activity of telavancin

against MRSA and VanA enterococci, compared to vancomycin, while the polar side chain improves tissue distribution (Kanafani 2006). Telavancin hydrochloride is available as a sterile lyophilized powder for injection.

HOSPITAL ACQUIRED PNEUMONIA

Hospital acquired pneumonia (HAP) is defined as pneumonia that occurs 48 hours or more after admission [Niederman 2005]. HAP may be differentiated by hospital location of onset (ICU vs. ward) and time of occurrence (early onset vs. late onset). Infections with multi-drug resistant (MDR) pathogens are more commonly associated with late-onset HAP and VAP (ventilator-associated pneumonia). HAP is an important cause of morbidity and mortality and accounts for approximately 25% of ICU infections [Richards 1999]. Mortality attributable to HAP is estimated to be between 33 and 50%.

Bacterial pathogens commonly associated with HAP include *Staphylococcus aureus* (particularly methicillin-resistant isolates), *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, and *Acinetobacter* species. The rates of polymicrobial infections and of infections by multi-drug resistant isolates are increasing [Fridkin 2001]. Over 50% of *S. aureus* infections in ICU environments are methicillin-resistant. *S. aureus* clinical isolates that are non-susceptible to vancomycin are currently rare, and most are susceptible to linezolid. Aspiration of oropharyngeal bacteria is the primary endogenous route of pathogen movement to the lower respiratory tract. Exogenous sources of infection include transmission from health care workers, nebulizers, biofilms, and ventilatory circuits.

Diagnosis of HAP should include collection and culture of lower respiratory secretions prior to antibiotic treatment. Acceptable samples include expectorated sputum, endotracheal aspirates, bronchoalveolar lavage samples, and bronchoalveolar brushes. Gram stains should be performed, and reports should include quantitation of epithelial cells and polymorphonuclear leukocytes. Bacteria present in the Gram stain preparation should be reported semi-quantitatively, with Gram stain morphology described. Culture media should include sheep blood agar, an enriched media for the recovery of fastidious bacteria and *Haemophilus* species (e.g. chocolate agar), and a medium designed to select Gram negative pathogens (e.g. MacConkey agar). Additional media and staining techniques should be included if specific etiologic agents are suspected (e.g. mycobacteria, *Legionella* sp., etc.).

Current recommendations for empiric therapy of HAP are grouped according to disease severity and risk factors for MDR pathogens. Patients with late onset HAP and with identified risk factors for MRSA should be treated with vancomycin or linezolid, according to guidelines published by the American Thoracic Society and the Infectious Diseases Society of America. Recent studies have demonstrated a high number of vancomycin treatment failures, possibly related to under-dosing [Moise 2000]. In a recent retrospective analysis [Wunderink 2003], patients with HAP due to MRSA had significantly better clinical cure and survival rates when treated with early-therapy linezolid, compared to those treated with vancomycin.

IN VITRO INFORMATION

MECHANISM OF ACTION

Glycopeptides inhibit biosynthesis of peptidoglycan (PG) by binding to the terminal D-alanyl-D-alanine dipeptide of the lipid II molecule. This binding results in steric hindrance of transglycosylases (which catalyze the transfer of Lipid II to growing PG strands) and transpeptidases (which catalyze peptide cross-linking) (Van Bambeke 2004). The blockage of PG biosynthesis results in inhibition of growth and eventual cell death (Bryskier 2005).

Because of their large size, glycopeptides are not able to cross the outer membrane of Gram negative bacteria, so their antimicrobial activity is limited to Gram positive organisms.

In addition to the mechanism described above, telavancin exhibits a second mechanism of action, which appears to involve disruption of the bacterial plasma membrane (described below).

Data from investigations of telavancin submitted in NDA 22110 generally support the claim for two distinct mechanisms of action, and for enhanced activity, compared to vancomycin and other comparators. Those studies demonstrated substrate-dependent inhibition of PG biosynthesis, both with regard to formation of immature PG and to cross-linking of mature PG strands. Inhibition of PG biosynthesis appeared to be enhanced, compared to vancomycin, an effect that may be attributable to a higher affinity of telavancin for cell membrane components. Investigations that linked mechanisms of action to antibacterial activity demonstrated MICs for telavancin-treated bacteria that were lower than glycopeptide comparators (vancomycin and/or teicoplanin). While the second proposed mechanism of action, disruption of the microbial cell membrane, appeared to play a role in the bactericidal activity of telavancin, it was unclear from the submitted studies that this mechanism was significant at obtainable free concentrations of the drug. Although increases in membrane permeability and disruption of membrane potential were observed at concentrations as low as 2 µg/ml (4X MIC), significant membrane alterations were not seen until telavancin concentrations approached 64X – 128X MIC (32 – 64 µg/ml).

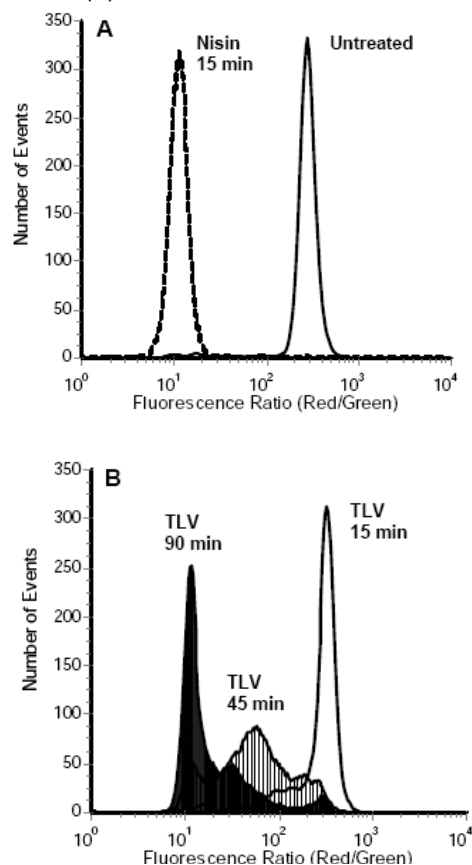
The Applicant has submitted information from a recent study, intended to further describe the mechanism of action of telavancin, specifically with regard to the molecule's effect on the bacterial cell membrane.

Investigators [Lunde 2009] measured bacterial membrane potential changes resulting from exposure to telavancin (and comparators). A flow cytometry assay, using diethyloxacarbocyanine dye, DiOC₂(3), as a fluorescent indicator, was employed to measure depolarization with greater accuracy than that reported in previous, similar, experiments. Observed bacterial isolates included a variety of *Staphylococcus aureus* phenotypes, including isolates susceptible to glycopeptides (ATCC 29213), methicillin-resistant isolates (MRSA, ATCC 33591), heterogeneous vancomycin-intermediate isolates (hVISA Mu3, ATCC 700698), vancomycin-intermediate isolates (VISA Mu50, ATCC 700699), and isolates nonsusceptible to daptomycin (MED2034, obtained from Theravance).

The investigators controlled for the possible effect on membrane potential caused by weakening of the cell wall by limiting the depolarization assay to 90 minutes, a time determined by experimental evidence involving timed inhibition of cell wall biosynthesis by penicillin G. Membrane potential was tested under conditions normally employed for antibiotic susceptibility testing (using cation-adjusted Mueller Hinton broth, physiologic temperature, and cell concentrations of 10⁶ CFU/ml).

Depolarization of the bacterial membrane by nisin (A), a pore-forming lantibiotic, and telavancin (B) are shown in Figure 1. Cells were exposed to 8 mcg/ml of telavancin. Depolarization was time-dependent, with broad depolarization observed at 90 minutes.

Figure 1: Dissipation of *S. aureus* Membrane Potential Measured by Flow Cytometry with DiOC₂(3)



Cell populations exhibiting depolarization appear towards the left on the x-axis. (A) Fully polarized (untreated) and depolarized (nisin, 8 µg/mL) *S. aureus* (ATCC 29213). (B) *S. aureus* incubated for 15, 45, and 90 min in the presence of 8 µg/mL telavancin.

Source: This submission, Section 5.3.5.4.1.2.2.1

The investigators compared concentration-dependent depolarization of telavancin, nisin, and vancomycin. Using nonlinear regression to derive IC₅₀ values from concentration response curves, the investigators demonstrated similar membrane depolarization activity of nisin and telavancin (IC₅₀ values of 2.9 mcg/ml and 3.6 mcg/ml, respectively). No IC₅₀ value could be determined for vancomycin (up to 96 mcg/ml). Against *S. aureus* isolates non-susceptible to other glycopeptides (vancomycin and daptomycin), telavancin demonstrated membrane depolarization activity comparable to that observed in glycopeptide-susceptible isolates (Table 1).

Table 1: Telavancin depolarization activity against phenotypically diverse *S. aureus*

Strain	Relevant phenotype	Depolarization (%) ^a
ATCC 33591	MRSA	77 ± 7
ATCC 700699	VISA (Mu50)	61 ± 3
ATCC 700698	hVISA (Mu3)	78 ± 4
MED2034	Daptomycin non-susceptible	77 ± 5

^a Percent depolarization is reported for treatment with 32 mcg/ml telavancin, and represents the mean ± standard deviation from three independent experiments

Source: Lunde 2009

In order to establish a role for Lipid-II binding in the observed depolarization of the bacterial membrane, the investigators conducted depolarization assays in the presence of a Lipid II competitor, N,N'-diacetyl-L-Lys-D-Ala-D-Ala (dKAA). In this experiment, concentration-dependent antagonism of the depolarization effect was observed, suggesting that Lipid II is required for telavancin-induced depolarization of the bacterial membrane. The dependence on Lipid-II for telavancin-induced membrane depolarization was also investigated using assays that measured depolarization in cells with altered levels of Lipid II. In this investigation (Table 2), decreased depolarization was noted in cells where Lipid II levels were decreased by treatment with fosfomycin, D-cycloserine, or bacitracin.

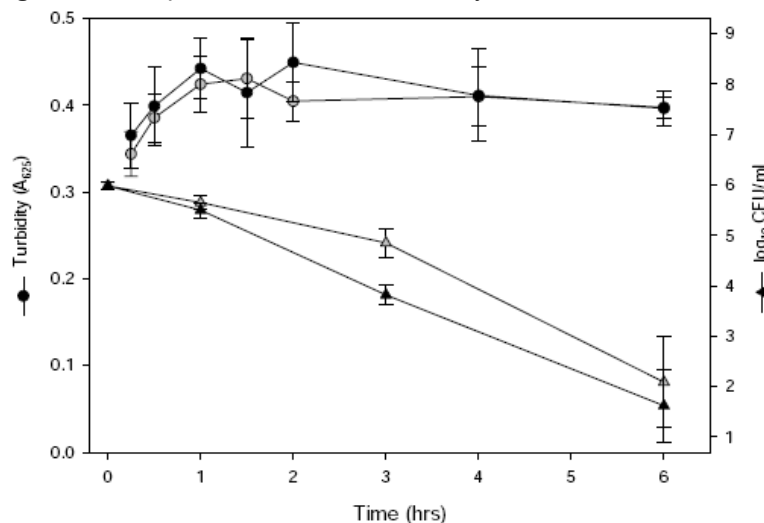
Table 2: Effect of Lipid II Synthesis on Depolarization of *S. aureus* by Telavancin

Antibiotic	Depolarization (%) ^a	
	Telavancin	Nisin
None	100	100
Fosfomycin	29	26
D-Cycloserine	38	36
Bacitracin	27	2

^a*S. aureus* (ATCC 29213) cells were pretreated 10 min prior to the addition of telavancin or nisin, and depolarization was calculated relative to control sample without pretreatment.
Source: This submission, Section 5.3.5.4.1.2.2.2

The same investigators examined the relationship of telavancin-induced membrane depolarization to cell lysis. Cell lysis was determined spectroscopically. Measured at 625 nm, cells exposed to concentrations of telavancin (and vancomycin) or 8 and 32 mcg/ml for 6 hours showed no significant change in optical density. The results are summarized in Figure 2 (vancomycin data not shown).

Figure 2: Comparison of Culture Turbidity to Viable Counts in *S. aureus* Exposed to Telavancin



Curves represent turbidity (circles) and viable counts (triangles) for cultures exposed to 8 µg/mL (grey) and 32 µg/mL (black) telavancin.
Source: This submission, Section 5.3.5.4.1.2.2.3

In Summary:

Investigations of telavancin generally support the claim for two distinct mechanisms of action, and for enhanced activity, compared to vancomycin and other comparators. Studies by the Applicant

demonstrate substrate-dependent inhibition of PG biosynthesis, both with regard to formation of immature PG and to cross-linking of mature PG strands. Inhibition of PG biosynthesis appears to be enhanced, compared to vancomycin; an effect that may be attributable to a higher affinity of telavancin for cell membrane components. In investigations that linked mechanisms of action to antibacterial activity, MICs for telavancin-treated bacteria were lower than glycopeptide comparators (vancomycin and/or teicoplanin). In the current submission, the Applicant has provided data that supports the contention that the second mechanism of action, depolarization of the microbial cell membrane, occurs at attainable drug levels, in the absence of cell lysis, and is dependent on association of telavancin with Lipid II.

Mechanism of Action Studies ~ Conclusions:

The applicant has provided data to support the principle mechanism of telavancin, involving interruption of late-stage glycopeptide synthesis, with concomitant cell wall disruption followed by cell death. The applicant has also provided acceptable data regarding the proposed second mechanism of action, involving disruption of the cell membrane in Gram positive bacteria of interest, including bacteria that are non-susceptible to vancomycin. Investigations support the contention that these mechanisms occur at attainable drug concentrations, in vivo.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

The following surveillance studies were conducted prior to release of telavancin to the market.

In NDA 22-110, the Applicant submitted data from two large prospective studies and seventeen other investigations of in vitro activity conducted to support the applicant's claim of activity against the pathogens generally associated with complicated skin and skin structure infections, including all organisms listed in that indication. MIC values for all tested isolates of *S. aureus* (including isolates resistant to other classes of antimicrobials, and isolates with specific virulence profiles), *S. pyogenes*, *S. agalactiae*, *S. anginosus*, *S. intermedius*, *S. constellatus*, and vancomycin-susceptible *E. faecalis* were all below the attainable drug levels, based on pharmacokinetic/pharmacodynamic analyses and Monte Carlo modeling, also submitted in that Application. Telavancin activity against vancomycin-intermediate *S. aureus* (VISA), heteroresistant vancomycin-intermediate *S. aureus*, and vancomycin-resistant *S. aureus* (VRSA), in those studies, was superior to vancomycin.

The current Application includes data from five new surveillance studies. The new studies are listed in Table 3. The largest study conducted in support of this NDA was an international prospective study conducted in 2007 (10,700 isolates). Other investigations included a study of 1500 methicillin-resistant *Staphylococcus aureus* (MRSA) isolates collected in Japan in 2006 [Hatano 2006], a study of 1005 streptococcal isolates (*Streptococcus pneumoniae*, β -hemolytic streptococci, and viridans group streptococci) from international surveillance studies, collected mainly between 2004-2007 [JMI Laboratories 2007], and two prospective bacteremia studies conducted in the UK and Ireland in 2005-2006 (2639 isolates) [Theravance Study Reports 08-6424-MCB-01 and 08-6424-MCB-02].

Table 3: Summary of Five Recent Studies of In Vitro Activity of Telavancin Against Gram-positive Clinical Isolates

Study No.	Study Name	Reference	Sources of Isolates	No. of Isolates	No. of Centers	Methods	Gram-positive Total	<i>S. aureus</i>	CoNS and other staphylococci ^a	<i>S. pneumoniae</i>	<i>S. pyogenes</i>	Other β -hemolytic streptococci	Bovis group streptococci	Viridans group streptococci	Enterococci	Miscellaneous Aerobes	Anaerobes
21	BSAC 2005	(74)	Blood	2705	25 ^b	Agar dilution	1330	244	205	230	88	140	21	159	243	0	0
22	BSAC 2006	(75)	Blood	2644	25 ^b	Agar dilution	1309	242	203	231	85	144	21	145	238	0	0
23	JMI Streptococcus Study 2007	(41)	Blood Skin Unknown	1005	94	Broth microdilution (frozen)	1005	0	0	205	0	300	0	500	0	0	0
24	Japanese Surveillance 2006	(36)	Respiratory Unknown	1500	1	Broth microdilution (frozen)	1500	1500	0	0	0	0	0	0	0	0	0
25	International Surveillance 2007	(40)	Blood Skin Respiratory Unknown	10700	105	Broth microdilution (dry-from)	10700	5895	1030	984	242	337	18	197	1949	41	7
Grand Total				18554	225		15844	7881	1438	1650	415	921	60	1001	2430	41	7

^a Includes non-spectated staphylococci.

^b The same centers were used for the BSAC 2005 and 2006 studies (74, 75).

Source: This submission, Section 5.3.5.4.1.4.2.2, Table 1

The large, 2007 international surveillance study (Protocol #07-AST-01) was performed by JMI Laboratories (North Liberty, IA), as part of the SENTRY Antimicrobial Surveillance Program. The majority (44.7%) of isolates analyzed in the study was collected in the US (geographic distribution of isolates is summarized in Table 4). All isolates were from clinical sources, with 10% from hospitalized patients with pneumonia (including hospital-acquired pneumonia).

Table 4: Geographic Sources of Isolates, 2007 International Surveillance Study

Geographic Region	Number of Sites	Number of Isolates	Percent of Total
United States	38	4782	44.7%
Canada	1	52	0.5%
Europe ^a	25	2673	25.0%
Latin America ^b	10	796	7.4%
Asia/South Pacific	31	2397	22.4%

^a: Includes Israel

^b: Includes Mexico and South America

Source: International Surveillance Study Report (40)

Of the 10,700 isolates analyzed, 55.1% (5,895) were *Staphylococcus aureus*, 9.6% (1,030) were coagulase-negative staphylococci, 18.2% (1,949) were *Enterococcus* species, 5.4% (579) were β -hemolytic streptococci, 1.8% (197) were viridans group streptococci, 9.2% (984) were *Streptococcus pneumoniae*, and 0.6% (66) were identified as "other Gram-positive species."

All isolate identification was confirmed by JMI laboratories, using the Vitek Identification System (bioMerieux, Hazelwood, MO). Susceptibility testing was performed by microbroth dilution techniques approved by CLSI, using frozen panels supplied by (b) (4). Cation-adjusted Mueller-Hinton broth was supplemented with 2-5% lysed horse blood for testing of *S. pneumoniae* and other fastidious streptococci. Interpretive criteria for comparator agents were those of CLSI M100-S18; 2008. Quality control was performed on each day of testing, using methods and quality control strains approved by CLSI. All but one quality control result were within acceptable ranges (the one discrepant result was re-tested and found acceptable). Quality control results are summarized in Table 5.

Table 5: Telavancin Quality Control Results, JMI Surveillance Study, 2007

Organism	Broth MIC (ug/ml)	Frequency	Acceptable CLSI Range
<i>E. faecalis</i> ATCC 29212	0.06 0.12 0.25	1 73 3	0.12 - 0.5
<i>S. aureus</i> ATCC 29213	0.12 0.25	61 21	0.12 - 1
<i>S. pneumoniae</i> ATCC 49619	≤0.015 0.03	43 21	0.004 - 0.03

Source: Study 07-AST-01

The results of the study are summarized in Table 6.

Telavancin MIC₉₀ value for *Staphylococcus aureus* isolates, including methicillin-resistant and –susceptible isolates) was 4-fold lower than those seen for vancomycin (0.25 mcg/ml for telavancin and 1.0 mcg/ml for vancomycin) and 8-fold lower than that seen for linezolid (2.0 mcg/ml). Telavancin MIC₉₀ values against all staphylococcal species were generally lower than all comparators, including vancomycin, teicoplanin, clindamycin, daptomycin, linezolid, and quinupristin/dalfopristin. Activity of telavancin against *S. aureus* isolates exclusively recovered from respiratory tract infections (predominantly hospital acquired pneumonia) was similar to that observed against all *S. aureus* isolates tested (all sources). Oxacillin resistance had no effect on telavancin potency in either *S. aureus* isolates or coagulase negative staphylococcal species. All staphylococcal isolates tested were inhibited by telavancin at ≤ 0.05 mcg/ml.

Against *Streptococcus pneumoniae* (including isolates non-susceptible to penicillin), the MIC₉₀ for telavancin was 0.03 mcg/ml (the vancomycin MIC₉₀ was ≤ 1 mcg/ml, the linezolid MIC₉₀ was 1 mcg/ml). Penicillin non-susceptibility had no effect on telavancin potency against isolates of *S. pneumoniae*. The MIC₉₀ value for *S. pneumoniae* isolates collected exclusively from respiratory sources was identical to that of the entire *S. pneumoniae* collection. All isolates of *S. pneumoniae* were inhibited by telavancin at ≤ 0.06 mcg/ml.

All vancomycin-susceptible enterococci, tested in this study, were inhibited by telavancin at ≤1 mcg/ml. Among vancomycin-resistant enterococcal isolates, 26.8% had a telavancin MIC of ≤1 mcg/ml and 76.6% had a telavancin MIC of ≤2 mcg/ml.

All viridans group streptococci and β-hemolytic streptococci (including *S. pyogenes*, *S. agalactiae*, and *Streptococcus* groups C and G) were inhibited by telavancin concentrations of ≤0.25 mcg/ml.

Table 6: MIC Statistics of Telavancin and Selected Comparators vs. Gram-positive Organisms from the 2007 International Surveillance Study

Organism (no. tested)	Agent	MIC (µg/mL)			%
		Range	50%	90%	Susceptible ^a
<i>S. aureus</i>					
All <i>S. aureus</i> (5895)	Telavancin	0.03-0.5	0.12	0.25	- ^b
	Vancomycin	≤ 0.12-4	1	1	> 99
	Teicoplanin ^c	≤ 2 - 8	≤ 2	≤ 2	100
	Clindamycin ^c	≤ 0.25 - > 2	≤ 0.25	>2	78
	Daptomycin	≤ 0.06 - 2	0.25	0.5	> 99
	Linezolid	0.25 - > 8	1	2	> 99
	Quinu/Dalfo ^d	≤ 0.25 - > 2	≤ 0.25	0.5	> 99
MRSA ^e (2658)	Telavancin	0.03 - 0.5	0.12	0.25	-
	Vancomycin	0.25 - 4	1	1	> 99
	Teicoplanin	≤ 2 - 8	≤ 2	≤ 2	100
	Clindamycin	≤ 0.25 - >2	≤ 0.25	> 2	56
	Daptomycin	≤ 0.06 - 2	0.25	0.5	> 99
	Linezolid	0.25 - > 8	1	2	> 99
	Quinu/Dalfo	≤ 0.25 - >2	0.5	0.5	> 99
MSSA ^f (3237)	Telavancin	0.03 - 0.5	0.12	0.25	-
	Vancomycin	≤ 0.15 - 2	1	1	100
	Teicoplanin	≤ 2 - 4	≤ 2	≤ 2	100
	Clindamycin	≤ 0.25 - >2	≤ 0.25	≤ 0.25	95
	Daptomycin	≤ 0.06 - 1	0.25	0.5	100
	Linezolid	0.25 - 2	1	2	100
	Quinu/Dalfo	≤ 0.25 - 2	≤ 0.25	0.5	> 99
Coagulase-negative staphylococci (CoNS)					
All CoNS (1030)	Telavancin	≤ 0.015 - 0.5	0.12	0.25	-
	Vancomycin	≤ 0.12 - 8	1	2	> 99
	Teicoplanin	≤ 2 - > 16	≤ 2	4	99
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	65
	Oxacillin	≤ 0.25 - > 2	> 2	> 2	22
	Daptomycin	≤ 0.06 - 4	0.25	0.5	> 99
	Linezolid	≤ 0.06 - 8	0.5	1	99
	Quinu/Dalfo	≤ 0.25 - > 2	≤ 0.25	0.5	99

Source: This submission, Section 5.3.5.4.1.4.3.1, Table 7

Table 6: MIC Statistics of Telavancin and Selected Comparators vs. Gram-positive Organisms from the 2007 International Surveillance Study (cont'd)

Organism (no. tested)	Agent	MIC (µg/mL)			% Susceptible ^a
		Range	50%	90%	
<i>S. epidermidis</i> (326)	Telavancin	0.03 - 0.25	0.12	0.12	-
	Vancomycin	≤ 0.12 - 4	2	2	100
	Teicoplanin	≤ 2 - 8	≤ 2	4	100
	Oxacillin	≤ 0.25 - > 2	> 2	> 2	15
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	61
	Daptomycin	≤ 0.06 - 1	0.25	0.5	100
	Linezolid	≤ 0.06 - > 8	0.5	1	99
	Quinu/Dalfo	≤ 0.25 - > 2	≤ 0.25	≤ 0.25	98
<i>S. haemolyticus</i> (58)	Telavancin	0.03 - 0.5	0.12	0.25	-
	Vancomycin	0.25 - 2	1	2	100
	Teicoplanin	≤ 2 - > 16	≤ 2	8	97
	Oxacillin	≤ 0.25 - > 2	> 2	> 2	16
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	71
	Daptomycin	≤ 0.06 - 0.5	0.25	0.5	100
	Linezolid	0.5 - 1	1	1	100
	Quinu/Dalfo	≤ 0.25 - 1	≤ 0.25	0.5	100
<i>S. hominis</i> (52)	Telavancin	≤ 0.015 - 0.12	0.12	0.12	-
	Vancomycin	0.5 - 2	1	2	100
	Teicoplanin	≤ 2 - 8	≤ 2	4	98
	Oxacillin	≤ 0.25 - > 2	> 2	> 2	23
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	83
	Daptomycin	≤ 0.06 - 0.5	0.25	0.25	100
	Linezolid	≤ 0.06 - 2	1	1	100
	Quinu/Dalfo	≤ 0.25 - 0.5	≤ 0.25	0.5	100
Other <i>Staphylococcus</i> spp. ⁹ (594)	Telavancin	≤ 0.015 - 0.5	0.12	0.25	-
	Vancomycin	≤ 0.12 - 8	1	2	> 99
	Teicoplanin	≤ 2 - > 16	≤ 2	4	99
	Oxacillin	≤ 0.25 - > 2	> 2	> 2	28
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	68
	Daptomycin	≤ 0.06 - 4	0.25	0.5	> 99
	Linezolid	0.25 - > 8	1	1	99
	Quinu/Dalfo	≤ 0.25 - 1	≤ 0.25	0.5	> 99

Source: This submission, Section 5.3.5.4.1.4.3.1, Table 7

Table 6: MIC Statistics of Telavancin and Selected Comparators vs. Gram-positive Organisms from the 2007 International Surveillance Study (cont'd)

Organism (no. tested)	Agent	MIC (µg/mL)			%
		Range	50%	90%	Susceptible ^a
<i>S. pneumoniae</i>					
All <i>S. pneumoniae</i> (n=984)	Telavancin	≤ 0.015 - 0.06	0.03	0.03	-
	Vancomycin	≤ 0.12 - ≤ 1	≤ 1	≤ 1	100
	Teicoplanin ^h	≤ 2	≤ 2	≤ 2	-
	Erythromycin	≤ 0.25 - > 2	≤ 0.25	> 2	61
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	79
	Levofloxacin	≤ 0.5 - > 4	1	1	99
	Linezolid	≤ 0.12 - 2	1	1	100
<i>S. pneumoniae</i> , Penicillin-NS ^j (368)	Telavancin	≤ 0.015 - 0.06	0.03	0.03	-
	Vancomycin	≤ 1	≤ 1	≤ 1	100
	Teicoplanin ^k	≤ 2	≤ 2	≤ 2	-
	Erythromycin	≤ 0.25 - > 2	> 2	> 2	25
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	53
	Levofloxacin	≤ 0.5 - >4	1	1	> 99
	Linezolid	≤ 0.12 - 2	1	1	100
β-Hemolytic Streptococci					
<i>S. pyogenes</i> (242)	Telavancin	≤ 0.015 - 0.25	0.03	0.06	-
	Vancomycin	≤ 0.12 - 0.5	0.25	0.5	100
	Teicoplanin	≤ 2	≤ 2	≤ 2	-
	Erythromycin	≤ 0.25 - > 2	≤ 0.25	≤ 0.25	92
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	≤ 0.25	98
	Levofloxacin	≤ 0.5 - 2	≤ 0.5	1	100
	Linezolid	0.25 - 2	1	1	100
	Daptomycin	≤ 0.06 - 0.25	≤ 0.06	≤ 0.06	100
<i>S. agalactiae</i> (260)	Telavancin	0.03 - 0.25	0.06	0.06	-
	Vancomycin	0.25 - 1	0.5	0.5	100
	Teicoplanin	≤ 2	≤ 2	≤ 2	-
	Erythromycin	≤ 0.25 - > 2	≤ 0.25	> 2	73
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	82
	Levofloxacin	≤ 0.5 - > 4	≤ 0.5	1	97
	Linezolid	0.5 - 2	1	1	100
	Daptomycin	≤ 0.06 - 0.25	0.12	0.25	100

Source: This submission, Section 5.3.5.4.1.4.3.1, Table 7

Table 6: MIC Statistics of Telavancin and Selected Comparators vs. Gram-positive Organisms from the 2007 International Surveillance Study (cont'd)

Organism (no. tested)	Agent	MIC (µg/mL)			% Susceptible ^a
		Range	50%	90%	
<i>Streptococcus</i> Group G (35)	Telavancin	0.03 - 0.12	0.03	0.06	-
	Vancomycin	0.25 - 0.5	0.25	0.5	100
	Teicoplanin	≤ 2	≤ 2	≤ 2	-
	Erythromycin	≤ 0.25 - > 2	≤ 0.25	> 2	71
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	92
	Levofloxacin	≤ 0.5 - > 4	≤ 0.5	1	94
	Linezolid	0.5 - 2	1	1	100
	Daptomycin	≤ 0.06 - 0.12	≤ 0.06	≤ 0.06	100
<i>S. dysgalactiae</i> /Group C ^l (30)	Telavancin	0.03 - 0.12	0.03	0.06	-
	Vancomycin	0.25 - 1	0.25	0.5	100
	Teicoplanin	≤ 2	≤ 2	≤ 2	-
	Erythromycin	≤ 0.25 - > 2	≤ 0.25	≤ 0.25	90
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	≤ 0.25	97
	Levofloxacin	≤ 0.5 - > 4	≤ 0.5	1	97
	Linezolid	0.5 - 1	1	1	100
	Daptomycin	≤ 0.06 - 0.25	≤ 0.06	0.12	100
Other β-hemolytic species ^m (12)	Telavancin	0.03 - 0.12	0.03	0.06	-
	Vancomycin	0.25 - 1	0.25	0.5	100
	Teicoplanin	≤ 2 - 4	≤ 2	≤ 2	-
	Erythromycin	≤ 0.25 - > 2	≤ 0.25	> 2	50
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	75
	Levofloxacin	≤ 0.5 - 1	≤ 0.5	1	100
	Linezolid	0.5 - 1	1	1	100
	Daptomycin	≤ 0.06 - 0.25	≤ 0.06	0.12	100

Source: This submission, Section 5.3.5.4.1.4.3.1, Table 7

Table 6: MIC Statistics of Telavancin and Selected Comparators vs. Gram-positive Organisms from the 2007 International Surveillance Study (cont'd)

Organism (no. tested)	Agent	MIC (µg/mL)			%
		Range	50%	90%	Susceptible ^a
Bovis group Streptococci					
<i>S. bovis</i> group ⁿ (18)	Telavancin	≤ 0.015 - 0.06	0.03	0.06	-
	Vancomycin	0.25 - 0.5	0.25	0.5	100
	Teicoplanin	≤ 2 - 4	≤ 2	≤ 2	-
	Erythromycin	≤ 0.25 - > 2	≤ 0.25	> 2	50
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	72
	Levofloxacin	≤ 0.5 - > 4	2	> 4	83
	Linezolid	0.5 - 1	1	1	100
	Daptomycin	≤ 0.06	≤ 0.06	≤ 0.06	100
Viridans Group Streptococci					
All viridans group Streptococci (197)	Telavancin	≤ 0.015 - 0.12	0.03	0.06	-
	Vancomycin	≤ 0.12 - 1	0.5	1	100
	Teicoplanin	≤ 2	≤ 2	≤ 2	-
	Erythromycin	≤ 0.25 - > 2	0.5	> 2	53
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	87
	Levofloxacin	≤ 0.5 - > 4	1	2	95
	Linezolid	0.12 - 2	1	1	100
	Daptomycin	≤ 0.06 - 2	0.25	0.5	> 99
Viridans group Streptococci, Penicillin-NS ⁱ (56)	Telavancin	≤ 0.015 - 0.12	0.03	0.06	-
	Vancomycin	0.25 - 1	0.5	0.5	100
	Teicoplanin	≤ 2	≤ 2	≤ 2	-
	Erythromycin	≤ 0.25 - > 2	2	> 2	30
	Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	80
	Levofloxacin	≤ 0.5 - > 4	1	2	95
	Linezolid	0.25 - 1	1	1	100
	Daptomycin	≤ 0.06 - 2	0.25	1	98

Source: This submission, Section 5.3.5.4.1.4.3.1, Table 7

Table 6: MIC Statistics of Telavancin and Selected Comparators vs. Gram-positive Organisms from the 2007 International Surveillance Study (cont'd)

Organism (no. tested)	Agent	MIC (µg/mL)			% Susceptible ^a
		Range	50%	90%	
<i>S. anginosus/milleri</i> (36)	Telavancin	≤ 0.015 - 0.06	0.03	0.06	-
<i>S. constellatus</i> (10)	Telavancin	0.03 - 0.06	0.03	0.06	-
<i>S. gordonii</i> (2)	Telavancin	0.06	-	-	-
<i>S. intermedius</i> (2)	Telavancin	0.03 - 0.06	-	-	-
<i>S. mitis</i> (14)	Telavancin	0.03 - 0.06	0.03	0.06	-
<i>S. mutans</i> (3)	Telavancin	0.03	-	-	-
<i>S. oralis</i> (7)	Telavancin	≤ 0.015 - 0.06	-	-	-
<i>S. parasanguis</i> (3)	Telavancin	0.03	-	-	-
<i>S. salivarius</i> (6)	Telavancin	0.03 - 0.06	-	-	-
<i>S. sanguis</i> (6)	Telavancin	0.03 - 0.06	-	-	-
<i>S. vestibularis</i> (1)	Telavancin	0.03	-	-	-
<i>Streptococcus</i> spp. (107)	Telavancin	≤ 0.015 - 0.12	0.03	0.06	-
Enterococci					
<i>E. faecalis</i> (1229)	Telavancin	0.03 - > 2	0.25	0.5	-
	Vancomycin	≤ 0.12 - > 16	1	2	97
	Teicoplanin	≤ 2 - > 16	≤ 2	≤ 2	98
	Ampicillin	≤ 1 - > 16	≤ 1	2	> 99
	Linezolid	0.25 - > 8	1	2	> 99
	Daptomycin	≤ 0.06 - 8	1	2	> 99
<i>E. faecalis</i> , vancomycin-S ^o (1197)	Telavancin	0.03 - 1	0.25	0.5	-
	Vancomycin	≤ 0.12 - 4	1	2	100
	Teicoplanin	≤ 2	≤ 2	≤ 2	100
	Ampicillin	≤ 1 - > 16	≤ 1	2	> 99
	Linezolid	0.25 - > 8	1	2	> 99
	Daptomycin	≤ 0.06 - 8	1	2	> 99

Source: This submission, Section 5.3.5.4.1.4.3.1, Table 7

Table 6: MIC Statistics of Telavancin and Selected Comparators vs. Gram-positive Organisms from the 2007 International Surveillance Study (cont'd)

Organism (no. tested)	Agent	MIC (µg/mL)			% Susceptible ^a
		Range	50%	90%	
<i>E. faecalis</i> , vancomycin-R ^P (30)	Telavancin	0.25 - >2	>2	>2	-
	Vancomycin	>16	>16	>16	0
	Teicoplanin	≤ 2 - > 16	>16	>16	17
	Ampicillin	≤ 1 - 8	≤ 1	2	100
	Linezolid	0.5 - 2	1	2	100
	Daptomycin	0.25 - 2	0.5	1	100
<i>E. faecium</i> (680)	Telavancin	≤ 0.015 - > 2	0.12	2	-
	Vancomycin	0.5 - > 16	1	> 16	55
	Teicoplanin	≤ 2 - > 16	≤ 2	> 16	60
	Ampicillin	≤ 1 - > 16	> 16	> 16	7
	Linezolid	0.5 - > 8	1	2	99
	Daptomycin	0.12 - 4	2	4	100
<i>E. faecium</i> , vancomycin-S ^o (377)	Telavancin	≤ 0.015 - 1	0.06	0.12	-
	Vancomycin	0.5 - 4	0.5	1	100
	Teicoplanin	≤ 2 - > 16	≤ 2	≤ 2	> 99
	Ampicillin	≤ 1 - > 16	> 16	> 16	12
	Linezolid	0.5 - > 8	2	2	> 99
	Daptomycin	0.12 - 4	2	4	100
<i>E. faecium</i> , vancomycin-R ^P (295)	Telavancin	0.03 - > 2	2	>2	-
	Vancomycin	>16	>16	>16	0
	Teicoplanin	≤ 2 - > 16	>16	>16	9
	Ampicillin	16 - > 16	>16	>16	0
	Linezolid	0.5 - > 8	1	2	98
	Daptomycin	0.25 - 4	2	2	100
<i>Enterococcus</i> spp. ^a (40)	Telavancin	0.03 - 1	0.25	0.5	-
	Vancomycin	0.25 - 8	1	8	88
	Teicoplanin	≤ 2	≤ 2	≤ 2	100
	Ampicillin	≤ 1 - > 16	≤ 1	4	93
	Linezolid	0.5 - 2	1	2	95
	Daptomycin	≤ 0.06 - 4	1	2	100

Source: This submission, Section 5.3.5.4.1.4.3.1, Table 7

Table 6: MIC Statistics of Telavancin and Selected Comparators vs. Gram-positive Organisms from the 2007 International Surveillance Study (cont'd)

Organism (no. tested)	Agent	MIC (µg/mL)			%
		Range	50%	90%	Susceptible ^a
Miscellaneous Gram-positive Aerobes					
<i>Bacillus</i> spp. (6)	Telavancin	0.03 - 0.25	-	-	-
<i>Corynebacterium</i> spp. (21)	Telavancin	≤ 0.015 - 0.06	0.03	0.03	-
<i>Erysipelothrix</i> spp. (1)	Telavancin	0.06	-	-	-
<i>Kocuria kristinae</i> (1)	Telavancin	≤ 0.015	-	-	-
<i>Lactobacillus</i> spp. (2)	Telavancin	> 2	-	-	-
<i>Lactococcus</i> spp. (3)	Telavancin	0.03 - 0.06	-	-	-
<i>Leuconostoc</i> spp. (1)	Telavancin	> 2	-	-	-
<i>Listeria monocytogenes</i> (2)	Telavancin	0.03	-	-	-
<i>Micrococcus</i> spp. (2)	Telavancin	≤ 0.015	-	-	-
<i>Turicella otiditis</i> (2)	Telavancin	≤ 0.015	-	-	-
Gram-positive Anaerobes					
<i>Aerococcus</i> spp. (5)	Telavancin	≤ 0.015 - 0.25	-	-	-
<i>Gemella</i> spp. (2)	Telavancin	0.03	-	-	-

^a Susceptibility based on CLSI breakpoints, where available (13).

^b Not available or not applicable.

^c Teicoplanin and clindamycin MIC statistics determined for 5,894 isolates.

^d Quinupristin/Dalfopristin.

^e MRSA, methicillin-resistant *Staphylococcus aureus*.

^f MSSA, methicillin-susceptible *Staphylococcus aureus*.

^g Includes *S. auricularis* (3 isolates), *S. capitis* (18), *S. caprae* (4), *S. cohnii* (3), *S. intermedius* (3), *S. lugdunensis* (14), *S. saprophyticus* (16), *S. simulans* (16), *S. warneri* (10), *S. xylosus* (14), *Staphylococcus* spp. (493).

^h Teicoplanin MIC statistics determined for 318 isolates.

ⁱ Penicillin-NS, penicillin-non-susceptible.

^j Penicillin breakpoint for meningitis (*S* ≤ 2 µg/mL).

^k Teicoplanin MIC statistics determined for 230 isolates.

^l Includes *S. dysgalactiae* ssp. *equisimilis* (4 isolates).

^m Includes Streptococcus Group F (6 isolates), *Streptococcus* spp. (6).

ⁿ Includes *S. bovis* (15 isolates), *S. equinus* (2), *S. gallolyticus* (1).

^o Vancomycin-S, vancomycin-susceptible.

^p Vancomycin-R, vancomycin-resistant.

^q Includes *E. avium* (10 isolates), *E. casseliflavus* (12), *E. durans* (3), *E. gallinarum* (10), *E. hirae* (4), and *Enterococcus* spp. (1).

Source: This submission, Section 5.3.5.4.1.4.3.1, Table 7

Telavancin was tested in 2005 and 2006 in the ongoing BSAC (British Society for Antimicrobial Chemotherapy) Bacteremia Resistance Surveillance Programme, against Gram-positive cocci. Theravance has included summary reports from this ongoing study as Report 08-6424-mcb-01 (2005) and Report 08-64240-mcb-02 (2006). The study employed susceptibility testing methods not approved by CLSI and the study did not fall within the scope of the FDA Good Laboratory Practice Regulations. Isolates were collected from clinical centers in the United Kingdom and Ireland. Susceptibility testing was performed using the BSAC agar dilution method. In 2005, 1,330 isolates were evaluated against telavancin. In 2006 1,309 isolates were tested. Testing was performed at a central laboratory. Quality control procedures were performed on each day of testing, using BSAC guidelines.

In the 2005 survey, there were 449 staphylococcal isolates tested (244 *S. aureus*, 129 *S. epidermidis*, 21 *S. haemolyticus*, 7 *S. capitis*, 23 *S. hominis*, 4 *S. warneri*, and 21

"unspeciated" staphylococci). The telavancin MIC₉₀ for all staphylococcal species tested was 0.25 mcg/ml. Against *S. aureus*, the MIC₉₀ was 0.5 mcg/ml (identical in oxacillin-susceptible and –resistant isolates, analyzed as sub-populations). The MIC values against *S. aureus* were normal and unimodal. The telavancin MIC₉₀ for coagulase-negative staphylococci was 0.25 mcg/ml (the vancomycin MIC₉₀ against the same collection was 2 mcg/ml), with no noted difference in oxacillin-susceptible and –resistant subpopulations. Telavancin was more active than all comparators (including cefoxitin, ciprofloxacin, clindamycin, daptomycin, erythromycin, fusidic acid, gentamicin, linezolid, minocycline, oxacillin, penicillin, piperacillin-tazobactam, rifampin, teicoplanin, tetracycline, tigecycline, trimethoprim, and vancomycin) against isolates of coagulase-negative staphylococci and "unspeciated" staphylococci.

The telavancin MIC₉₀ for isolates of *S. pneumoniae* (n = 230) tested in the 2005 survey, was ≤ 0.03 mcg/ml. Only one penicillin-resistant isolate was identified, with a telavancin MIC of ≤ 0.03 mcg/ml. Thirty erythromycin-resistant isolates were identified, with a telavancin MIC₉₀ of ≤ 0.03 mcg/ml.

Results of the 2005 BSAC Survey are summarized in Table 7.

Table 7: Telavancin MIC₉₀ values for Gram-positive pathogens analyzed in the 2005 BSAC Survey (species with ≥ 10 isolates tested)

Organism	MIC _{range} (mcg/ml)	MIC ₉₀ (mcg/ml)
All <i>S. aureus</i> (n = 244)	0.12 – 0.5	0.5
MRSA (n = 88)	0.12 – 0.5	0.25
MSSA (n = 156)	0.12 – 0.5	0.5
All CoNS (n = 184)	0.06 – 0.5	0.25
MRCoNS (n = 143)	0.06 – 0.5	0.25
<i>S. pneumoniae</i> (n = 230)	≤ 0.03 – 0.06	≤ 0.03
<i>S. pyogenes</i> (n = 88)	≤ 0.03 – 0.12	≤ 0.06
<i>S. agalactiae</i> (n = 65)	≤ 0.03 – 0.12	0.12
<i>S. dysgalactiae</i> (n = 12)	≤ 0.03 – 0.06	0.06
<i>S. oralis</i> (n = 63)	≤ 0.03 – 0.12	0.06
<i>S. salivarius</i> (n = 10)	≤ 0.03 – 0.12	0.12
<i>S. sanguis</i> (n = 17)	≤ 0.03 – 0.12	0.12
All <i>E. faecalis</i> (n = 138)	0.06 – 16	1
Vancomycin-susceptible <i>E. faecalis</i> (n = 136)	0.06 – 1	1
All <i>E. faecium</i> (n = 90)	≤ 0.03 – 8	4
Vancomycin-resistant <i>E. faecium</i> (n = 36)	0.06 – 8	8
Vancomycin-susceptible <i>E. faecium</i> (n = 54)	≤ 0.03 – 0.25	0.25

MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; CoNS = coagulase-negative Staphylococcus species; MRCoNS = methicillin-resistant coagulase-negative Staphylococcus species
Source: compiled from data in Study Report 08-6426-MCB-01

In the 2006 survey, there were 445 staphylococcal isolates tested, including 242 *S. aureus* isolates. The telavancin MIC₉₀ for all staphylococcal species tested was 0.5 mcg/ml. Against *S. aureus*, the MIC₉₀ was 0.5 mcg/ml (identical in oxacillin-susceptible and –resistant isolates, analyzed as sub-populations). The MIC values against *S. aureus* were unimodal. The telavancin MIC₉₀ for coagulase-negative staphylococci was 0.25 mcg/ml (the vancomycin MIC₉₀ against the same collection was 2 mcg/ml), with no noted difference in oxacillin-susceptible and –resistant subpopulations. Telavancin was more active than all comparators (identical to comparators in 2005 survey, above) against isolates of coagulase-negative staphylococci and "unspeciated" staphylococci.

The telavancin MIC₉₀ for isolates of *S. pneumoniae* (n = 231) tested in the 2006 survey, was ≤ 0.015 mcg/ml. Thirty-one erythromycin-resistant isolates were identified, with a telavancin

MIC₉₀ of ≤ 0.015 mcg/ml.

Results of the 2006 BSAC Survey are summarized in Table 8.

Table 8: Telavancin MIC₉₀ values for Gram-positive pathogens analyzed in the 2006 BSAC Survey (species with ≥ 10 isolates tested)

Organism	MIC _{range} (mcg/ml)	MIC ₉₀ (mcg/ml)
All <i>S. aureus</i> (n = 242)	0.12 – 0.5	0.5
MRSA (n = 109)	0.12 – 0.5	0.5
MSSA (n = 133)	0.12 – 0.5	0.5
All CoNS (n = 203)	0.03 – 0.5	0.25
MRCoNS (n = 158)	0.06 – 0.5	0.25
<i>S. pneumoniae</i> (n = 231)	≤ 0.008 – 0.12	0.015
<i>S. pyogenes</i> (n = 85)	≤ 0.03 – 0.12	0.06
<i>S. agalactiae</i> (n = 82)	≤ 0.03 – 0.25	0.12
<i>S. dysgalactiae</i> (n = 15)	≤ 0.03 – 0.06	0.06
<i>S. anginosus</i> (n = 21)	0.015 – 0.06	0.03
<i>S. oralis</i> (n = 49)	≤ 0.008 – 0.06	0.03
<i>S. parasanguis</i> (n = 13)	0.03 – 0.12	0.06
<i>S. sanguis</i> (n = 27)	0.015 – 0.06	0.06
All <i>E. faecalis</i> (n = 142)	0.03 – 8	0.5
Vancomycin-susceptible <i>E. faecalis</i> (n = 138)	≤ 0.03 – 0.5	0.5
All <i>E. faecium</i> (n = 81)	≤ 0.03 – 4	2
Vancomycin-resistant <i>E. faecium</i> (n = 26)	0.06 – 4	2
Vancomycin-susceptible <i>E. faecium</i> (n = 55)	≤ 0.03 – 0.25	0.12

MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; CoNS = coagulase-negative Staphylococcus species; MRCoNS = methicillin-resistant coagulase-negative Staphylococcus species
Source: compiled from data in Study Report 08-6426-MCB-02

The Applicant has provided the study report from an investigation of telavancin activity against 1500 MRSA isolates collected in Japan, primarily from respiratory sources [Hatano 2006]. Susceptibility testing was performed using microbroth dilution methods approved by CLSI. Quality control was performed on each day of testing, using *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212. Comparators included vancomycin, linezolid, daptomycin, and tigecycline. The collection of isolates included none that were vancomycin-intermediate (VISA), vancomycin-resistant (VRSA), or linezolid non-susceptible. The results of this investigation are summarized in Table 9. MIC₉₀ value of telavancin (0.5 mcg/ml) were similar to (within 1 doubling dilution) those observed for all comparators with the exception of linezolid (2 mcg/ml).

Table 9: MIC Statistics of Telavancin and Selected Comparators for 1500 MRSA Isolates Collected in Japan in 2006

Agent	MIC (µg/mL)		
	Range	50%	90%
Telavancin	0.12 - 0.5	0.25	0.5
Vancomycin	0.25 - 2	1	1
Linezolid	1 - 4	2	2
Daptomycin	0.12 - 2	0.5	0.5
Tigecycline	0.12 - 1	0.25	0.5

Source: This submission, Section 5.3.5.4.1.4.2.4.1, Table 10

JMI Laboratories (North Liberty, Iowa) conducted a study designed to investigate the activity of telavancin against *S. pneumoniae* with defined antibiograms, including multidrug-resistant (MDR) patterns (n = 205), and eight other species of streptococci (100 isolates of each), including

S. anginosus (aka *S. milleri*), *S. constellatus*, *S. intermedius*, *S. mitis*, *S. oralis*, *S. agalactiae* (group B), *S. dysgalactiae* sub. *equisimilis* (group C), and Group G β -hemolytic streptococci. Result of the study indicated that telavancin was active against viridans group streptococci (MIC₉₀ 0.03-0.06 mcg/ml), β -hemolytic streptococci group B, C, and G (MIC₉₀ 0.03-0.6 mcg/ml) and all tested resistant phenotypes of *S. pneumoniae* (MIC₉₀ 0.015 mcg/ml). The results for telavancin tested against resistant phenotypes of *S. pneumoniae* are summarized in Table 10.

Table 10: Telavancin MIC results for pneumococcal isolates having nine different patterns of resistance (n = 205)

Resistance pattern (no. tested) ^a	MIC (μ g/ml):		
	50%	90%	Range
Pan-S (16)	0.015	0.015	0.008-0.015
PEN-NS (30)	0.008	0.015	0.008-0.015
PEN AND CXM-NS (10)	0.015	0.015	0.008-0.015
ERY-R (10)	0.008	0.015	0.008-0.015
LEVO-R (10)	0.015	0.015	0.008-0.015
TET-R (10)	0.015	0.015	0.008-0.015
T/S-R (11)	0.015	0.015	0.004-0.015
ERY, CM, TET-R (10)	0.015	0.015	0.008-0.015
Multidrug-R (98) ^b	0.015	0.015	0.008-0.015
All strains (205)	0.015	0.015	0.004-0.015

a. S = susceptible; R = resistant; NS = non-susceptible; PEN = penicillin; CXM = cefuroxime; ERY = erythromycin; LEVO = levofloxacin; TET = tetracycline; and T/S = trimethoprim/sulfamethoxazole; CM = clindamycin.

b. Multidrug-R = resistance to PEN, CXM, CM, ERY, TET and T/S (six drug classes).

Source: This application, Report 06-THE-02

In Summary:

In addition to summarized data originally submitted in support of NDA 22110, the Applicant has provided study reports from five investigations of the in vitro activity of telavancin, conducted since that submission. Telavancin overall activity against isolates of *S. aureus* and *S. pneumoniae* (the primary pathogens in the proposed indications), analyzed in these studies, is summarized in Tables 11 and 12, respectively.

Table 11: Summary of Activity of Telavancin Against *S. aureus*: Previously Reported and Recent Prospective Surveillance Studies

Study	No. Isolates	MIC (μ g/mL)		
		Range	50%	90%
2004-2005 US Surveillance [31]	2299	0.03 - 1	0.25	0.5
2004-2005 EU Surveillance [30]	1785	$\leq$ 0.015 - 1	0.25	0.5
BSAC 2005 [74]	244	0.12 - 0.5	0.25	0.5
BSAC 2006 [75]	242	0.12 - 0.5	0.25	0.5
Japanese Surveillance 2006 [36]	1500	0.12 - 0.5	0.25	0.5
International Surveillance 2007 [40]	5895	0.03 - 0.5	0.12	0.25

Source: This submission, Section 5.3.5.4.1.4.2.6, Table 14

Table 12: Summary of Activity of Telavancin Against *S. pneumoniae*: Previously Reported and Recent Prospective Surveillance Studies

Study	No. Isolates	MIC (µg/mL)		
		Range	50%	90%
2004-2005 US Surveillance {31}	276	0.002 - 0.06	0.015	0.03
2004-2005 EU Surveillance {30}	179	≤ 0.001 - 0.06	0.015	0.03
BSAC 2005 {74}	230	≤ 0.03 - 0.06	≤ 0.03	≤ 0.03
BSAC 2006 {75}	231	≤ 0.008 - 0.12	≤ 0.008	0.015
JMI Streptococcus Study {41}	205	0.004 - 0.015	0.015	0.015
International Surveillance 2007 {40}	984	≤ 0.015 - 0.06	0.03	0.03

Source: This submission, Section 5.3.5.4.1.4.2.6, Table 15

Overall telavancin activity, as reported in the large in vitro studies, against pathogens associated with HAP (including Enterococcus species, viridans group streptococci, β-hemolytic streptococci, and bovis group streptococci is summarized in Tables 13 and 14.

Table 13: Summary of Activity of Telavancin Against Vancomycin-susceptible Enterococcus Species: Previously Reported and Recent Prospective Surveillance Studies

Study	No. Isolates	MIC (µg/mL)		
		Range	50%	90%
<i>E. faecalis</i>, vancomycin-S				
2004-2005 US Surveillance {31}	429	0.12 - 1	0.25	0.5
2004-2005 EU Surveillance {30}	426	0.06 - 1	0.25	0.5
BSAC 2005 {74}	136	0.06 - 1	0.5	1
BSAC 2006 {75}	138	≤ 0.03 - 0.5	0.25	0.5
International Surveillance 2007 {40}	1197	0.03 - 1	0.25	0.5
<i>E. faecium</i>, vancomycin-S				
2004-2005 US Surveillance {31}	92	≤ 0.015 - 0.5	0.12	0.25
2004-2005 EU Surveillance {30}	276	0.03 - 1	0.12	0.25
BSAC 2005 {74}	54	≤ 0.03 - 0.25	0.12	0.25
BSAC 2006 {75}	55	≤ 0.03 - 0.25	0.06	0.12
International Surveillance 2007 {40}	377	≤ 0.015 - 1	0.06	0.12

Source: This submission, Section 5.3.5.4.1.4.2.6, Table 16

Table 14: Summary of Activity of Telavancin Against Individual Non-Pneumococcal

Streptococcus Species: Previously Reported and Recent Prospective Studies

Group/Species	Study	No. Isolates	MIC (µg/mL)		
			Range	50%	90%
β-Hemolytic streptococci					
Group A (<i>S. pyogenes</i>)	2004-2005 US Surveillance [31]	68	0.015 - 0.12	0.03	0.06
	2004-2005 EU Surveillance [30]	54	0.015 - 0.12	0.03	0.03
	BSAC 2005 [74]	88	≤ 0.03 - 0.12	0.06	0.06
	BSAC 2006 [75]	85	≤ 0.03 - 0.12	0.06	0.06
	International Surveillance 2007 [40]	242	≤ 0.015 - 0.25	0.03	0.06
Group B (<i>S. agalactiae</i>)	2004-2005 US Surveillance [31]	45	0.03 - 0.12	0.06	0.06
	2004-2005 EU Surveillance [30]	48	≤ 0.008 - 0.12	0.06	0.06
	BSAC 2005 [74]	65	≤ 0.03 - 0.12	0.12	0.12
	BSAC 2006 [75]	82	≤ 0.03 - 0.25	0.06	0.12
	International Surveillance 2007 [40]	260	0.03 - 0.25	0.06	0.06
	JMI Streptococcus Study [41]	100	0.015 - 0.06	0.03	0.06
Group C (<i>S. dysgalactiae</i> , including ssp. <i>equisimilis</i>)	2004-2005 US Surveillance [31]	10	0.03 - 0.06	0.03	0.06
	2004-2005 EU Surveillance [30]	9	≤ 0.008 - 0.12	-- ^a	--
	BSAC 2005 [74]	13	≤ 0.03 - 0.12	0.06	0.06
	BSAC 2006 [75]	16	≤ 0.03 - 0.06	≤ 0.03	0.06
	International Surveillance 2007 [40]	30	0.03 - 0.12	0.03	0.06
	JMI Streptococcus Study [41]	100	0.015 - 0.06	0.03	0.03
Group F	2004-2005 US Surveillance [31]	4 7	0.015 - 0.06	--	--
	and 2004-2005 EU Surveillance [30]		--	--	
	combined		--	--	
	International Surveillance 2007 [40]				
Group G	2004-2005 US Surveillance [31]	18	0.03 - 0.25	0.06	0.12
	2004-2005 EU Surveillance [30]	15	0.03 - 0.25	0.03	0.06
	BSAC 2005 [74]	62	≤ 0.03 - 0.12	0.06	0.06
	BSAC 2006 [75]	46	≤ 0.03 - 0.12	0.06	0.06
	International Surveillance 2007 [40]	35	0.03 - 0.12	0.03	0.06
	JMI Streptococcus Study [41]	100	0.015 - 0.12	0.03	0.06
Bovis Group Streptococci					
<i>S. bovis</i> group	BSAC 2005 [74]	21	≤ 0.03 - 0.12	0.06	0.12
	BSAC 2006 [75]	21	0.03 - 0.12	0.06	0.12
	International Surveillance 2007 [40]	15	≤ 0.015 - 0.06	0.03	0.06
<i>S. equinus</i>	International Surveillance 2007 [40]	2	0.03	--	--
<i>S. gallolyticus</i>	International Surveillance 2007 [40]	1	0.06	--	--
Viridans Group Streptococci					
Anginosus Group					
<i>S. anginosus/milleri</i>	2004-2005 EU Surveillance [30]	1	0.03	--	--
	BSAC 2005 [74]	26	≤ 0.03 - 0.12	≤ 0.03	0.06
	BSAC 2006 [75]	21	0.015 - 0.06	0.015	0.03
	International Surveillance 2007 [40]	36	≤ 0.015 - 0.06	0.03	0.06
	JMI Streptococcus Study [41]	100	0.002 - 0.06	0.03	0.03
<i>S. constellatus</i>	BSAC 2005 [74]	3	≤0.03	--	--
	BSAC 2006 [75]	4	0.015	--	--
	International Surveillance 2007 [40]	10	0.03 - 0.06	0.03	0.06
	JMI Streptococcus Study [41]	100	0.015 - 0.06	0.03	0.03
<i>S. intermedius</i>	2004-2005 US Surveillance [31]	2	0.03 - 0.06	--	--
	BSAC 2005 [74]	2	≤ 0.03	--	--
	BSAC 2006 [75]	5	0.015 - 0.03	--	--
	International Surveillance 2007 [40]	2	0.03 - 0.06	--	--
	JMI Streptococcus Study [41]	100	0.015 - 0.25	0.03	0.06

Source: This submission, Section 5.3.5.4.1.4.2.6, Table 17

Table 14: (cont'd)

Group/Species	Study	No. Isolates	MIC (µg/mL)		
			Range	50%	90%
Mitis Group					
<i>S. mitis</i>	2004-2005 US Surveillance {31}	1	0.12	--	--
	BSAC 2005 {74}	14	≤ 0.03 - 0.06	≤ 0.03	≤ 0.03
	BSAC 2006 {75}	7	≤ 0.008 - 0.015	--	--
	International Surveillance 2007 {40}	14	0.03 - 0.06	0.03	0.06
	JMI Streptococcus Study {41}	100	0.008 - 0.06	0.03	0.03
<i>S. oralis</i>	BSAC 2005 {74}	63	≤ 0.03 - 0.12	≤ 0.03	0.06
	BSAC 2006 {75}	49	≤ 0.008 - 0.06	0.03	0.03
	International Surveillance 2007 {40}	7	≤ 0.015 - 0.06	--	--
	JMI Streptococcus Study {41}	100	0.015 - 0.06	0.03	0.03
<i>S. parasanguis</i>	BSAC 2005 {74}	9	≤ 0.03 - 0.06	--	--
	BSAC 2006 {75}	13	0.03 - 0.12	0.03	0.06
	International Surveillance 2007 {40}	3	0.03	--	--
Mutans Group					
<i>S. mutans</i>	BSAC 2005 {74}	2	0.06 - 0.12	--	--
	BSAC 2006 {75}	1	0.12	--	--
	International Surveillance 2007 {40}	3	0.03	--	--
Sanguis Group					
<i>S. gordonii</i>	BSAC 2005 {74}	4	≤ 0.03	--	--
	BSAC 2006 {75}	6	0.03 - 0.06	--	--
	International Surveillance 2007 {40}	2	0.06	--	--
<i>S. sobrinus</i>	BSAC 2005 {74}	1	≤ 0.03	--	--
<i>S. sanguis</i>	BSAC 2005 {74}	17	≤ 0.03 - 0.12	≤ 0.03	0.12
	BSAC 2006 {75}	27	0.015 - 0.06	0.03	0.06
	International Surveillance 2007 {40}	6	0.03 - 0.06	--	--
Salivarius Group					
<i>S. salivarius</i>	BSAC 2005 {74}	10	≤ 0.03 - 0.12	≤ 0.03	0.12
	BSAC 2006 {75}	5	0.06	--	--
	International Surveillance 2007 {40}	6	0.03 - 0.06	--	--
<i>S. vestibularis</i>	BSAC 2005 {74}	8	≤ 0.03 - 0.12	≤ 0.03	--
	BSAC 2006 {75}	7	≤ 0.008 - 0.12	--	--
	International Surveillance 2007 {40}	1	0.03	--	--

^a MIC statistics not determined for N < 10 isolates

Source: This submission, Section 5.3.5.4.1.4.2.6, Table 17

Antimicrobial Spectrum of Activity Studies ~ Conclusions:

Data submitted from large prospective surveillance studies and other investigations of in vitro activity, including investigations conducted in support of NDA 22110, support the applicant's claim of activity against the pathogens generally associated with hospital acquired pneumonia, including the organisms listed in the proposed indication for telavancin. MIC values for all tested isolates of *S. aureus* and *S. pneumoniae* (including isolates resistant to other classes of antimicrobials, and isolates with specific virulence profiles) were below attainable drug concentrations that can be achieved with the telavancin dosing regimen being proposed by the Applicant.

RESISTANCE STUDIES

Glycopeptide resistance in enterococci, first described in European isolates in 1988 [Courvalin 2006] has become widespread since that time. The resistance mechanisms have been characterized phenotypically and genotypically [Leclercq 1988]. Of the six different types of enterococcal vancomycin-resistance, VanA and VanB are the most common clinically observed varieties. Both are inducible and both may be transferred by mobile elements. Resistance is conferred by the production of peptidoglycan (PG) precursors that have a low affinity for glycopeptides, and by the elimination of high-affinity PG precursors (precursors with C-terminal D-Ala residues) that are the normal constituents of peptidoglycan polymerization. VanA resistance is induced by a variety of glycopeptides (including teicoplanin and telavancin), while

VanB appears to be primarily induced by vancomycin only.

Staphylococcal resistance to glycopeptides is rare. Vancomycin-resistant *S. aureus* (VRSA; MIC ≥ 16 $\mu\text{g/ml}$) has been isolated three times in the U.S., and all isolates were positive for the VanA gene cluster [Weigel 2003]. Vancomycin-intermediate *S. aureus* (VISA; MIC = 4 – 8 $\mu\text{g/ml}$) is seen more often than VRSA, but is also uncommon in clinical settings. VISA isolates appear to have decreased (or absent) levels of specific transpeptidases (PBP 4), which may result in a buildup of cell wall precursors. This excess concentration of uncross-linked precursors may act to absorb glycopeptides, effectively reducing the action of the antimicrobial. The isolation of GISA is most often associated with patients undergoing long-term vancomycin therapy. *Staphylococcus aureus* isolates may exhibit heteroresistance to glycopeptides, which is determined by the presence of resistant sub-populations in vitro. Heteroresistant vancomycin-intermediate *S. aureus* (hVISA) may represent a precursor to the development of VISA, and hVISA has been associated with vancomycin therapy failures (Moore 2003).

Glycopeptide resistance in the streptococci has not been observed.

In NDA 22-110, the Applicant provided data from well-controlled studies to demonstrate a low potential for development of resistance to telavancin in bacterial species considered in the proposed indications. Although Van-A type vancomycin-resistant enterococcal species are not included in the proposed indications for telavancin (vancomycin-susceptible *E. faecalis* is listed in the proposed indications for the treatment of cSSSI), the data from resistance suggests a possible role for this resistance mechanism in staphylococcal species (e.g. vancomycin-resistant *S. aureus*). Surveillance, regarding the development and spread of this resistance mechanism is warranted. *S. aureus* heteroresistance to telavancin was not observed.

In addition to referencing studies of telavancin resistance submitted in support of NDA 22-110, the Applicant has provided data from four recent studies, as well as an overview of telavancin activity against *S. pneumoniae* (not included in the indications proposed in NDA 22110).

In an investigation of the ability of telavancin to induce expression of *vanA* and *vanB* operons in vancomycin-resistant enterococcus, isolates of *E. faecium* (*VanA*) and *E. faecalis* (*VanA* and *VanB*), listed in Table 15, were exposed to telavancin, vancomycin, or teicoplanin and harvested during the exponential growth phase. VanX dipeptidase activity and protein was assayed using D-Alanyl-(R)-phenylthioglycine as a substrate, to monitor the expression of VAN-resistance genes.

Table 15: *Enterococcus* spp. Isolates Used in the Study of Induction of VanX

Organism	Strain	Relevant Phenotype	MIC ($\mu\text{g/mL}$)			Source or Reference
			Telavancin	Vancomycin	Teicoplanin	
<i>E. faecalis</i>	BM4110 ^a	Vancomycin-susceptible	1	2	0.5	(16)
	BM4110/pIP816-1 ^b	VanA	8	1024	256	(2)
	ATCC 51575	VanB	1	256	0.5	ATCC ^c
	ATCC 51299	VanB	1	16	1	ATCC
<i>E. faecium</i>	ATCC 51599	VanA	8	1024	256-512	ATCC

^a Streptomycin-resistant derivative of JH2

^b Natural plasmid pIP816-1 carrying Tn1546

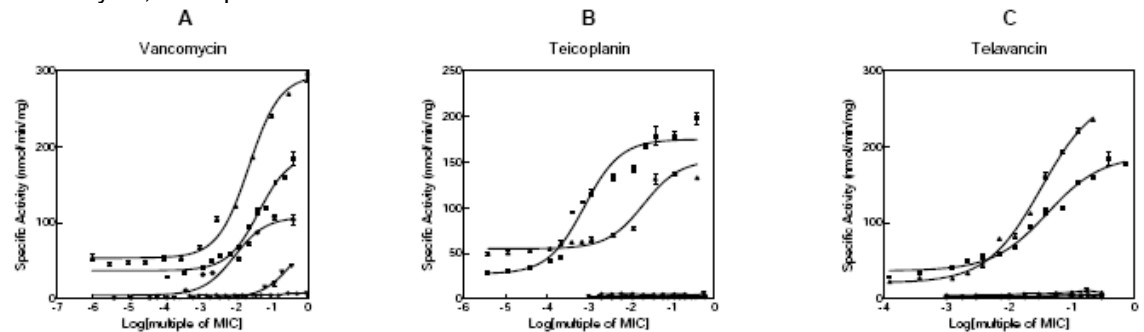
^c ATCC, American Type Culture Collection

Source: This submission, Section 5.3.5.4.1.3.2.1

The results of the investigation are summarized in Figure 3. Vancomycin induced dipeptidase activity in VanA and VanB enterococci (A), but teicoplanin and telavancin induced VanX dipeptidase activity in VanA isolates but not in VanB isolates (B and C).

Figure 3: Specific Activity of VanX in VanA and VanB Enterococci Grown in the Presence of

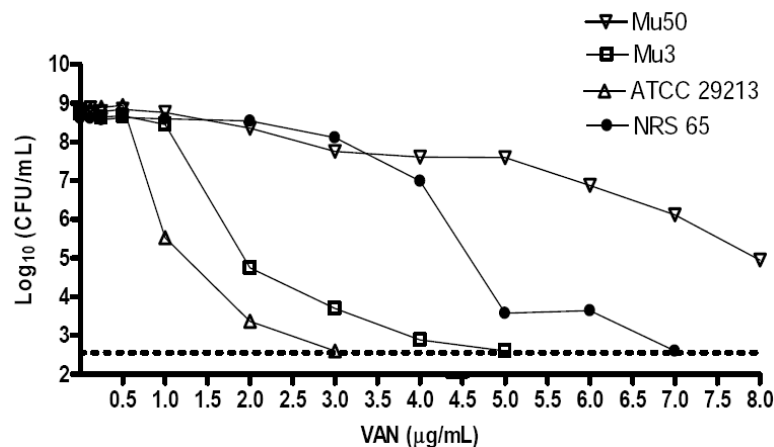
Vancomycin, Teicoplanin or Telavancin



(A) Vancomycin induced dipeptidase activity in VanA and VanB enterococci. Higher levels of activity were observed in VanA strains at comparable MIC values. (B) Teicoplanin induced VanX activity in VanA enterococci but not in the VanB strains. (C) Telavancin induced VanX activity in VanA but not in VanB enterococci. (▲) ATCC 51559 (VanA), (■) BM4110/pIP816-1 (VanA), (●) ATCC 51575 (VanB), (▼) ATCC 51299 (VanB), (●) BM4110 (vancomycin-susceptible).
Source: This submission, Section 5.3.5.4.1.3.2.1, Figure 1

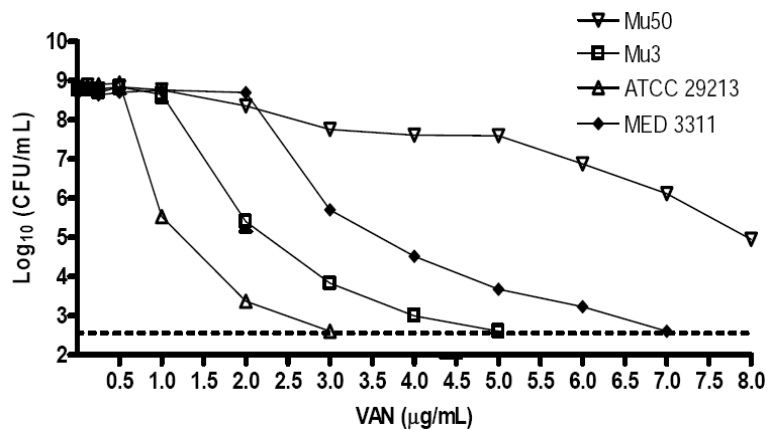
In a population analysis profile (PAP) study, submitted to support NDA 22110, *S. aureus* type strains ATCC 29213 (vancomycin-susceptible, ATCC 700698 (hVISA Mu3), and ATCC 700699 (VISA Mu3) were analyzed for heteroresistance to telavancin. In this study, no isolates were identified with an MIC greater than 1 mcg/ml (the proposed breakpoint for telavancin against *S. aureus*). The Applicant has submitted data from a second PAP study intended to further characterize the possibility of telavancin heteroresistance in isolates of *S. aureus*. The vancomycin PAP-AUC ratio was defined as: AUC of test isolate/AUC of hVISA Mu3. Analyzed isolates were characterized as VSSA, hVISA, and VISA, based on the determined ratio (<0.9, 0.9 – 1.3) and <1.3, respectively). The tested isolates included three recent clinical isolates (two, MED 3306 and MED 3314, identified as hVISA, and one, MED 3311, identified as VISA) and four reference isolates (Mu50 and NRS65, both identified as VISA, ATCC 29213, identified as VSSA, and Mu3, identified as hVISA). The results of the analysis are summarized in Figures 4 through 13. No subpopulations were identified, in this study, with reduced susceptibility to telavancin.

Figure 4: Vancomycin Population Analysis Profiles for *S. aureus* ATCC 29213, Mu3, Mu50, and NRS 65



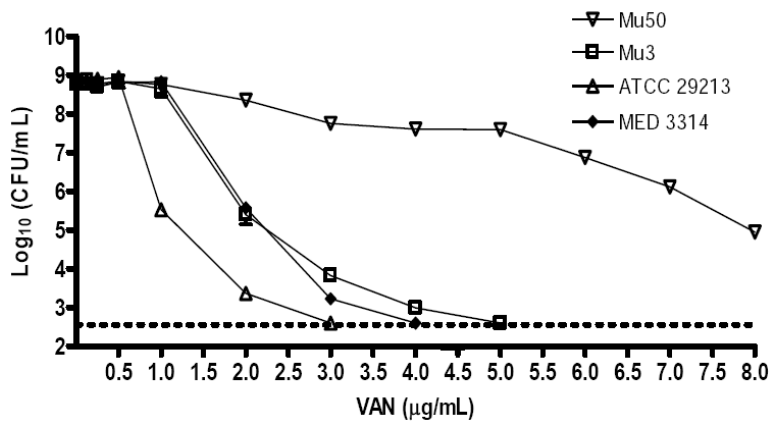
Source: This submission, Section 5.3.5.4.1.3.2.2, Figure 2

Figure 5: Vancomycin Population Analysis Profiles for *S. aureus* MED 3311



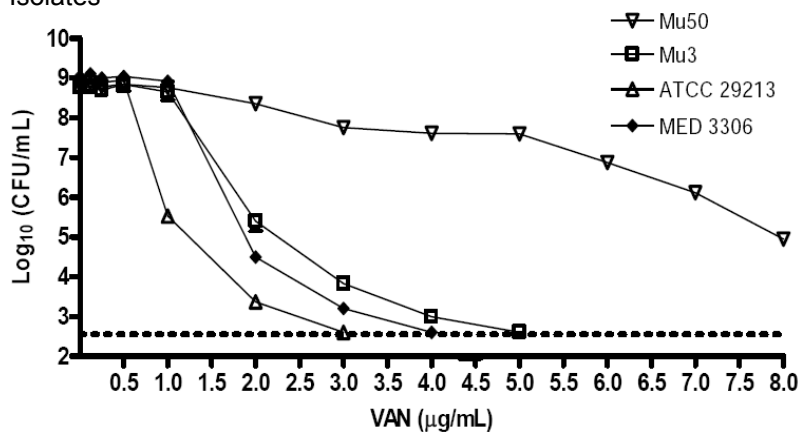
Source: This submission, Section 5.3.5.4.1.3.2.2, Figure 3

Figure 6: Vancomycin Population Analysis Profiles for *S. aureus* MED 3314 and Reference Isolates



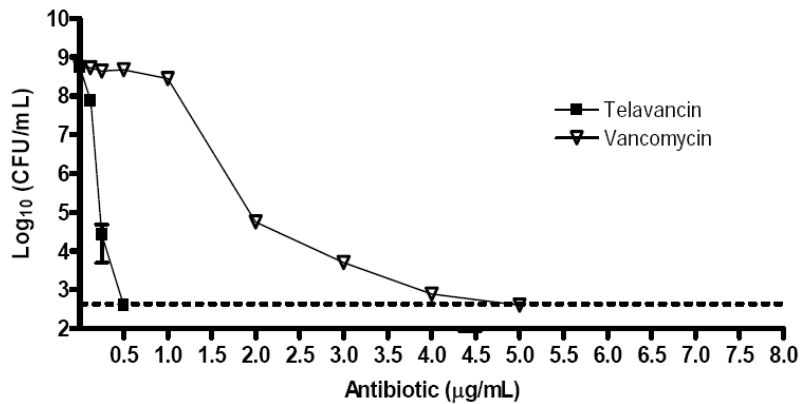
Source: This submission, Section 5.3.5.4.1.3.2.2, Figure 4

Figure 7: Vancomycin Population Analysis Profiles for *S. aureus* MED 3306 and Reference Isolates



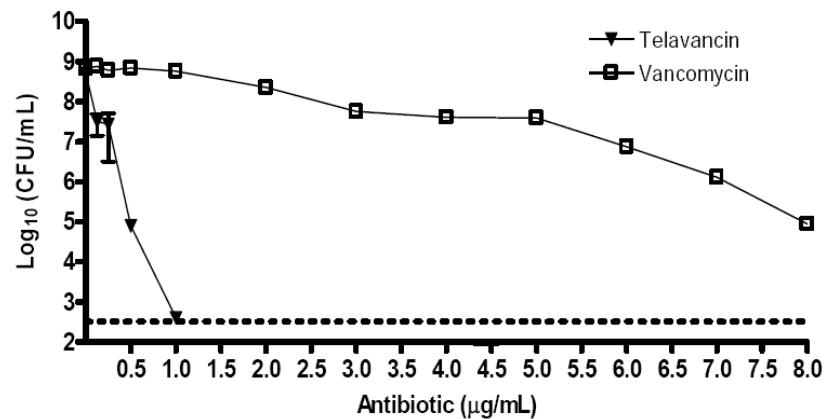
Source: This submission, Section 5.3.5.4.1.3.2.2, Figure 5

Figure 8: Telavancin and Vancomycin Population Analysis Profiles for *S. aureus* Mu3 (hVISA)



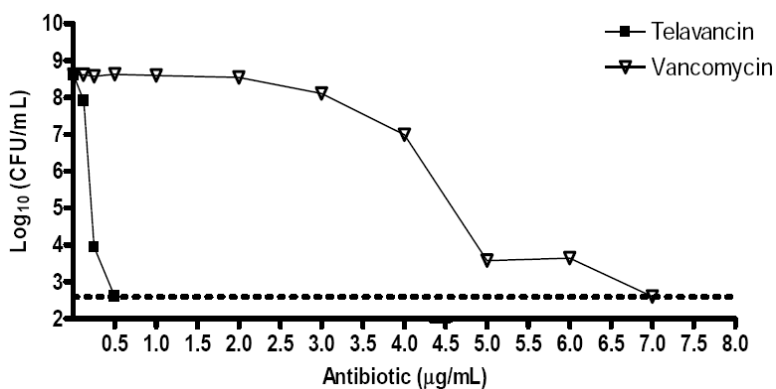
Source: This submission, Section 5.3.5.4.1.3.2.2, Figure 6

Figure 9: Telavancin and Vancomycin Population Analysis Profiles for *S. aureus* Mu50 (VISA)



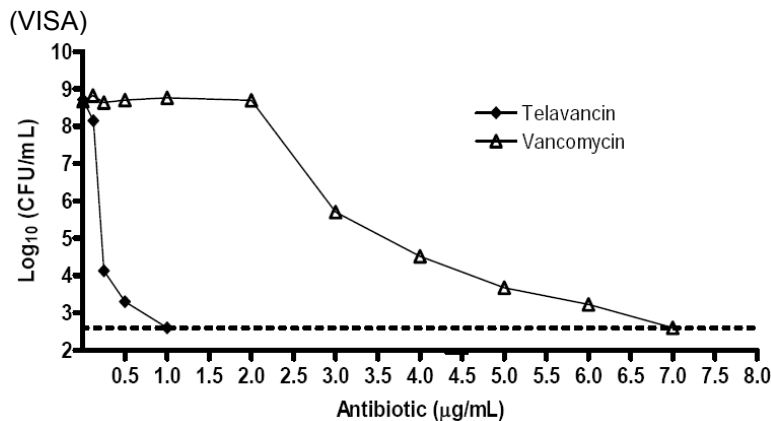
Source: This submission, Section 5.3.5.4.1.3.2.2, Figure 7

Figure 10: Telavancin and Vancomycin Population Analysis Profiles for *S. aureus* NRS65 (VISA)



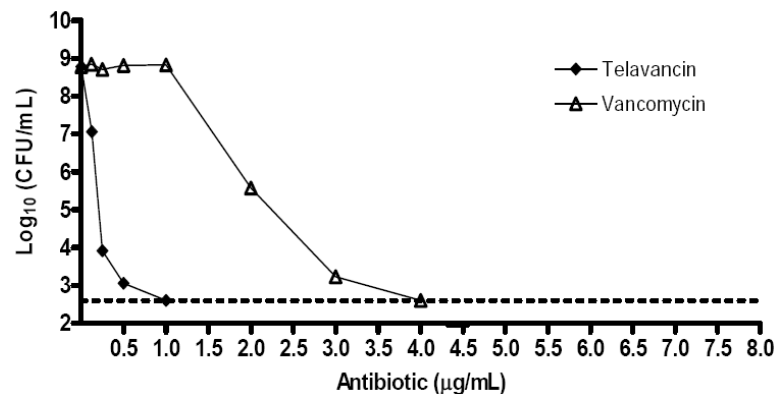
Source: This submission, Section 5.3.5.4.1.3.2.2, Figure 8

Figure 11: Telavancin and Vancomycin Population Analysis Profiles for *S. aureus* MED 3311



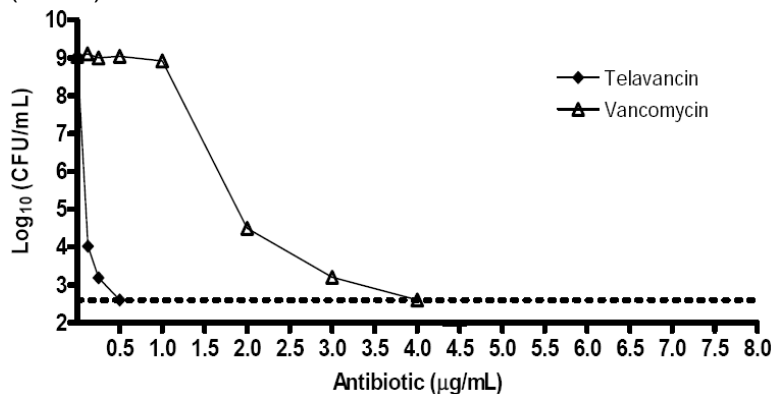
Source: This submission, Section 5.3.5.4.1.3.2.2, Figure 9

Figure 12: Telavancin and Vancomycin Population Analysis Profiles for *S. aureus* MED 3314 (hVISA)



Source: This submission, Section 5.3.5.4.1.3.2.2, Figure 10

Figure 13: Telavancin and Vancomycin Population Analysis Profiles for *S. aureus* MED 3306 (hVISA)



Source: This submission, Section 5.3.5.4.1.3.2.2, Figure 10

The Applicant has provided a preliminary report from a study designed to investigate the ability of telavancin to select resistant mutants from populations of vancomycin-susceptible and – nonsusceptible MRSA and vancomycin-susceptible enterococci [Clark 2008]. Recent clinical isolates were tested, including 10 MRSA isolates (4 vancomycin-susceptible (VSSA), 4 vancomycin-intermediate(VISA), and 2 heterogeneous-VISA (hVISA)), 1 vancomycin-susceptible

E. faecalis, and 1 vancomycin-susceptible *E. faecium*. Susceptibility testing was performed using CLSI-approved broth macrodilution techniques. Serial passages were performed using the dilution 1-2 dilutions below the MIC for the particular organism and drug, with daily passage until a >4 fold increase in MIC was found (50 passages maximum, 14 passages minimum). Resistant clones, if isolated, were subcultured 10 times in drug-free medium to establish stability of resistance. The relatedness of parental isolates and resistant clones was tested by pulse-field gel electrophoresis. The results of this investigation are summarized in Table 16. Telavancin yielded an elevated MIC clone in one VSSA isolate after 43 days (with no subsequent elevation afterwards, through Day 50). In comparison, daptomycin yielded resistant clones in 4 of 10 MRSA isolates and both enterococcal isolates.

Table 16: Multistep Resistance Selection Results

Species	Strain		MIC (µg/mL)				
			Telavancin	Vancomycin	Teicoplanin	Daptomycin	Linezolid
<i>S. aureus</i>	SA525 (VSSA)	Initial MIC	0.5	2	1	1	4
		Final (Pass. No.)	1 (50)	8 (50)	8 (21)	8 (20)	16 (50)
		Post Subculture	-	-	4	2	-
	SA 547 (VSSA)	Initial MIC	0.5	2	2	1	4
		Final (Pass. No.)	2 (50)	8 (50)	16 (35)	8 (21)	32 (48)
		Post Subculture	-	-	4	4	32
	SA262 (VSSA)	Initial MIC	0.5	4	1	1	4
		Final (Pass. No.)	4 (34)	4 (50)	4 (50)	8 (16)	>32 (22)
		Post Subculture	1	-	-	4	32
	SA248 (VSSA)	Initial MIC	0.25	1	0.5	0.5	4
		Final (Pass. No.)	2 (43)	2 (50)	4 (32)	4 (41)	16 (50)
		Post Subculture	2	-	1	0.5	-
	SA618 (hVISA)	Initial MIC	0.5	2	4	2	4
		Final (Pass. No.)	2 (50)	8 (50)	16 (50)	16 (14)	16 (50)
		Post Subculture	-	-	-	8	-
	SA873 (hVISA)	Initial MIC	0.5	2	2	1	2
		Final (Pass. No.)	2 (50)	4 (50)	16 (27)	2 (50)	8 (50)
		Post Subculture	-	-	4	-	-
	SA555 (VISA)	Initial MIC	1	8	16	16	2
		Final (Pass. No.)	2 (50)	8 (50)	32 (50)	32 (50)	4 (50)
		Post Subculture	-	-	-	-	-
	SA1287 (VISA)	Initial MIC	0.5	4	4	4	4
		Final (Pass. No.)	2 (50)	8 (50)	16 (50)	8 (50)	16 (50)
		Post Subculture	-	-	-	-	-
	SA1948 (VISA)	Initial MIC	0.5	4	2	4	4
		Final (Pass. No.)	2 (50)	16 (50)	32 (14)	8 (50)	8 (50)
		Post Subculture	-	-	16	-	-
	SA770 (VISA)	Initial MIC	0.5	4	4	1	4
		Final (Pass. No.)	2 (50)	8 (50)	16 (50)	8 (35)	8 (50)
		Post Subculture	-	-	-	4	-
<i>E. faecalis</i>	<i>E. faecalis</i> HMC568 (Van-S)	Initial MIC	1	2	1	2	2
		Final (Pass. No.)	1 (50)	2 (50)	2 (50)	16 (21)	32 (35)
		Post Subculture	-	-	-	16	32
<i>E. faecium</i>	<i>E. faecium</i> HMC651 (Van-S)	Initial MIC	0.25	1	1	4	2
		Final (Pass. No.)	1 (50)	1 (50)	2 (50)	32 (24)	2 (50)
		Post Subculture	-	-	-	16	-

Source: This submission, Section 5.3.5.4.1.3.2.3, Table 2

The Applicant has provided a brief summary of telavancin activity against resistant isolates of *S. pneumoniae* from data collected and analyzed in the 2007 International Surveillance Program (JMI, North Liberty, Iowa), submitted in support of NDA 22-110. In this study, the telavancin MIC₉₀ (984 recent clinical isolates, including 64 with an MIC > 2 mcg/ml) was 0.03 mcg/ml.

Resistance Studies ~ Conclusions:

The Applicant has provided, as reference to NDA 22-110 and in information from investigations undertaken since that submission, sufficient data to demonstrate a low potential for development of resistance to bacterial species considered in the proposed indications. Data presented in this Application suggest that telavancin is an inducer of the VanA operon, but does not induce activity of the VanB operon. Population analysis profiles have not detected heteroresistance to telavancin in isolates of *S. aureus*. No resistance to telavancin was noted in isolates collected in clinical trials.

ANTIMICROBIAL INTERACTION STUDIES

In NDA 22-110, the applicant presented data from two independent investigations, employing both checkerboard microdilution studies and time-kill studies, to describe interactions of telavancin with other antimicrobials commonly used to treat complicated skin and skin structure infections. Modest synergy was observed in the checkerboard microdilution studies against staphylococci, enterococci, and streptococci (including *S. pneumoniae*), but no synergy between either telavancin and imipenem, or telavancin and cefepime, was observed against strains of MRSA and MSSA (ATCC 33591 and ATCC 29213, respectively), in the time-kill studies. No antagonism was noted in any of the drug interaction investigations.

The Applicant has submitted preliminary data from an ongoing investigation of synergistic interactions between telavancin and rifampin, gentamicin, cefepime, ceftriaxone, oxacillin, meropenem, and ciprofloxacin [Lin 2008]. In the study, telavancin was studied alone and in combination with rifampin, gentamicin, cefepime, ceftriaxone, oxacillin, meropenem, and ciprofloxacin against 22 MRSA isolates, including 6 identified as "community acquired", 2 hVISA, 8 VISA, and 3 VRSA. Standard broth microdilution techniques were used to determine MICs, with viability counts performed at 0, 3, 6, and 12 hours. The investigators defined synergy as "≥ 2 log₁₀ reduction in CFU/ml between the antimicrobial combination and its more active agent at each time point compared to time 0 h." The preliminary results of this study are summarized in Table 17. Telavancin was active against all tested isolates, including hVISA and VISA, at concentrations ≤ 1 mcg/ml, and displayed synergy against all tested isolates, at sub-MIC concentrations, in combination with β-lactams, gentamicin, rifampin, and ciprofloxacin.

Table 17: In Vitro Antimicrobial Interactions Studied by Time-Kill

Isolate/ phenotype	N ^a	Number of Strain at 24 hrs Showing Interaction for Telavancin Tested in Combination with													
		Gentamicin		Rifampin		Cefepime		Ceftriaxone		Oxacillin		Meropenem		Ciprofloxacin	
		A ^b	S ^c	A	S	A	S	A	S	A	S	A	S	A	S
All	22	2	20	7	15	3	19	1	21	6	16	1	21	5	17
VSSA	9	0	9	2	7	1	8	0	9	5	4	0	9	1	8
hVISA	2	0	2	0	2	0	2	0	2	0	2	0	2	1	1
VISA	8	1	7	3	5	1	7	1	7	0	8	1	7	2	6
VRSA	3	1	2	2	1	1	2	0	3	1	2	0	3	1	2

^a Number of isolates tested

^b Additive effect

^c Synergistic effect

Source: This submission, Section 5.3.5.4.1.7.3.1, Table 1

Antimicrobial Interaction Studies ~ Conclusions:

In data presented in this Application as well as in NDA 22-110, the Applicant has demonstrated modest synergy of telavancin with β-lactams, rifampin, ciprofloxacin, and gentamicin, against isolates of *S. aureus*, including methicillin-resistant and vancomycin-non-susceptible phenotypes. Telavancin activity is additive with other studied drug combinations. No antagonism has been demonstrated with telavancin and any tested antimicrobial.

EFFECTS OF MISCELLANEOUS FACTORS ON ACTIVITY

I. PROTEIN BINDING

Telavancin is highly protein-bound (~90%) in human serum, principally to serum albumin. Over a range of studied concentrations (1 to 500 µg/ml), the drug was approximately 88 to 92% bound. Studies in skin blister fluid demonstrated similar protein binding (85.5% at a concentration of 100 mcg/ml). Hepatic or renal insufficiency did not markedly alter levels of serum protein binding.

In NDA 22110, the Applicant submitted data from the three studies of protein binding on telavancin activity indicate that while activity is diminished in the presence of human serum or specific serum proteins (e.g. HSA), bactericidal activity consistently remains, at telavancin concentrations exceeding 4x MIC, against tested strains of Gram positive pathogens (*S. aureus*

and *E. faecalis* strains).

The Applicant has provided additional information regarding the effect of human serum albumin, human serum, and mouse serum on the in vitro activity of telavancin against isolates of *S. aureus*.

In one study [Tsuji 2008], investigators evaluated the effect of protein binding on the MIC values of telavancin, daptomycin, vancomycin, and teicoplanin against five clinical isolates of *S. aureus* (4 MRSA and 1 MSSA). MICs were determined using microbroth dilution techniques approved by CLSI. Evaluations included incubation in Mueller-Hinton broth (MHB, cation adjusted) without supplementation and in MHB with 4 g/dl human albumin, 100% mouse serum, and 50% human serum. The results of the investigation are summarized in Table 18. The investigators concluded that the calculated extent of protein binding, based on MIC changes for telavancin and daptomycin (62-70% and 58-66%, respectively) suggest that the impact of protein binding on the activity of these glycopeptides may be less than that predicted by studies analyzing on free fraction concentrations.

Table 18: Effect of Human Serum Albumin, Human Serum and Mouse Serum on MIC Values Obtained for Telavancin When Tested Against Clinical Isolates of *S. aureus*

Phenotype ^a	Strain ID	SCCmec Type	MIC (µg/mL)			
			CAMHB ^b	40 g/dL HSA ^b	50% HS ^b	100% MS ^b
HA-MRSA	494	Type II	0.25	1	1	0.5
HA-MRSA	67	Type II	0.125	0.5	1	2
CA-MRSA	IE	Type IV	0.125	1	1	1
CA-MRSA	MW2	Not Reported	0.25	1	1	1
MSSA	1199	Not Reported	0.125	0.5	0.25	1

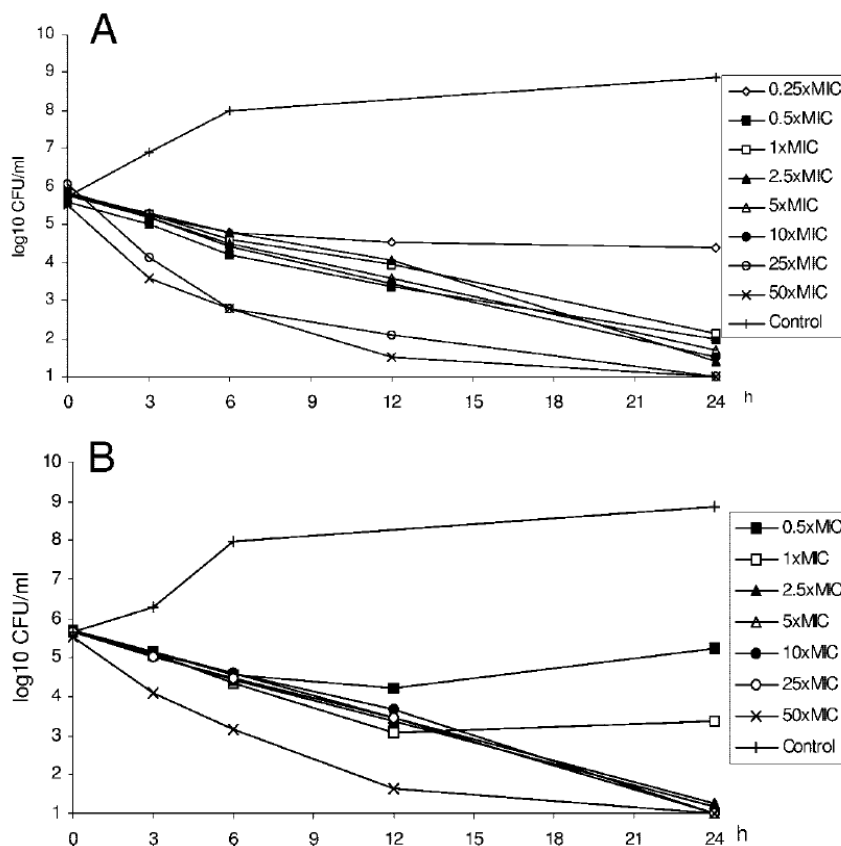
^a HA-MRSA, hospital-associated methicillin-resistant *S. aureus*; CA-MRSA, community-associated methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*

^b CAMHB, cation adjusted Mueller-Hinton Broth; HSA, human serum albumin; HS, human serum; MS, mouse serum

Source: This submission, Section 5.3.5.4.1.6.2.2, Table 2

In a second study [Odenholt 2007], researchers investigated the rate and extent of killing by telavancin in the presence and absence of human serum (4 g/dl) or human albumin (50%). Two *S. aureus* isolates were tested (methicillin susceptible *S. aureus* ATCC 13709 and methicillin-resistant *S. aureus* ATCC 33591). The investigators noted a minimal effect of human serum or human albumin on the killing activity of telavancin. Figure 14 illustrates the killing curves for telavancin against the methicillin-resistant *S. aureus* isolate in broth and in 40 g/liter human albumin.

Figure 14: Killing curves for telavancin against *S. aureus* 33591 (MRSA) in broth (static experiments) (A) and in 40-g/liter human albumin (B). Values shown are means of two experiments



II. INTRACELLULAR ACTIVITY

In NDA 22-110 the applicant provided data to support the claim of intracellular activity of telavancin against strains of *S. aureus*. The activity appears to be localized in lysosomes and is concentration-dependent, which further supports a claim for enhanced efficacy of the antimicrobial, since phagocytosis of Gram positive cocci (and concomitant intracellular killing) represents a significant strategy in the limitation of the infectious process.

No additional information was provided in the current submission, regarding the intracellular activity of telavancin.

III. ACTIVITY AGAINST BIOFILMS

In NDA 22-110, the Applicant presented data from an investigation of a biofilm model, designed to demonstrate the activity of telavancin against non-planktonic bacterial communities. Data from that investigation supported the claim that telavancin is active in penetrating biofilms, is capable of reducing bacterial counts in in vitro biofilms models, and exceeds the activity of both glycopeptide and some non-glycopeptide comparators in both respects.

In this submission, the Applicant has provided a report from a recent study of the in vitro activity of telavancin and vancomycin against biofilm-producing staphylococcal and enterococcal isolates [LaPlante 2009]. The investigators used the minimal biofilm eradication concentration (MBEC) assay activity of the two glycopeptides against biofilm-embedded bacteria. Conventional MIC testing was performed using broth microdilution techniques approved by CLSI. All assays were performed in quadruplicate. MBEC was defined as the minimal concentration of antibiotic

required to eradicate growth in the 24-hour biofilms. Minimum biofilm inhibitory concentration (MBIC) was also assayed, and was defined as the lowest microbroth dilution with visible growth after incubation in biofilms and antibiotic for 24 hours. Tested bacteria included *S. aureus* ATCC 35556, *S. epidermidis* ATCC 35984, *E. faecalis* ATCC 29212, and three clinical *S. aureus* isolates. In this study, the investigators demonstrated no activity of vancomycin against any of the biofilm-embedded bacteria, with an assayed MBEC of ≥ 512 mcg/ml. The MBEC of telavancin ranged from 0.125 to 2 mcg/ml, with biofilm inhibition demonstrated at concentrations lower than the MIC.

IV. POSTANTIBIOTIC EFFECT

In the NDA 22-110 submission, the applicant supplied data from in vitro investigations that support a 2 – 6 hour postantibiotic effect (PAE) of telavancin against strains of *S. aureus*, including MSSA, MRSA, and VISA. A prolonged PAE was demonstrated against *S. pyogenes* and *S. agalactiae*. PAE against isolates of enterococcus was diminished, compared to the other tested pathogens, but vancomycin-susceptible *E. faecalis* demonstrated notable PAE (1.1 hours).

In this submission, the Applicant has provided a study report from a recent investigation [Pankuch 2009] of the post-antibiotic effect (PAE), the post-antibiotic subMIC effect (PA-SME), and the subMIC effect (SME) of telavancin against a panel of Gram-positive pathogens. The tested isolates included 2 hVISA, 4 VISA, 1 VRSA, 1 *S. pyogenes*, 1 *S. agalactiae*, 2 *E. faecalis* (vancomycin-susceptible) and 1 *E. faecium* (vancomycin-susceptible).

PAE was as defined as the time required for counts of an antibiotic exposed culture (initial inoculum 5×10^6 CFU/ml) to increase by 1 log₁₀ after removal of antibiotic by dilution (minus growth control). For PA-SME determination, telavancin was added after dilution to produce sub-inhibitory concentrations of 0.2, 0.3 and 0.4 x MIC. SME determinations included the same addition of telavancin to culture tubes, but did not include the initial exposure to the drug (and no dilution step). The results of the study are summarized in Table 19. The PAE ranges for telavancin against staphylococci, streptococci, and enterococci were 0.9 – 3.9 hours, 0.4 - 6.7 hours, and 0.3 – 2.2 hours, respectively. The PA-SME ranges (at 0.4 x MIC) were 6.7 - >10.7 hours for staphylococci, >10.7 - >11.0 hours for streptococci, and >10 - >10.8 hours for enterococci. The SME ranges (at 0.4 x MIC) were 0.8 – 10.6 hours, 0.4 - >11.0 hours, and 3.6 – 10.0 hours, for staphylococci, streptococci, and enterococci, respectively.

Table 19: PAE, SME and PA-SME of Telavancin against Eleven Staphylococci, Two Streptococci, and Three Enterococci

Organism	MIC (µg/mL)	PAE	Effect (hr)					
			0.2X MIC		0.3X MIC		0.4X MIC	
			SME	PA-SME	SME	PA-SME	SME	PA-SME
MRSA								
ATCC 33591	0.25	1.5, 2.0	0.3, 0.3	7.7, 8.0	1.4, 1.4	>10.0, >10.3	2.3, 3.5	>10.0, >10.3
SA 1130	0.12	1.4, 1.6	0, 0.4	5.4, 5.8	2.0, 4.4	10.0, >10.5	6.5, 6.9	>10.0, >10.5
SA 1307	0.12	1.1, 1.6	1.1, 1.0	6.0, 6.4	2.6, 3.1	>10.5, >10.6	6.3, 6.5	>10.5, >10.6
SA 1316	0.12	1.8, 2.0	0.7, 1.1	2.9, 3.1	5.1, 5.2	5.4, 5.6	6.0, 6.1	>10.7, >10.6
hVISA								
SA618	0.12	1.7, 2.4	0.3, 0.8	5.7, 6.5	1.5, 1.6	8.3, 9.8	2.3, 4.3	10.3, >10.3
SA873	0.12	1.2, 1.6	0, 0.3	3.6, 4.0	0.5, 0.8	4.8, 6.0	1.0, 1.8	6.7, 7.0
VISA								
SA555	0.5	3.4, 3.9	0.3, 0.3	5.9, 6.0	1.7, 2.3	10.3, >10.6	4.3, 5.4	>10.3, >10.6
SA770	0.25	1.6, 2.3	0.7, 0.8	3.8, 5.0	0.8, 1.8	6.3, 8.3	0.8, 1.9	9.6, >10.7
SA1287	0.5	1.2, 1.8	0, 0.3	5.1, 5.2	0.4, 0.7	8.6, 10.0	0.8, 1.2	>10.3, >10.0
SA1984	0.25	0.9, 1.4	1.0, 1.0	6.8, 8.6	2.6, 3.0	>10.0, >10.6	10, 10.6	>10.0, >10.6
VRSA								
SA510	0.5	1.3, 2.0	1.9, 2.5	5.6, 5.8	2.3, 3.1	6.0, 6.6	3.6, 5.0	8.1, 8.8
<i>S. pyogenes</i>	0.06	6.1, 6.7	0, 0	8.7, 10.7	0, 0.4	>10.7, >10.7	0.4, 0.7	>10.7, >10.7
<i>S. agalactiae</i>	0.12	0.4, 1.0	0.2, 0.4	0.8, 2.1	2.1, 2.7	4.7, 6.2	>10.7, >11.0	>10.7, >11.0
<i>E. faecalis</i>	0.25	0.3, 0.7	0.8, 0.7	5.3, 5.8	2.0, 2.8	>10.7, >10.8	3.6, 4.0	>10.7, >10.8
	0.25	1.5, 2.2	0.1, 0.6	3.9, 5.1	2.6, 3.2	7.2, 7.6	9.6, 10.0	>10.6, >10.8
<i>E. faecium</i>	0.12	1.2, 1.6	1.2, 1.8	1.9, 2.2	7.2, 7.7	8.9, 9.3	8.8, 9.9	>10.0, >10.5

Source: This submission, Section 5.3.5.4.1.6.2.4, Table 3

V. EFFECT OF PULMONARY SURFACTANT

In NDA 22-110, the Applicant provided data regarding the activity of the effect of commercially available pulmonary surfactant (Survanta™) on the antimicrobial activity of telavancin (Report 05-6424-MB-03). In an investigation using standard checkerboard methodology, no antagonism of telavancin activity was observed at concentrations up to 1 mg/ml pulmonary surfactant. Of the other glycopeptide antimicrobials tested, vancomycin and teicoplanin also demonstrated no antagonism, while daptomycin was inhibited up to 32-fold against *S. aureus* isolates and 128-fold against *S. pneumoniae* isolates.

VI. ANTIMICROBIAL ACTIVITY OF PRIMARY HUMAN METABOLITES

The Applicant has provided the study report (Report 07-6424-MCB-01) from an investigation designed to describe the in vitro antimicrobial activity of the primary human metabolites of telavancin; AMI-11352, AMI-11353, and AMI-11355. CLSI broth microdilution techniques were used to determine the MICs of a panel of Gram-positive pathogens that included reference strains and recent clinical isolates. The results of the investigation are summarized in Table 20. The in vitro activity of the primary telavancin metabolites were similar, and were each ≥ 8-fold higher than that of telavancin.

Table 20: MIC Values of Telavancin, AMI-11352, AMI-11353, AMI-11355, and Vancomycin

Organism	Isolate	MIC (µg/mL)				
		Telavancin	AMI-11352	AMI-11353	AMI-11355	Vancomycin
<i>S. aureus</i>	ATCC 29213	0.5	4	4	8	1
<i>S. aureus</i>	ATCC 33591	0.5	8	8	8	2
<i>E. faecalis</i>	ATCC 29212	0.5	16	16	16	4
<i>S. pneumoniae</i>	ATCC 49619	≤0.03	1	2	2	0.5
<i>S. agalactiae</i>	MED 2038	0.25	4	4	4	1
<i>S. pyogenes</i>	MED 2040	0.125	1	2	2	0.5

Source: This submission, Section 5.3.5.4.1.6.2.1, Table 1

Miscellaneous Studies ~ Conclusions:

Telavancin is approximately 90% protein bound, primarily by albumin. Studies presented in this Application and in NDA 22-110 indicate that telavancin retains in vitro activity against the principle respiratory pathogens sought in the proposed indication, in the presence of albumin or human serum. Recent studies also suggest that telavancin activity is not inhibited by pulmonary surfactant. Telavancin is active against isolates of *S. aureus* in stationary growth phase, and has demonstrated activity against isolates of *S. aureus*, *S. epidermidis*, and *E. faecalis* in a biofilm model. The postantibiotic effect of telavancin, against isolates of *S. aureus* (including methicillin-susceptible and –resistant isolates, as well as vancomycin-non-susceptible isolates) ranges from one to six hours. The antimicrobial activity of the three primary telavancin metabolites (AMI-11352, AMI-11353, and AMI-11355) is ≥ 8-fold higher than that of telavancin.

BACTERICIDAL ACTIVITY

I. Minimum Bactericidal Concentration Studies

(b) (4)

The Applicant has provided no new data in this submission from studies using the MBC method to describe the bactericidal activity of telavancin.

II. Time-kill Studies

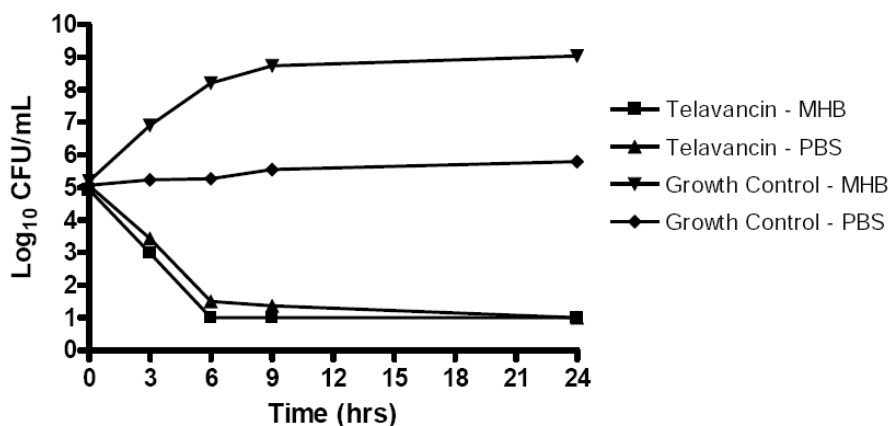
In NDA 22-110, the applicant submitted data from time-kill kinetic studies to support a claim of bactericidal activity of telavancin against a variety of *S. aureus* isolates, including isolates susceptible and non-susceptible to methicillin, and isolates non-susceptible to vancomycin. This activity generally occurs at low multiples of the MIC and at concentrations consistent with therapeutic levels, even at trough concentrations. Bactericidal activity against tested isolates of *S. pneumoniae* (bactericidal at ≤ 2 x MIC, or up to 0.06 mcg/ml), and β-hemolytic streptococci (*S. pyogenes* and *S. agalactiae*) was also demonstrated. At low fixed concentrations activity against the β-hemolytic streptococci was variable (i.e. concentrations representing C_{min} for vancomycin in healthy adults dosed at 10 mg/kg). Telavancin demonstrated modest bactericidal activity against isolates of enterococcus, with killing occurring only at high drug concentrations. Telavancin bactericidal activity against enterococci was superior to comparators, though, in most cases.

The Applicant has provided study reports from two investigations of the bactericidal activity of

telavancin against *S. aureus* isolates in a stationary growth phase.

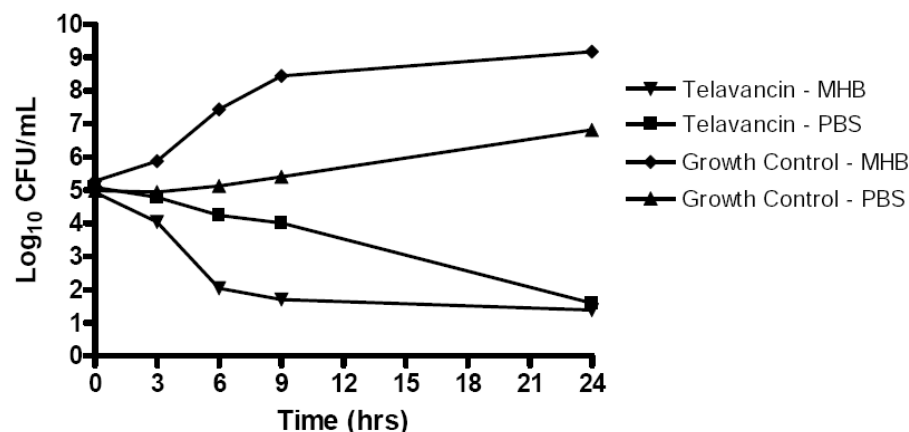
In the first study [Odenholt 2007], investigators tested the bactericidal activity of telavancin against *S. aureus* isolates in both exponential and stationary growth phases by testing isolates in either nutrient-rich or –depleted media. Tested isolates included a methicillin-resistant strain (ATCC 33591) and a methicillin-susceptible strain (ATCC 13709). The results of the investigation are summarized in Figures 15 and 16. For the methicillin-susceptible isolate, complete killing was demonstrated in both types of media within 6 hours (Fig 15). For the methicillin-resistant isolate (Fig 16), the initial killing rate against the isolate grown in nutrient broth was higher than that grown in saline, but complete killing was observed against both isolates within 24 hours.

Figure 15: Time-kill Plots Comparing the Activity of 10x MIC (10 µg/mL) Telavancin against Exponential and Stationary Phase of Methicillin-susceptible *S. aureus* ATCC 13709



Source: This submission, Section 5.3.5.4.1.5.3.1, Figure 1

Figure 16: Time-kill Plots Comparing the Activity of 10x MIC (10 µg/mL) Telavancin against Exponential and Stationary Phase of Methicillin-resistant *S. aureus* ATCC 33591

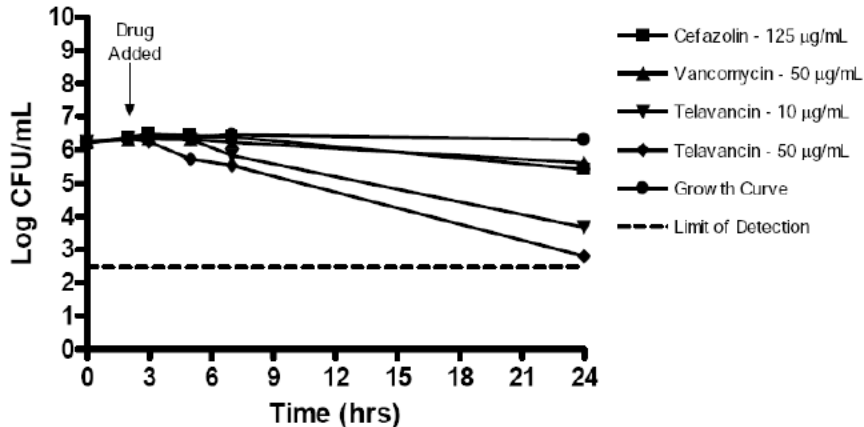


Source: This submission, Section 5.3.5.4.1.5.3.1, Figure 2

In the second study [Clouse 2007], investigators described the bactericidal activity of telavancin and comparators against isolates of methicillin-susceptible and –resistant *S. aureus* in peritoneal dialysate fluid (PDF), a nutrient-poor medium with bacteriostatic activity. Sixteen duplicate concentration-time-kill experiments were conducted in commercially obtained PDF, to compare killing rates of the antimicrobials. The results of the investigation are summarized in Figures 17 and 18. Telavancin, at both 10 mcg/ml and 50 mcg/ml exhibited statistically better kill ($P < 0.05$)

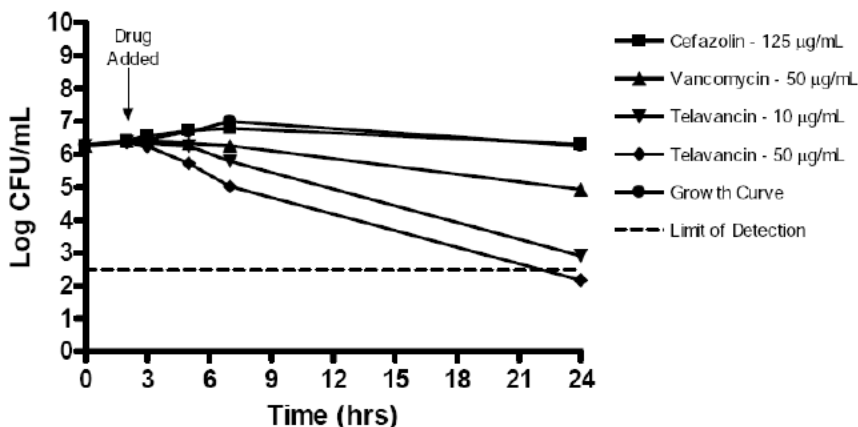
than cefazolin and vancomycin against both staphylococcal isolates, with more rapid killing observed in the 50 mcg/ml telavancin determination (compared to the 10 mcg/ml concentration).

Figure 17: Time-kill Plots Comparing the Activity of Telavancin, Vancomycin and Cefazolin in Peritoneal Dialysis Fluid against Methicillin-susceptible *S. aureus* (ATCC 29213)



Source: This submission, Section 5.3.5.4.1.5.3.1, Figure 3

Figure 18: Time-kill Plots Comparing the Activity of Telavancin, Vancomycin and Cefazolin in Peritoneal Dialysis Fluid against Methicillin-resistant *S. aureus* (ATCC 33592)



Source: This submission, Section 5.3.5.4.1.5.3.1, Figure 4

Bactericidal Activity ~ Conclusions:

The Applicant has submitted data, in NDA 22110 and this Application, from time-kill kinetic studies to support a claim of bactericidal activity of telavancin against a variety of strains of *S. aureus*, including methicillin-susceptible and -resistant phenotypes, as well as isolates non-susceptible to vancomycin, and against isolates of *S. pneumoniae*. This activity generally occurs at low multiples of the MIC and at concentrations consistent with therapeutic levels, even at trough concentrations.

(b) (4)

HUMAN AND ANIMAL STUDIES

ANIMAL DISEASE MODELS

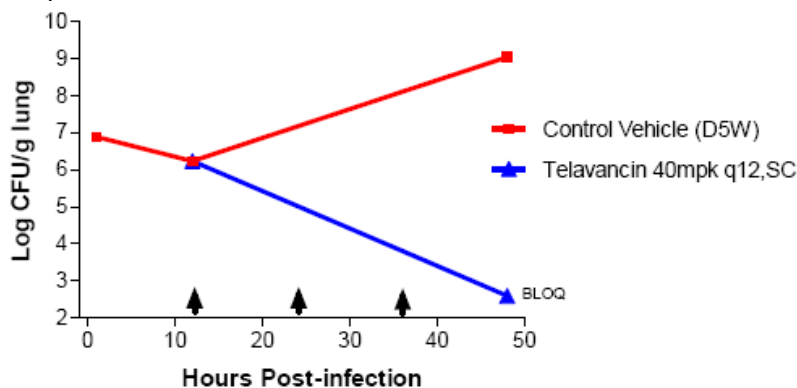
In NDA 22-110, the Applicant submitted data from a variety of animal models, including the mouse neutropenic thigh (MNT) model, murine subcutaneous infection (MSI) model, endocarditis infection model, pneumonia infection model, bacteremic infection model, and meningitis infection

model. Data from animal in vivo studies supported the use of $AUC_{(0-24)}/MIC$ as the best PK/PD predictor of antimicrobial efficacy for unbound (free) telavancin. Comparison of data from the MNT and MSI models suggested that immune status may play a minor role in telavancin efficacy.

In this submission, the Applicant has provided study reports from four additional studies, including a neutropenic mouse pneumonia model, a neutropenic mouse bacteremia model), a rabbit chronic osteomyelitis model, and a mouse acute suppurative osteomyelitis model.

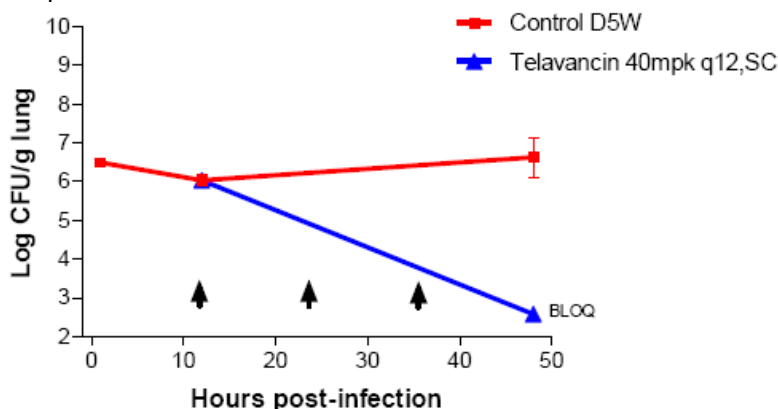
In a neutropenic mouse pneumonia model (Report 08-6424-PH-03), female BALB/c mice were rendered neutropenic, and inoculated nasally with 50 μ l (log 6.7-6.9 CFU/mL) of either *Streptococcus pneumoniae* MED 45 (penicillin-nonsusceptible) or *S. pneumoniae* MED 306 (penicillin-susceptible). Mice were dosed three times, subcutaneously (40 mg/kg q 12 hr), starting 12 hours after inoculation. The mice were euthanized at 48 hours, and lung titers were determined. The results of the study are summarized in Figures 19 and 20. The telavancin MIC against both isolates was 0.12 mcg/ml. Against *S. pneumoniae* MED 45, telavancin produced a 3.65 log CFU/g reduction in lung bacteria, with no deaths in the telavancin-treated group (1/6 mice in the control group died). Against *S. pneumoniae* MED 306, telavancin produced a 3.45 log CFU/g reduction in lung bacteria (there were no deaths in either the telavancin or control treatment group).

Figure 19: Efficacy of Telavancin (TLV) Against *S. pneumoniae* Strain MED 45 in the Neutropenic Murine Pneumonia Model



Arrows denote the time of dosing
Source: This Submission; Report 08-6424-PH-03, Figure 1

Figure 20: Efficacy of Telavancin (TLV) Against *S. pneumoniae* Strain MED 306 in the Neutropenic Murine Pneumonia Model



Arrows denote the time of dosing

Source: This Submission; Report 08-6424-PH-03, Figure 2

The in vivo efficacy of telavancin against *S. aureus* isolates with reduced susceptibility to vancomycin was studied in a neutropenic mouse bacteremia model (Report 08-6424-PH-01). In this study, female NSA mice were rendered neutropenic and inoculated with bacteria intraperitoneally. Test isolates included VISA HIP5836, VISA Mu50, and hVISA Mu3. Animals were dosed twice (at 4 and 16 hours post-infection) with either telavancin (40 mg/kg, SC, q 12 hours) or vancomycin (110 mg/kg, SC, q 12 hours). Control animals were dosed once, 4 hours post-infection, with vehicle. Designated test animals were euthanized at 12, 24, and 48 hours post-treatment. Control animals were euthanized at 0, 4, and 16 hours post-treatment. Bacterial counts were performed on blood and spleen tissue. The results of the study are summarized in Table 21. In this investigation, telavancin was more active than vancomycin in reducing the blood and spleen titers of all three vancomycin-nonsusceptible *S. aureus* isolates.

Table 21: Minimum Inhibitory Concentrations (MIC) and Blood/Spleen Counts

<i>S. aureus</i> Isolate	MIC (µg/mL)	Blood (log CFU/mL)*	Spleen (log CFU/g)*
HIP5836			
Pre-treatment titre	—	5.5 ± 0.41	8.0 ± 0.24
Vancomycin	8	3.6 ± 0.69	7.7 ± 0.49
Telavancin	1	1.0 ± 0.0 [†]	3.8 ± 0.16 [†]
Untreated	—	6.5 ± 0.21	9.4 ± 0.13
Mu50			
Pre-treatment titre	—	3.6 ± 0.20	7.2 ± 0.13
Vancomycin	8	2.6 ± 0.99	6.1 ± 0.73
Telavancin	0.5	1.0 ± 0.0 [†]	3.2 ± 0.33 [†]
Untreated	—	5.5 ± 0.69	8.4 ± 0.38
Mu3			
Pre-treatment titre	—	4.4 ± 0.28	7.3 ± 0.20
Vancomycin	2	4.5 ± 0.79	7.5 ± 0.33
Telavancin	0.25	1.0 ± 0.0 ^{††}	3.1 ± 0.14 ^{††}
Untreated	—	5.9 ± 0.54	8.9 ± 0.19

CFU, colony-forming units; MIC, minimum inhibitory concentration

*Titre at the onset of treatment (pre-treatment titre); at 48 h after treatment initiation (for telavancin- or vancomycin-treated animals), or at 12 h after the initiation of treatment (for untreated animals; no untreated animals survived beyond this time point)

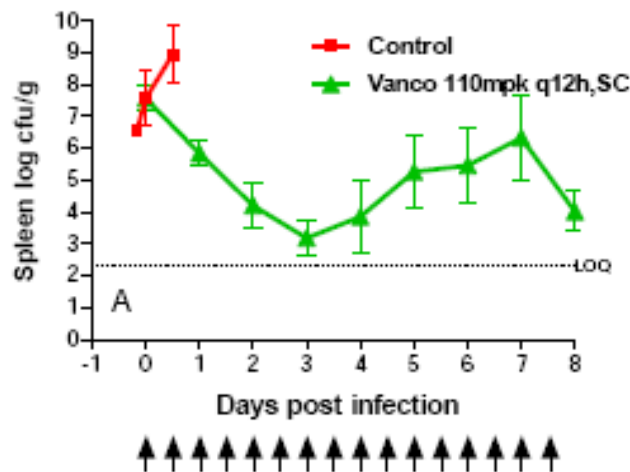
[†]P<0.05 vs. pre-treatment titre and vancomycin

^{††}P<0.05 vs. pre-treatment titre

Source: this Submission; Reports 08-6424-PH-01, Table 1

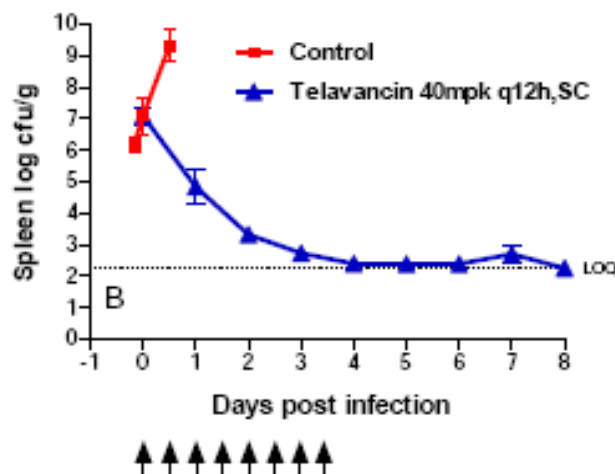
In a second study using the neutropenic mouse bacteremia model, investigators compared the efficacy of sub-chronic treatment with telavancin and vancomycin (Report 08-6424-PH-02). Female NSA mice were rendered neutropenic and inoculated intraperitoneally with *S. aureus* Mu3 (hVISA). Mice were treated (4 hours post-inoculation) with either telavancin (40 mg/kg, q 12 hr, SC for 4 days) or vancomycin (110 mg/kg, q 12 hr, SC for 8 day). A third group received no treatment. Animals (groups of 5) were euthanized at pre-treatment and at 24 hour intervals for 8 days. Figures 21 and 22 summarize spleen titer results for the two treatment protocols. Telavancin reduced titers by Day 3, with sustained reduction for the test period. Vancomycin initially reduced titers, but an upsurge was noted between Days 3 and 7. Vancomycin-treated mice remained bacteremic throughout the test period, while no telavancin-treated animals were bacteremic after Day 1.

Figure 21: Efficacy of 8-day Treatment with Vancomycin on Spleen titres in the Neutropenic Murine Bacteremia Model of *S. aureus* Mu3 (hVISA) infection



Source: This submission, Section 5.3.5.4.1.9.2.2, Figure 2

Figure 22: Efficacy of 8-day Treatment with Telavancin on Spleen titres in the Neutropenic Murine Bacteremia Model of *S. aureus* Mu3 (hVISA) infection



Source: This submission, Section 5.3.5.4.1.9.2.2, Figure 2

Animal Disease Models ~ Conclusions:

The applicant has submitted data from animal in vivo studies that supports the use of $AUC_{(0-24)}/MIC$ as the best PK/PD predictor of antimicrobial efficacy for unbound (free) telavancin. Data from neutropenic mouse thigh models suggest that a $AUC_{(0-24)}/MIC$ ratio of 219 results in a one log₁₀ reduction in CFU/g against methicillin-resistant *S. aureus* with an MIC of 1 mcg/ml. Animal models of infection suggest that immune status may play a minor role in telavancin efficacy.

PHARMACOKINETIC / PHARMACODYNAMIC STUDIES

The pharmacokinetics of telavancin was investigated in eleven clinical pharmacology studies (data and summaries submitted in NDA 22-110). Telavancin pharmacokinetics was approximately linear up to a dose of 12.5 mg/kg in healthy volunteers. Peak and trough concentrations, following a single 10 mg/kg dose, were 105 ± 12 mcg/ml and 8.02 ± 1.84 mcg/ml, respectively. Following repeated doses (10 mg/kg every 25 hours for 3 days) the mean plasma

C_{max} was 116 ± 30 mcg/ml (trough concentrations were 8.11 ± 2.28 mcg/ml). The primary elimination route for telavancin is by renal clearance.

Studies included the antibacterial activity of primary metabolites. Additional studies, describing the activity of the three primary human metabolites of telavancin were submitted in this application and are reviewed above.

In NDA 22-110, the Applicant provided data from a variety of studies to support the proposed pharmacokinetic parameters. Monte Carlo simulation, based on the proposed dosage (10 mg/kg) support a susceptible breakpoint as high as 2 µg/ml (based on > 99% target attainment at that concentration).

Since submission of NDA 22-100, the Applicant conducted a Phase 1 study to determine the steady-state concentrations of telavancin in alveolar macrophages, epithelial lining fluid (ELF), and plasma. The study enrolled 20 healthy volunteers, each of who received 3 daily 10mg/kg doses. Specimens were collected by bronchoscopy on Day 3 at 4, 8, 12 or 24 hours post-infusion (five subjects sampled at each collection time). The mean concentrations in ELF were 3.73 mcg/ml at 8 hours, 1.77 mcg/ml at 12 hours, and 0.89 mcg/ml at 24 hours. The concentration in alveolar macrophages exceeded 10 mcg/ml at all time points.

In another investigation of telavancin PK in human epithelial lining fluid [Lodise 2008], population modeling and Monte Carlo simulation were employed to estimate the penetration of telavancin into the ELF. Plasma and ELF PK data were obtained from 20 healthy volunteers. Concentration-time profiles were modeled using a three-compartment model. Monte Carlo simulation of 9,999 subjects was used to estimate the AUC_{ELF} and free drug in plasma AUC_{plasma} and to calculate an ELF/plasma penetration ratio. The investigators determined that in uninfected lung tissue, the median AUC_{ELF} is approximately 75% of the free AUC_{plasma} . While these data suggest that telavancin penetrates into ELF in non-infected lung tissue, it is unclear whether these levels are comparable in diseased tissue, or whether the observed concentration is sufficient for inhibition of the target pathogens.

Pharmacokinetic / Pharmacodynamic Studies ~ Conclusions:

In NDA 22-110, the Applicant provided data from a variety of studies to support the proposed pharmacokinetic parameters. Monte Carlo simulation, based on the proposed dosage (10 mg/kg) supports a susceptible breakpoint as high as 2 µg/ml (based on > 99% target attainment at that concentration). Additional information, provided in this Application, suggests that telavancin is concentrated in human alveolar macrophages (exceeding 10 mcg/ml) and that the AUC of the antimicrobial in epithelial lining fluid (in uninfected lung tissue) is approximately 75% that of AUC_{plasma} .

CLINICAL TRIALS

Previous Complicated Skin and Skin Structure Infection Studies

NDA 22-110 included data from pivotal clinical trials (Studies 202a, 202b, 0017, and 0018). Each of the studies was a double-blind, randomized, active-controlled comparison of telavancin with standard therapy. Exclusions included infections with vancomycin-resistant enterococcal species (VRE). Phase 2 comparators included an anti-staphylococcal penicillin or vancomycin. Vancomycin was the sole comparator in Phase 3 trials. Initial dosing in the clinical trials was set at 7.5 mg/kg IV. Based on pharmacokinetic/pharmacodynamic data and Monte Carlo simulation, the dosage was increased to 10 mg/kg IV. The 202b (Post Amendment) study, and the two Phase 3 trials studied telavancin at the 10 mg/kg dose. The clinical microbiology review of that application was based on the Post Amendment Study 202b and the two ATLAS studies (0017 and 0018). Data from post-amendment clinical trials indicated that telavancin is efficacious in

infections involving pathogens in the proposed indication [complicated skin and skin structure infections caused by *S. aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group, and vancomycin-susceptible *Enterococcus faecalis*]. Isolates analyzed from the ME population were primarily Gram positive pathogens, and were recovered mainly from major abscesses, deep/extensive cellulitis, and wound infections. Similar eradication rates, for organisms in the proposed indication, were seen in the telavancin-treated population and the vancomycin-treated population. Telavancin was active against certain specific resistant phenotypes (e.g. methicillin-resistant *S. aureus*), but study design prohibited the observation of activity against vancomycin-resistant phenotypes (e.g. vancomycin-resistant *S. aureus*, vancomycin-resistant enterococcus species). Incidence of superinfection and colonization, developed in the course of those clinical trials, was low.

Hospital Associated Pneumonia Studies

In the current submission, the Applicant has submitted data from two Phase 3 studies that were designed to compare the safety and efficacy of telavancin and vancomycin in the treatment of hospital associated pneumonia (HAP) due to a confirmed Gram positive pathogen. The study was enriched for methicillin-resistant *S. aureus*-associated HAP by enrollment of subjects with known risk factors (including nursing home admissions, hospitalization within the previous 6 months, prior MRSA infection, antibiotic treatment within the previous 3 months, and geographic prevalence).

The two Phase 3 trials, Study 0015 and Study 0019, were given the acronym ATTAIN. The studies were double-blind, randomized, active controlled, noninferiority trials, comparing telavancin 10 mg/kg IV q 24 hours with standard therapy (vancomycin 1 g IV q 12 hours) (Table 21). Subjects were treated for a minimum of 7 days and a maximum of 21 days. The initial noninferiority margin was 20% for the primary endpoint of clinical responses at Test of Cure (TOC). Post hoc analysis included determination of a mortality endpoint and a post hoc clinical noninferiority margin of 14%. The two studies were analyzed separately and as pooled data. Other efficacy parameters included by-patient microbiological response at the Follow-up Visit (TOC), by pathogen microbiological response at TOC, and clinical response at the End-of-Therapy (EOT) visit. The criteria for efficacy evaluations are summarized in Table 23. The criteria for evaluating microbiologic response are summarized in Table 24. Inclusion criteria included "identification of an organism consistent with a respiratory pathogen isolated from cultures of respiratory tract, sputum, or blood samples."

Aztreonam and/or metronidazole could be added for treatment of Gram-negative aerobes and facultative pathogens, and for anaerobic bacteria. Nafcillin could be substituted for vancomycin in cases where *S. aureus* was identified as the principle pathogen and was found susceptible to oxacillin. Subjects were considered to have received adequate therapy if antibiotics with in vitro activity against all Gram-negative isolates recovered at the baseline visit, was administered from Study Day 1 through end of therapy. Subjects with no baseline pathogens were considered to have received inadequate Gram-negative therapy if they 1) never received at least one antibiotic with in vitro Gram-negative activity, or 2) did not receive at least one antibiotic with in vitro Gram-negative activity until Study Day 3 or later.

The study population analysis definitions are summarized in Table 22. The All Treated (AT) population included 1503 subjects (749 randomized to telavancin, 754 randomized to vancomycin). The Modified All-Treated (MAT) population included 1089 subjects (560 randomized to telavancin, 529 randomized to vancomycin). The Clinically Evaluable (CE) population included 44% of the subjects in the AT population (654 subjects, with 312 randomized to telavancin, 342 randomized to vancomycin). The Microbiologically Evaluable (ME) population included 480 subjects (243 randomized to telavancin, 237 randomized to vancomycin). Demographics were well balanced in compared analysis populations. The majority of subjects were 65 years of age or older, and the majority (58%) were in the ICU at Baseline.

Comorbidities, including congestive heart failure, diabetes, and hypertension, were common in all analysis populations.

Table 21: Completed Efficacy and Safety Studies of Telavancin in Hospital-acquired Pneumonia

Type	ID	Title	Objective	Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Treated Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Tx	Study Status
Efficacy	0015	A Phase 3, Randomized, Double Blind, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Hospital-acquired Pneumonia with a Focus on Patients with Infections Due to Methicillin-Resistant <i>Staphylococcus aureus</i>	Efficacy and Safety	Double blind, randomized active-controlled	Telavancin for injection, 10 mg/kg IV q 24h	372	Gram-positive pneumonia acquired while residing in a health care facility	7 to 21 days	Complete
					Vancomycin 1 g IV q 12hr	374			
Efficacy	0019	A Phase 3, Randomized, Double Blind, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Hospital-acquired Pneumonia with a Focus on Patients with Infections Due to Methicillin-Resistant <i>Staphylococcus aureus</i>	Efficacy and Safety	Double blind, randomized active-controlled	Telavancin for injection, 10 mg/kg IV q 24h	377	Gram-positive pneumonia acquired while residing in a health care facility	7 to 21 days	Complete
					Vancomycin 1 g IV q 12hr	380			

Source: This submission, Section 5.3.5.4.1.10.3, Table 8

Table 22: Definition of Analysis Populations in Studies 0015 and 0019

Analysis Population	– Definition
All-treated (AT)	– All patients who receive any amount of study medication.
Modified All-treated (MAT)	– All patients in the AT Population who also have a baseline pathogen identified, defined as an organism known to cause pneumonia identified from baseline respiratory cultures from sputum, endotracheal aspirate (ETA), blind bronchial suctioning (BBS), bronchoalveolar lavage (BAL), mini-BAL, or protected specimen brush (PSB). If baseline respiratory cultures did not identify a respiratory pathogen (or if baseline respiratory cultures were not available), then an organism known to cause pneumonia that was identified from baseline blood cultures would qualify a patient for the MAT Population..
Clinically Evaluable (CE)	All patients in the AT Population (1) whose adherence to protocol expectations makes it reasonable to infer that his/her clinical outcome reflects the effect of study medication, or (2) who died on or after Study Day 3, where the death is attributable to the HAP episode under study. To be deemed to have adhered to protocol expectations, and on that basis be included in the CE Population, a patient must meet the following criteria: - o Patient complied with the following <u>inclusion criteria</u>: • #2, which requires certain clinical signs and symptoms consistent with pneumonia • #3, which requires a chest radiograph consistent with the diagnosis of pneumonia • #4, which requires the availability of appropriate specimens for Gram stain and culture, and venous access for dosing. - o Patient did not violate the following <u>exclusion criteria</u> (or was approved for enrollment by the Medical Monitor): • #1, which excludes patients who have received more than a specified amount of potentially effective systemic antibiotic therapy for Gram-positive pneumonia immediately prior to randomization. • #2, which excludes patients with respiratory tract specimens or sputum with only Gram-negative bacteria. • #3, which excludes patients with MSSA or <i>S. pneumoniae</i> who also require more than a specified amount of concomitant antibiotic therapy for Gram-negative coverage that has activity versus MSSA or <i>S. pneumoniae</i>. • #4, which excludes patients with known or suspected pulmonary disease that precludes evaluation of therapeutic response, cystic fibrosis, or active tuberculosis. • #5, which excludes patients with known or suspected <i>Legionella pneumophila</i> pneumonia. • #6, which excludes patients who are known or suspected to be infected with an organism that is not susceptible to medications permitted by the protocol. • #7, which excludes patients with documented or suspected meningitis, endocarditis, or osteomyelitis. - o Patient did not have pneumonia due to <i>Stenotrophomonas maltophilia</i> or <i>Burkholderia cepacia</i> at Baseline. - o Patient did not have a persistent <i>S. aureus</i> bacteremia. - o If the patient received prior (i.e., pre-study) treatment with vancomycin or teicoplanin, the patient was not a treatment failure to that treatment. - o The patient was treated with the study medication assigned by the randomization.
Analysis Population	– Definition
	- o The patient received at least 80% of intended doses of active study medication. - o The patient did not receive potentially effective concomitant systemic antibiotic therapy for more than 2 calendar days. - o Patient was a "failure" at EOT, or else was either a "cure" or a "failure" at TOC. - o If the patient was a "failure" at EOT, then the EOT assessment was made between Study Day 0P and Study Day 5P inclusive. Otherwise, the TOC assessment was made between Study Day 6P and Study Day 28P inclusive. - o If the patient was a "cure," the patient received study medication daily through Study Day 5. - o If the patient was a "failure," the patient received study medication daily through Study Day 3."
Microbiologically evaluable	All patients in the CE Population who also had a baseline Gram-positive pathogen recovered from respiratory specimens or blood cultures. Note that the ME Population is a subset of both the MAT and CE Populations.

Source: This submission, Section 5.3.5.4.1.10.3, Table 9

Table 23: Criteria for Efficacy Evaluation in Studies 0015 and 0019

Response ¹	Criteria
Clinical Response at End-of-Therapy	
Failure:	At least one of the following: • Persistence or progression of signs and symptoms of pneumonia that still require antibiotic therapy • Termination of study medication due to "lack of efficacy" and initiation within 2 calendar days of therapy with a potentially effective anti-staphylococcal medication • Death on or after Day 3 attributable to primary infection
Cure:	• Investigator determined that signs and symptoms of pneumonia improved to the point that no further antibiotics for pneumonia are required, and • Baseline radiographic findings improved or did not progress
Indeterminate:	• Inability to determine outcome
Clinical Response at Test-of-cure evaluation (unless a failure at End of Therapy)	
Failure:	At least one of the following: • Relapsed pneumonia with the same Gram-positive organism after termination of study medication • Death after the end of study medication therapy attributable to primary infection (i.e., pneumonia)
Cure:	• Signs and symptoms of pneumonia resolved, and • Baseline radiographic findings improved or did not progress
Indeterminate:	• Inability to determine outcome

¹ Protocol outcome designation

Source: This submission, Section 5.3.5.4.1.10.3, Table 10

Table 24: Microbiological Response By-Patient and By-Pathogen in Studies 0015 and 0019

Response ¹	Criteria
Microbiological Response By-Patient	
Patients with one or more pathogens isolated at Baseline were assigned a By-Patient Microbiological Response at the Follow-up visit.	
The following preliminary categorizations were made for each culture within the specified evaluation's analysis window:	
Eradicated	All baseline respiratory pathogens were eradicated (confirmed or presumed), no superinfection, and no new infection; colonization may be present and a Clinical Response of "Success".
Persisted ²	At least one baseline respiratory pathogen was present (confirmed or presumed), and a Clinical Response of "Failure".
Indeterminate:	No culture data were available, and Clinical Response of "Indeterminate".
Missing	No culture data were available, and Clinical Response was "Missing".
Microbiological Response By-Pathogen	
By-Pathogen Microbiological Response was to be determined at the Follow-up visit only for Gram-positive pathogens isolated at the baseline evaluation from an appropriate source.	
Preliminary categorization of each culture within the specified evaluation's analysis window was to be done as follows:	
Confirmed Eradicated	The absence of the given baseline pathogen from the culture, or "No Growth" was recorded on the CRF. (Blood cultures were either negative or not available)
Presumed Eradicated ⁴	No respiratory tract culture data were available, and a Clinical Response of "Cure".
Confirmed Persisted ³	At least one baseline pathogen was documented as present from either the respiratory tract cultures or blood cultures.
Presumed Persisted ³	No respiratory tract culture data were available, and a Clinical Response of "Failure".
Indeterminate:	No respiratory tract culture data were available, and a Clinical Response of "Indeterminate".
Missing	No respiratory tract culture data were available, and Clinical Response was "Missing".
Potential Superinfection	Respiratory pathogen was isolated from respiratory tract cultures during the course of treatment. ³

¹ Microbiological response correlated to clinical response: Eradicated = Cure; Persisted = Failed

² For analysis, Eradicated or Presumed Eradicated was considered "Eradicated".

³ For analysis, Persisted or Presumed Persisted was considered "Persisted". Baseline pathogens were also categorized by susceptibility to study medication (i.e., development of resistance).

⁴ "Colonization" was not distinguished from "Infection" for pathogens identified post-baseline in these studies.

Source: This submission, Section 5.3.5.4.1.10.3, Table 11

Microbiological evaluation included pre-treatment baseline collection of respiratory specimens (BAL, mini-BAL, protected specimen brush (PSB), blind bronchial suction (BBS), or endotracheal aspirate (ETA) for culture and Gram stain, blood culture (x2), and urinary antigen testing for *Legionella pneumophila*. Respiratory specimens were graded for adequacy based on the presence of > 25 polymorphonuclear leukocytes and < 10 epithelial cells per high power field (100 x magnification). Collection of respiratory specimens was repeated on Day 4, if clinically indicated. Blood cultures were repeated if the initial cultures were positive or if clinically indicated. Initial processing and culture of specimens, as well as Gram stain interpretation, was performed by the local laboratory. The studies focused on "respiratory pathogens", including all species sought in the proposed indication, including isolates collected by respiratory and blood culture, and bacteria identified by urinary antigen testing. Any isolate recovered from blood culture was considered a "pathogen." If blood culture isolates differed from respiratory isolates, the respiratory isolate was considered the baseline pathogen. If no respiratory pathogens were isolated at baseline, but blood cultures were positive, the blood culture isolate was considered the baseline pathogen. Multiple baseline pathogens were allowed for analysis purposes. If more than one resistance phenotype of a particular species was identified at baseline, all were tracked separately for eradication analysis.

Isolates recovered in culture were sub-cultured and sent to

(b) (4)

(b) (4) for identification to species level and susceptibility testing (by both MIC and disk diffusion methods). Isolates collected in South Africa, Europe and Russia were tested in the (b) (4) laboratory in (b) (4). Isolates collected in all other countries were tested in the (b) (4) laboratory in (b) (4). Staphylococcus aureus isolates (methicillin-susceptible and -resistant) were shipped to (b) (4) for Pantone-Valentine Leukocidin (PVL) screening.

Isolates were identified at (b) (4) primarily by automated methods, employing the Vitek System (bioMerieux, Durham, NC). Susceptibility testing was performed by both the MIC and disk diffusion methods.

Three different MIC panel formats were utilized, using methods approved by CLSI for broth microdilution testing. All isolates were subcultured to trypticase-soy agar + 5% sheep blood, 18-24 hours before testing. Isolates were suspended in cation adjusted Mueller-Hinton broth (without polysorbate 80), and adjusted to a concentration of approximately 5×10^4 CFU/ml. Panels were incubated at 35°C in ambient atmospheric conditions, and read at 16-20 hours (streptococcal susceptibility panels were incubated for 20-24 hours).

For disk diffusion susceptibility determinations, the Kirby-Bauer method was employed, according to methods approved by CLSI. Mueller-Hinton agar plates were swabbed with approximately 10^8 CFU/ml of the isolate (5% sheep blood was added to the Mueller-Hinton agar, for testing of streptococcal isolates). Plates were incubated in ambient atmospheric conditions at 35°C for 16-18 hours (streptococcal isolates were incubated in 5-7% CO₂ for 20-24 hours).

All bacterial isolates were cryo-preserved by the central testing laboratory.

STUDY 0015

Study 0015 enrolled the first subject on 8 February 2005 and the last visit was completed on 11 July 2007. There were 761 subjects randomized at 201 centers (381 in the telavancin arm and 380 in the vancomycin arm), and 746 subjects treated. The original protocol for Study 0015 allowed imipenem for Gram-negative coverage, as well as aztreonam and/or metronidazole. In order to limit potential bias, possibly resulting from the synergistic activity of linezolid with the glycopeptides, use of linezolid was removed in Protocol Amendment 1.

Acute renal failure was more prevalent in subjects randomized to the telavancin group (9% vs. 5% in the vancomycin group). Approximately 27% of subjects enrolled in Study 0015 met the definition of having ventilator-associated pneumonia. Demographics were generally balanced between the two arms of the study.

Table 25 summarizes the number of Study 0015 subjects analyzed by treatment group.

Table 25: Summary of patients included in each Study 0015 analysis population by treatment group

	Telavancin 10 mg/kg Number (%) of Patients [1]	Vancomycin
Randomized	381	380
Safety (As-treated)	372	374
Efficacy Populations (As-randomized)		
All-treated (AT)	372 (100%)	374 (100%)
Modified All-treated (MAT)	257 (69%)	247 (66%)
Clinically Evaluable (CE)	141 (38%)	172 (46%)
Microbiologically Evaluable (ME)	108 (29%)	113 (30%)
ME as Percent of CE	77%	66%

[1] Percentages are calculated relative to the number of patients treated (AT)
 AT – all patients who received at least one dose of study medication.
 MAT – those AT patients who had a respiratory pathogen isolated at Baseline.
 CE – those AT patients whose adherence to the protocol made it reasonable to infer that their clinical response reflected the effect of the study medication.
 ME – those CE patients who had at least one Gram-positive pathogen that was associated with pneumonia

Source: This submission; Module 2.7.6.3, page 10

STUDY 0019

Study 0019 enrolled the first subject on 23 January 2005 and the last visit was completed on 2 May 2007. There were 771 subjects randomized at 250 centers (386 in the telavancin arm and 385 in the vancomycin arm), and 757 subjects treated. As in Study 0015, the original protocol for Study 0019 allowed imipenem for Gram-negative coverage, as well as aztreonam and/or metronidazole. In order to limit potential bias, possibly resulting from the synergistic activity of linezolid with the glycopeptides, use of linezolid was removed in Protocol Amendment 1.

Approximately 30% of the subjects enrolled in Study 0019 met the definition for ventilator-associated pneumonia.

Table 26 summarizes the number of Study 0019 subjects analyzed by treatment group.

Table 26: Summary of patients included in each Study 0019 analysis population by treatment group

	Telavancin 10 mg/kg Number (%) of Patients [1]	Vancomycin
Randomized	386	385
Safety (As-treated)	379	378
Efficacy Populations (As-randomized)		
All Treated (AT)	377 (100%)	380 (100%)
Modified All-treated (MAT)	303 (80%)	282 (74%)
Clinically Evaluable (CE)	171 (45%)	170 (45%)
Microbiologically Evaluable (ME)	135 (36%)	124 (33%)
ME as Percent of CE	79%	73%

[1] Percentages are calculated relative to the number of patients treated (AT)
 AT – all patients who received at least one dose of study medication.
 MAT – those AT patients who had a respiratory pathogen isolated at Baseline.
 CE – those AT patients whose adherence to the protocol made it reasonable to infer that their clinical response reflected the effect of the study medication.
 ME – those CE patients who had at least one Gram-positive pathogen that was associated with pneumonia

Source: This submission; Module 2.7.6.3, page 28

SUMMARY OF CLINICAL STUDIES

Table 27 summarizes the numbers of subjects included in each analysis population for Studies 0015 and 0019 (and combined). The most common reason for exclusion from the

Microbiologically Evaluable (ME) population was "no Gram-positive pathogen at baseline" (noted in 45% of exclusions in the telavancin arms, and in 48% of exclusions in the vancomycin arms).

Table 27: Data Sets Analyzed – Studies 0015 and 0019, Individually and Combined – AT Population

	0015		Number of Patients 0019		Total	
	Telavancin 10 mg/kg (N=372)	Vancomycin (N=374)	Telavancin 10 mg/kg (N=377)	Vancomycin (N=380)	Telavancin 10 mg/kg (N=749)	Vancomycin (N=754)
All-treated (AT)	372 (100%)	374 (100%)	377 (100%)	380 (100%)	749 (100%)	754 (100%)
Modified All-treated (MAT)	257 (69%)	247 (66%)	303 (80%)	282 (74%)	560 (75%)	529 (70%)
Respiratory Pathogens	249 (97%)	245 (99%)	297 (98%)	279 (99%)	546 (98%)	524 (99%)
Blood Pathogens Only	8 (3%)	2 (<1%)	6 (2%)	3 (1%)	14 (3%)	5 (<1%)
Clinically Evaluable (CE)	141 (38%)	172 (46%)	171 (45%)	170 (45%)	312 (42%)	342 (45%)
Microbiologically Evaluable (ME)	108 (29%)	113 (30%)	135 (36%)	124 (33%)	243 (32%)	237 (31%)
Respiratory Pathogens	105 (97%)	113 (100%)	134 (99%)	123 (99%)	239 (98%)	236 (100%)
Blood Pathogens Only	3 (3%)	0	1 (<1%)	1 (<1%)	4 (2%)	1 (<1%)
ME as % of CE Population	77%	66%	79%	73%	78%	69%

Note: MAT, CE, and ME percentages are calculated relative to the number in the AT population.

Output file: ISE_t_analpop_at_01.rtf

Source: Dataset(s): ADSL Program: \SCE\LOCAL\SANDBOX_2393719\Biostat\td-6424\hap\ISE\src\programs\t_analpop.sas Run Date: 29JUL08/10:46 by wabanadmin on NET_ASrv SASv9.1

Source: This submission, Section 5.3.5.4.1.10.3, Table 12

Table 28 summarizes the type and location of respiratory specimens sampled for bacterial culture, from the All Treated (AT) population. The specimen types were generally well balanced between the vancomycin and telavancin arms in both clinical trials, with sputum, endotracheal aspirate, and BAL representing 90% of the collected respiratory specimens. Endotracheal aspiration produced the highest number of positive cultures. Invasive methods were culture positive 77% of the time in the telavancin arm, and 80% of the time in the vancomycin arm.

Table 28: Type and Location of Respiratory Tract Specimen Collection – Studies 0015 and 0019 Individually and Combined – AT Population

	Number of Patients[4]					
	0015		0019		Total	
	Telavancin 10 mg/kg (N=372)	Vancomycin (N=374)	Telavancin 10 mg/kg (N=377)	Vancomycin (N=380)	Telavancin 10 mg/kg (N=749)	Vancomycin (N=754)
Sputum	169 (45%)	174 (47%)	151 (40%)	164 (43%)	320 (43%)	338 (45%)
Culture Positive [1]	104 (62%)	105 (60%)	104 (69%)	111 (68%)	208 (65%)	216 (64%)
Culture Negative	65 (38%)	69 (40%)	47 (31%)	53 (32%)	112 (35%)	122 (36%)
Endotracheal Aspirate	132 (35%)	134 (36%)	171 (45%)	180 (47%)	303 (40%)	314 (42%)
Culture Positive [1]	100 (76%)	97 (72%)	147 (86%)	140 (78%)	247 (82%)	237 (75%)
Culture Negative	32 (24%)	37 (28%)	24 (14%)	40 (22%)	56 (18%)	77 (25%)
Bronchoalveolar Lavage	20 (5%)	22 (6%)	34 (9%)	27 (7%)	54 (7%)	49 (6%)
Culture Positive [1]	15 (75%)	17 (77%)	27 (79%)	22 (81%)	42 (78%)	39 (80%)
< 10 ⁴ CFU/mL	1 (7%)	4 (24%)	3 (11%)	2 (9%)	4 (10%)	6 (15%)
≥ 10 ⁴ CFU/mL	6 (40%)	8 (47%)	16 (59%)	10 (45%)	22 (52%)	18 (46%)
Quantitation not done	8 (53%)	5 (29%)	8 (30%)	10 (45%)	16 (38%)	15 (38%)
Culture Negative	5 (25%)	5 (23%)	7 (21%)	5 (19%)	12 (22%)	10 (20%)
Mini-bronchoalveolar Lavage	27 (7%)	21 (6%)	19 (5%)	10 (3%)	46 (6%)	31 (4%)
Culture Positive [1]	18 (67%)	14 (67%)	17 (89%)	9 (90%)	35 (76%)	23 (74%)
< 10 ⁴ CFU/mL	6 (33%)	2 (14%)	3 (18%)	1 (11%)	9 (26%)	3 (13%)
≥ 10 ⁴ CFU/mL	7 (39%)	7 (50%)	11 (65%)	5 (56%)	18 (51%)	12 (52%)
Quantitation not done	5 (28%)	5 (36%)	3 (18%)	3 (33%)	8 (23%)	8 (35%)
Culture Negative	9 (33%)	7 (33%)	2 (11%)	1 (10%)	11 (24%)	8 (26%)
Protected Specimen Brush	2 (<1%)	2 (<1%)	0	1 (<1%)	2 (<1%)	3 (<1%)
Culture Positive [1]	1 (50%)	2 (100%)	0	1 (100%)	1 (50%)	3 (100%)
≥ 10 ³ CFU/mL	1 (100%)	1 (50%)	0	1 (100%)	1 (100%)	2 (67%)
Quantitation not done	0	1 (50%)	0	0	0	1 (33%)
Culture Negative	1 (50%)	0	0	0	1 (50%)	0
Blinded Bronchial Suction	12 (3%)	9 (2%)	6 (2%)	2 (<1%)	18 (2%)	11 (1%)
Culture Positive [1]	10 (83%)	7 (78%)	4 (67%)	2 (100%)	14 (78%)	9 (82%)
Culture Negative	2 (17%)	2 (22%)	2 (33%)	0	4 (22%)	2 (18%)
Other [2]	7 (2%)	9 (2%)	2 (<1%)	2 (<1%)	9 (1%)	11 (1%)
Culture Positive [1]	6 (86%)	9 (100%)	1 (50%)	1 (50%)	7 (78%)	10 (91%)
Culture Negative	1 (14%)	0	1 (50%)	1 (50%)	2 (22%)	1 (9%)
All Invasive Methodologies [3]	68 (18%)	62 (17%)	61 (16%)	42 (11%)	129 (17%)	104 (14%)
Culture Positive [1]	50 (74%)	48 (77%)	49 (80%)	35 (83%)	99 (77%)	83 (80%)
Culture Negative	18 (26%)	14 (23%)	12 (20%)	7 (17%)	30 (23%)	21 (20%)

[1] A positive culture is defined as identification of at least one respiratory tract pathogen.

[2] Other methods: Nares, Protected Endotracheal Specimen, and Quantitative Tracheal Lavage.

[3] Bronchoalveolar lavage, mini-bronchoalveolar lavage, protected specimen brush, or blinded bronchial washing and other.

[4] If more than one specimen type was taken at baseline, then the patient will be counted under each specimen type taken. If a patient has more than one specimen of the same type, then the patient is counted only once and the culture is deemed positive if any specimen is positive. For quantitative cultures, if multiple pathogens are identified, the patient will be counted only once for each specimen type taken under the highest quantification parameter.

Source: This submission, Section 5.3.5.4.1.10.3, Table 16

Table 29 summarizes the species of bacterial pathogens collected from telavancin-treated subjects in the two clinical trials. The numbers and percentages of bacterial species, particularly with regard to the principle pathogens (respiratory pathogens sought in the proposed indications) were similar in the vancomycin arm (e.g. there were 130 *S. aureus* isolates collected from sputum in the telavancin arm, compared to 134 *S. aureus* isolates collected from sputum in the vancomycin arm). *Staphylococcus aureus* was the most common pathogen isolated from any source, with methicillin-resistant phenotypes dominant. Most subjects had only one or two respiratory pathogens. Gram negative respiratory pathogens were isolated from < 25% of specimens (with *Pseudomonas aeruginosa*, *Acinetobacter calcoaceticus*, *A. baumannii*, and *Klebsiella pneumonia* isolated most frequently).

Table 29: Respiratory Pathogens Isolated at Baseline by Method of Specimen Collection from Telavancin Patients MAT Population

	Number of Patients [1]					
	Sputum (N=208)	Endo- tracheal Aspiration (N=247)	Broncho- alveolar Lavage (N=42)	Mini- broncho- alveolar Lavage (N=35)	Blind Bronchial Suctioning (N=14)	Other [2] (N=8)
Gram-positive Pathogens						
STAPHYLOCOCCUS AUREUS	130 (63%)	174 (70%)	29 (69%)	27 (77%)	8 (57%)	5 (63%)
- MRSA	82 (39%)	113 (46%)	15 (36%)	10 (29%)	7 (50%)	4 (50%)
- MSSA	52 (25%)	61 (25%)	14 (33%)	17 (49%)	1 (7%)	1 (13%)
STREPTOCOCCUS PNEUMONIAE	12 (6%)	9 (4%)	5 (12%)	3 (9%)	2 (14%)	0
ENTEROCOCCUS FAECALIS	6 (3%)	5 (2%)	1 (2%)	0	0	1 (13%)
ENTEROCOCCUS FAECIUM	2 (<1%)	1 (<1%)	1 (2%)	0	0	0
Gram-negative Pathogens						
PSEUDOMONAS AERUGINOSA	37 (17.8%)	60 (24.3%)	10 (23.8%)	2 (5.7%)	1 (7.1%)	0
ACINETOBACTER CALCOACETICUS	16 (7.7%)	32 (13.0%)	2 (4.8%)	2 (5.7%)	1 (7.1%)	0
KLEBSIELLA PNEUMONIAE	14 (6.7%)	20 (8.1%)	5 (11.9%)	1 (2.9%)	1 (7.1%)	0
ESCHERICHIA COLI	13 (6.3%)	14 (5.7%)	6 (14.3%)	2 (5.7%)	1 (7.1%)	2 (25.0%)
STENOTROPHOMONAS MALTOPHILIA	12 (5.8%)	12 (4.9%)	2 (4.8%)	2 (5.7%)	0	0
HAEMOPHILUS INFLUENZAE	11 (5.3%)	10 (4.0%)	2 (4.8%)	2 (5.7%)	0	0
ENTEROBACTER CLOACAE	8 (3.8%)	7 (2.8%)	2 (4.8%)	1 (2.9%)	0	0
PROTEUS MIRABILIS	3 (1.4%)	7 (2.8%)	0	1 (2.9%)	0	0
ACINETOBACTER BAUMANNII	1 (0.5%)	6 (2.4%)	0	0	0	0
SERRATIA MARCESCENS	4 (1.9%)	6 (2.4%)	0	2 (5.7%)	0	0
CITROBACTER KOSERI	0	2 (0.8%)	0	0	0	0
ENTEROBACTER AEROGENES	3 (1.4%)	2 (0.8%)	0	0	0	1 (12.5%)
ENTEROBACTER SPP	0	2 (0.8%)	0	1 (2.9%)	0	0
KLEBSIELLA OXYTOCA	3 (1.4%)	2 (0.8%)	0	0	0	0
PROTEUS VULGARIS	0	2 (0.8%)	0	0	0	0
ACHROMOBACTER XYLOSOXIDANS	1 (0.5%)	1 (0.4%)	0	0	0	0
ACINETOBACTER LWOFFII	0	1 (0.4%)	0	0	0	0
BURKHOLDERIA CEPACIA	0	1 (0.4%)	0	0	0	0
CHRYSEOBACTERIUM MENINGOSEPTICUM	0	1 (0.4%)	0	0	0	0
CITROBACTER FREUNDII COMPLEX	1 (0.5%)	1 (0.4%)	1 (2.4%)	0	1 (7.1%)	0
SERRATIA LIQUEFACIENS	0	1 (0.4%)	0	0	0	0
EMPEDOBACTER BREVIS	1 (0.5%)	0	0	0	0	0
ENTEROBACTER HORMAECHAEI	0	0	0	0	0	1 (12.5%)
HAEMOPHILUS PARAHAEOMOLYTICUS	1 (0.5%)	0	0	0	0	0
PROVIDENCIA STUARTII	1 (0.5%)	0	0	0	0	0
PSEUDOMONAS PUTIDA	2 (1.0%)	0	0	0	1 (7.1%)	0
Pathogens by Gram Stain						
Single Gram-positive Pathogen Only	96 (46%)	95 (38%)	17 (40%)	21 (60%)	7 (50%)	5 (63%)
Multiple Gram-positive Pathogens Only	6 (3%)	8 (3%)	3 (7%)	2 (6%)	0	0
Single Gram-negative Pathogen Only	50 (24%)	48 (19%)	3 (7%)	6 (17%)	4 (29%)	1 (13%)
Multiple Gram-negative Pathogens Only	12 (6%)	15 (6%)	4 (10%)	0	0	1 (13%)
Mixed Gram-positive and Gram-negative Pathogens	44 (21%)	81 (33%)	15 (36%)	6 (17%)	3 (21%)	1 (13%)
Number of Pathogens						
1 Pathogen	146 (70%)	143 (58%)	20 (48%)	27 (77%)	11 (79%)	6 (75%)
2 Pathogens	44 (21%)	71 (29%)	16 (38%)	4 (11%)	3 (21%)	2 (25%)
3 Pathogens	14 (7%)	21 (9%)	4 (10%)	2 (6%)	0 (0%)	0 (0%)
4 or More Pathogens	4 (2%)	12 (5%)	2 (5%)	2 (6%)	0 (0%)	0 (0%)

[1] Sample size in the column headings represents the number of patients with positive cultures from that source.

[2] Other methods: Bronchial Suction via Fibrobronch, Pleural Effusion, Pleural Fluid, Pleural Tissue, and Tracheostomy Aspire.

Source: This submission, Section 5.3.5.4.1.10.3, Table 17

Table 30 compares the study populations in the telavancin and vancomycin arms of the two studies (and combined) as subpopulations based on categorization of methicillin-resistant *S. aureus*. The number of MRSA isolates was comparable between the two arms, and in the analysis groups.

Table 30: Population Presented as Subpopulations Based on MRSA Categorization

	0015		Number of Patients 0019		Total	
	Telavancin 10 mg/kg	Vancomycin	Telavancin 10 mg/kg	Vancomycin	Telavancin 10 mg/kg	Vancomycin
All Treated	372 (100%)	374 (100%)	377 (100%)	380 (100%)	749 (100%)	754 (100%)
AT(MRSA)	115 (31%)	114 (30%)	118 (31%)	117 (31%)	233 (31%)	231 (31%)
CE(MRSA)	70 (19%)	84 (22%)	69 (18%)	70 (18%)	139 (19%)	154 (20%)
AT(MRSA-C)	257 (69%)	260 (70%)	259 (69%)	263 (69%)	516 (69%)	523 (69%)
AT - CE(MRSA)	302 (81%)	290 (78%)	308 (82%)	310 (82%)	610 (81%)	600 (80%)

Note: AT(MRSA) = AT patients with MRSA at baseline; CE(MRSA) = CE patients with MRSA at baseline.
AT(MRSA-C) = AT patients in whom MRSA was not identified at baseline.
AT - CE(MRSA) = AT patients who are not in the CE(MRSA) subpopulation.
Source: This submission, Section 5.3.5.4.1.10.3, Table 19

Table 31 lists the respiratory pathogens cultured at baseline from subjects in each arm of both studies (MAT population). The principle Gram-positive respiratory pathogens (*Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Enterococcus faecalis*) were well balanced between the two arms in both studies. In 43% of the telavancin-treatment group subjects and 46% of the vancomycin-treatment group subjects, a single Gram-positive pathogen was the only organism cultured at baseline. Study 0019 had a larger percentage of mixed Gram-positive/Gram-negative cultures at baseline, compared to Study 0015. Approximately 25% of baseline respiratory cultures yielded only Gram-negative isolates. The majority of bacterial isolates were cultured only from respiratory specimens (91% for the telavancin arm, 92% for the vancomycin arm). Respiratory pathogens were isolated from blood and respiratory baseline cultures in 6% of telavancin-treated subjects and 7% of vancomycin-treated subjects. Respiratory pathogens were isolated from baseline blood cultures-only in 3% of telavancin-treated subjects and < 1% of vancomycin-treated subjects. Of the respiratory pathogens isolated from blood, the majority were *S. aureus* (32 of 48 in the telavancin-treated subjects, 29 of 44 in the vancomycin-treated subjects).

Table 31: Respiratory Pathogens from Baseline Cultures – MAT Population

	Number of Patients					
	0015		0019		Total	
	Telavancin 10 mg/kg (N=257)	Vancomycin (N=247)	Telavancin 10 mg/kg (N=303)	Vancomycin (N=282)	Telavancin 10 mg/kg (N=560)	Vancomycin (N=529)
Any Respiratory Tract Pathogen	249 (96.9%)	245 (99.2%)	297 (98.0%)	279 (98.9%)	546 (97.5%)	524 (99.1%)
Pathogen Isolated from Respiratory Tract Only	229 (89%)	228 (92%)	283 (93%)	257 (91%)	512 (91%)	485 (92%)
Pathogen Isolated from Both Respiratory Tract and Blood	20 (8%)	17 (7%)	14 (5%)	22 (8%)	34 (6%)	39 (7%)
Gram-positive Pathogens	181 (70%)	178 (72%)	220 (73%)	205 (73%)	401 (72%)	383 (72%)
STAPHYLOCOCCUS AUREUS	168 (65.4%)	170 (68.8%)	199 (65.7%)	178 (63.1%)	367 (65.5%)	348 (65.8%)
- MRSA	111 (43.2%)	113 (45.7%)	117 (38.6%)	117 (41.5%)	228 (40.7%)	230 (43.5%)
- MSSA	61 (23.7%)	57 (23.1%)	83 (27.4%)	63 (22.3%)	144 (25.7%)	120 (22.7%)
STREPTOCOCCUS PNEUMONIAE	15 (5.8%)	7 (2.8%)	14 (4.6%)	23 (8.2%)	29 (5.2%)	30 (5.7%)
ENTEROCOCCUS FAECALIS	3 (1.2%)	6 (2.4%)	10 (3.3%)	13 (4.6%)	13 (2.3%)	19 (3.6%)
ENTEROCOCCUS FAECIUM	1 (0.4%)	0	3 (1.0%)	1 (0.4%)	4 (0.7%)	1 (0.2%)
Gram-negative Pathogens	118 (46%)	111 (45%)	171 (56%)	155 (55%)	289 (52%)	266 (50%)
PSEUDOMONAS AERUGINOSA	43 (16.7%)	36 (14.6%)	67 (22.1%)	56 (19.9%)	110 (19.6%)	92 (17.4%)
ACINETOBACTER CALCOACETICUS	15 (5.8%)	18 (7.3%)	41 (13.5%)	34 (12.1%)	56 (10.0%)	52 (9.8%)
KLEBSIELLA PNEUMONIAE	14 (5.4%)	19 (7.7%)	26 (8.6%)	34 (12.1%)	40 (7.1%)	53 (10.0%)
ESCHERICHIA COLI	18 (7.0%)	7 (2.8%)	18 (5.9%)	11 (3.9%)	36 (6.4%)	18 (3.4%)
HAEMOPHILUS INFLUENZAE	15 (5.8%)	9 (3.6%)	10 (3.3%)	8 (2.8%)	25 (4.5%)	17 (3.2%)
STENOTROPHOMONAS MALTOPHILIA	8 (3.1%)	8 (3.2%)	18 (5.9%)	6 (2.1%)	26 (4.6%)	14 (2.6%)
ENTEROBACTER CLOACAE	6 (2.3%)	9 (3.6%)	12 (4.0%)	9 (3.2%)	18 (3.2%)	18 (3.4%)
PROTEUS MIRABILIS	5 (1.9%)	9 (3.6%)	5 (1.7%)	6 (2.1%)	10 (1.8%)	15 (2.8%)
SERRATIA MARCESCENS	7 (2.7%)	3 (1.2%)	4 (1.3%)	4 (1.4%)	11 (2.0%)	7 (1.3%)
ACINETOBACTER BAUMANNII	3 (1.2%)	2 (0.8%)	4 (1.3%)	4 (1.4%)	7 (1.3%)	6 (1.1%)
KLEBSIELLA OXYTOCA	2 (0.8%)	2 (0.8%)	3 (1.0%)	6 (2.1%)	5 (0.9%)	8 (1.5%)
ENTEROBACTER AEROGENES	3 (1.2%)	2 (0.8%)	3 (1.0%)	2 (0.7%)	6 (1.1%)	4 (0.8%)
CITROBACTER FREUNDII COMPLEX	1 (0.4%)	1 (0.4%)	3 (1.0%)	1 (0.4%)	4 (0.7%)	2 (0.4%)
ACHROMOBACTER XYLOXIDANS	1 (0.4%)	2 (0.8%)	1 (0.3%)	1 (0.4%)	2 (0.4%)	3 (0.6%)
CITROBACTER KOSERI	0	0	2 (0.7%)	2 (0.7%)	2 (0.4%)	2 (0.4%)
CHRYSEOBACTERIUM MENINGOSEPTICUM	1 (0.4%)	1 (0.4%)	0	1 (0.4%)	1 (0.2%)	2 (0.4%)
ENTEROBACTER SPP	1 (0.4%)	0	2 (0.7%)	0	3 (0.5%)	0
PROVIDENCIA STUARTII	1 (0.4%)	1 (0.4%)	0	1 (0.4%)	1 (0.2%)	2 (0.4%)
PSEUDOMONAS PUTIDA	3 (1.2%)	0	0	0	3 (0.5%)	0
BURKHOLDERIA CEPACIA	0	0	1 (0.3%)	1 (0.4%)	1 (0.2%)	1 (0.2%)
PROTEUS VULGARIS	0	0	2 (0.7%)	0	2 (0.4%)	0
SERRATIA LIQUEFACIENS	0	1 (0.4%)	1 (0.3%)	0	1 (0.2%)	1 (0.2%)
ACINETOBACTER LWOFFII	0	0	1 (0.3%)	0	1 (0.2%)	0
BURKHOLDERIA PSEUDOMALLEI	0	0	0	1 (0.4%)	0	1 (0.2%)
CITROBACTER AMALONATICUS	0	1 (0.4%)	0	0	0	1 (0.2%)
CITROBACTER FREUNDII	0	0	0	1 (0.4%)	0	1 (0.2%)
EMPEDOBACTER BREVIS	0	0	1 (0.3%)	0	1 (0.2%)	0
ENTEROBACTER ASBURIAE	0	1 (0.4%)	0	0	0	1 (0.2%)
ENTEROBACTER HORMAECHII	1 (0.4%)	0	0	0	1 (0.2%)	0
FUSOBACTERIUM NUCLEATUM	0	0	1 (0.3%)	0	1 (0.2%)	0
HAEMOPHILUS PARAHAEOMOLYTICUS	1 (0.4%)	0	0	0	1 (0.2%)	0
HAFNIA ALVEI	0	1 (0.4%)	0	0	0	1 (0.2%)
PROVIDENCIA ALCALIFACIENS	0	1 (0.4%)	0	0	0	1 (0.2%)
PROVIDENCIA RETTGERI	0	1 (0.4%)	0	0	0	1 (0.2%)
Pathogens by Gram Type						
Gram-positive Pathogens Only	131 (51%)	134 (54%)	126 (42%)	124 (44%)	257 (46%)	258 (49%)
Single Pathogen	121 (47%)	127 (51%)	120 (40%)	115 (41%)	241 (43%)	242 (46%)
Multiple Pathogens	10 (4%)	7 (3%)	6 (2%)	9 (3%)	16 (3%)	16 (3%)
Gram-negative Pathogens Only	68 (26%)	67 (27%)	77 (25%)	74 (26%)	145 (26%)	141 (27%)
Single Pathogen	56 (22%)	53 (21%)	57 (19%)	56 (20%)	113 (20%)	109 (21%)
Multiple Pathogens	12 (5%)	14 (6%)	20 (7%)	18 (6%)	32 (6%)	32 (6%)
Mixed Gram-positive/Gram-negative Infection	50 (19%)	44 (18%)	94 (31%)	81 (29%)	144 (26%)	125 (24%)
Number of Pathogens						
1 Pathogen	177 (71%)	180 (73%)	177 (60%)	171 (61%)	354 (65%)	351 (67%)
2 Pathogens	48 (19%)	50 (20%)	89 (30%)	85 (30%)	137 (25%)	135 (26%)
3 Pathogens	19 (8%)	11 (4%)	20 (7%)	19 (7%)	39 (7%)	30 (6%)
4 or More Pathogens	5 (2%)	4 (2%)	11 (4%)	4 (1%)	16 (3%)	8 (2%)

Note: More than one pathogen may have been present in any patient
Source: This submission, Section 5.3.5.4.1.10.3, Table 21

Table 32 summarizes the telavancin MIC ranges for the key respiratory pathogens isolated from baseline cultures in the MAT population. The table includes one isolate of *E. faecalis* where the initial susceptibility test indicated an MIC value of 2 mcg/ml. Re-testing in duplicate resulted in an MIC of 1 mcg/ml for this isolate. All MIC₉₀ values were lower than the achievable serum and epithelial lining fluid levels for telavancin (discussed elsewhere in this review).

Table 32: Telavancin MIC Population Distributions for Key Species Isolated from Patients in Studies 0015 and 0019 – MAT Population

Organism	Study	N	No. of Isolates Inhibited at Telavancin Concentration (ug/mL) [1]										MIC (ug/mL)		
			0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2		Range	50%	90%
ENTEROCOCCUS FAECALIS	US	8							5	3			0.5 - 1	0.5	-
	NON-US	26						3	12	10	1		0.25 - 2	0.5	1
	GLOBAL	34						3	17	13	1		0.25 - 2	0.5	1
STAPHYLOCOCCUS AUREUS, ALL	US	143					3	93	46	1			0.12 - 1	0.25	0.5
	NON-US	507				2	10	257	214	24			0.06 - 1	0.25	0.5
	GLOBAL	650				2	13	350	260	25			0.06 - 1	0.25	0.5
STAPHYLOCOCCUS AUREUS, MRSA	US	94					2	61	30	1			0.12 - 1	0.25	0.5
	NON-US	315				2	1	110	179	23			0.06 - 1	0.5	0.5
	GLOBAL	409				2	3	171	209	24			0.06 - 1	0.5	0.5
STAPHYLOCOCCUS AUREUS, MSSA	US	49					1	32	16				0.12 - 0.5	0.25	0.5
	NON-US	192					9	147	35	1			0.12 - 1	0.25	0.5
	GLOBAL	241					10	179	51	1			0.12 - 1	0.25	0.5
STREPTOCOCCUS PNEUMONIAE	US	8	1	1	6								0.008 - 0.03	0.03	-
	NON-US	46	4	29	12	1							0.008 - 0.06	0.015	0.03
	GLOBAL	54	5	30	18	1							0.008 - 0.06	0.015	0.03

Source: This submission, Section 5.3.5.4.1.10.3, Table 23

The MIC₅₀, MIC₉₀ and MIC_{range} values for isolates collected from respiratory specimens, in the clinical trials (MAT population) for both telavancin and vancomycin, are compared in Table 33. MIC₉₀ values for each species (and phenotype) is one doubling dilution less for telavancin, compared to vancomycin, with the exception of isolates of *E. faecalis* collected from vancomycin-treated subjects. Table 34 provides the same information for isolates collected from baseline blood cultures.

Table 33: Susceptibility of Gram-Positive Pathogens Isolated from Baseline Respiratory in Studies 0015 and 0019 to Telavancin and Vancomycin – MAT Population

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

Source: This submission, Section 5.3.5.4.1.10.3, Table 24

Table 34: Susceptibility of Gram-Positive Pathogens Isolated from Baseline Blood in Studies

0015 and 0019 to Telavancin and Vancomycin – MAT Population

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

Source: This submission, Section 5.3.5.4.1.10.3, Table 25

The by-pathogen eradication rates for the principle Gram-positive respiratory pathogens collected in the clinical trials (ME Population), is summarized in Table 35. Eradication rates were notably higher in telavancin-treated subjects, compared to vancomycin-treated subjects, in Study 0015, which included substantially more patients with renal failure and other chronic comorbidities (including diabetes mellitus) than Study 0019. Microbiological eradication rates were similar, between the two treatment arms, against *S. aureus* (including MRSA) in the pooled results, but differed in the individual studies (e.g. eradication of MRSA by telavancin was approximately 5% higher than eradication by vancomycin, in Study 0015, and approximately 5% lower than eradication by vancomycin in Study 0019).

Table 35: By-pathogen Microbiological Eradication Rates at Test-of-cure – ME Population, Studies 0015 and 0019; Gram-positive pathogens at Baseline

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

Source: This submission, Section 5.3.5.4.1.10.3, Table 26

Microbial eradication rates in the ME population were comparable in the telavancin-treated subjects and vancomycin subjects (Table 36). The majority of subjects had a single Gram-positive respiratory pathogen isolated (164 in the telavancin arm, 165 in the vancomycin arm), and in this group, microbial eradication was higher in the telavancin treated subjects (82.9% for the telavancin-treated subjects and 75.8% for the vancomycin-treated subjects, in the pooled data, ME population). This difference was also observed in the individual studies.

Table 36: By-patient Microbiological Response at Test-of-cure – ME Population, Studies 0015

and 0019

	0015		Number of Patients 0019		Total	
	Telavancin 10 mg/kg	Vancomycin	Telavancin 10 mg/kg	Vancomycin	Telavancin 10 mg/kg	Vancomycin
By-patient Microbiological Response						
Eradicated	86 (79.6%)	85 (75.2%)	103 (76.3%)	96 (77.4%)	189 (77.8%)	181 (76.4%)
Persisted	22 (20.4%)	28 (24.8%)	32 (23.7%)	28 (22.6%)	54 (22.2%)	56 (23.6%)
- Total -	108 (100.0%)	113 (100.0%)	135 (100.0%)	124 (100.0%)	243 (100.0%)	237 (100.0%)
Difference (95% CI) [1]	4.4% (-6.6% , 15.4%)		-1.1% (-11.4% , 9.2%)		1.4% (-6.1% , 9.0%)	
Eradication Rate by Number of Pathogens						
Single Gram-positive Pathogen Only	67 / 82 (81.7%)	66 / 88 (75.0%)	69 / 82 (84.1%)	59 / 77 (76.6%)	136 / 164 (82.9%)	125 / 165 (75.8%)
Difference (95% CI) [1]	6.7% (-5.6% , 19.0%)		7.5% (-4.8% , 19.8%)		7.1% (-1.7% , 15.9%)	
Multiple Gram-positive Pathogens Only	5 / 6 (83.3%)	0 / 2 (0.0%)	3 / 5 (60.0%)	7 / 7 (100.0%)	8 / 11 (72.7%)	7 / 9 (77.8%)
Mixed Gram-positive and Gram-negative	14 / 20 (70.0%)	19 / 23 (82.6%)	31 / 48 (64.6%)	30 / 40 (75.0%)	45 / 68 (66.2%)	49 / 63 (77.8%)
Difference (95% CI) [1]	-12.6% (-36.8% , 13.2%)^A		-10.4% (-29.5% , 8.6%)		-11.1% (-25.8% , 4.8%)^A	

[1] Difference in eradication rates (telavancin - vancomycin); two-sided 95% confidence interval

^A = Confidence interval uses Agresti-Caffo adjustment. Pooled analysis is stratified by study.

Source: This submission, Section 5.3.5.4.1.10.3, Table 27

Tables 37 through 40 summarize the MIC and zone diameter results versus microbiological eradication rates for isolates of *S. aureus* (MRSA and MSSA) recovered in the combined clinical trials (global and US results, ME population). No *S. aureus* isolate was recovered with an MIC greater than 1 mcg/ml. The disk diffusion results indicated a relatively narrow range (16 – 21 mm) for *S. aureus* zone diameters.

Table 37: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin MIC Value: Global (ME Population)

				Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
				Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV mic (ug/mL)											
S. aureus	OX:R[1]	0.12	1 (100%)					1 (100%)			
		0.25	43 (72%)	17 (28%)				41 (68%)	19 (32%)		
		0.5	44 (79%)	12 (21%)				44 (79%)	12 (21%)		
		1	4 (80%)	1 (20%)				4 (80%)	1 (20%)		
		Missing	13 (65%)	7 (35%)				13 (65%)	7 (35%)		
		- Total -	105	37	0	0		103	39		
	OX:S[1]	0.12	3 (100%)					3 (100%)			
		0.25	46 (79%)	12 (21%)				45 (78%)	13 (22%)		
		0.5	14 (93%)	1 (7%)				14 (93%)	1 (7%)		
		Missing	8 (89%)	1 (11%)				8 (89%)	1 (11%)		
		- Total -	71	14	0	0		70	15		

[1] S = Susceptible, R = Resistant. A patient can have multiple mic values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_GLOBAL_ALL_MIC_SAUR_115 Program: ltd-6424haplmicro_analysis\programs\it_micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASrv SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 115

Table 38: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by

Baseline Telavancin MIC Value: US Patients (ME Population)

				Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
				Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV mic (ug/mL)											
S. aureus	OX:R[1]	0.12	1 (100%)					1 (100%)			
		0.25	13 (68%)	6 (32%)				13 (68%)	6 (32%)		
		0.5	5 (83%)	1 (17%)				5 (83%)	1 (17%)		
		Missing	4 (57%)	3 (43%)				4 (57%)	3 (43%)		
		- Total -	23	10		0	0	23	10		
S. aureus	OX:S[1]	0.12	1 (100%)					1 (100%)			
		0.25	5 (83%)	1 (17%)				5 (83%)	1 (17%)		
		0.5	6 (86%)	1 (14%)				6 (86%)	1 (14%)		
		- Total -	12	2		0	0	12	2		

[1] S = Susceptible, R = Resistant. A patient can have multiple mic values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_US_ALL_MIC_SAUR_117 Program: \td-6424\hap\micro_analysis\programs\micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASRV SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 117

Table 39: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin Zone Diameter Value: Global (ME Population)

				Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
				Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV Zone Diameter (mm)											
S. aureus	OX:R[1]	16	7 (78%)	2 (22%)				7 (78%)	2 (22%)		
		17	27 (71%)	11 (29%)				26 (68%)	12 (32%)		
		18	32 (74%)	11 (26%)				32 (74%)	11 (26%)		
		19	17 (81%)	4 (19%)				17 (81%)	4 (19%)		
		20	8 (80%)	2 (20%)				8 (80%)	2 (20%)		
		21	1 (100%)						1 (100%)		
		Missing	13 (65%)	7 (35%)				13 (65%)	7 (35%)		
		- Total -	105	37		0	0	103	39		
S. aureus	OX:S[1]	16	6 (100%)					6 (100%)			
		17	25 (83%)	5 (17%)				24 (80%)	6 (20%)		
		18	18 (75%)	6 (25%)				18 (75%)	6 (25%)		
		19	11 (85%)	2 (15%)				11 (85%)	2 (15%)		
		20	2 (100%)					2 (100%)			
		21	1 (100%)					1 (100%)			
		Missing	8 (89%)	1 (11%)				8 (89%)	1 (11%)		
		- Total -	71	14		0	0	70	15		

[1] S = Susceptible, R = Resistant. A patient can have multiple Zone Diameter values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_GLOBAL_ALL_ZONE_SAUR_121 Program: \td-6424\hap\micro_analysis\programs\micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASRV SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 121

Table 40: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by

Baseline Telavancin Zone Diameter Value: US Patients (ME Population)

				Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
				Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV Zone Diameter (mm)											
S. aureus	OX:R[1]	16	6 (75%)	2 (25%)				6 (75%)	2 (25%)		
		17	6 (60%)	4 (40%)				6 (60%)	4 (40%)		
		18	6 (86%)	1 (14%)				6 (86%)	1 (14%)		
		19	1 (100%)					1 (100%)			
		Missing	4 (57%)	3 (43%)				4 (57%)	3 (43%)		
		- Total -	23	10	0	0		23	10		
	OX:S[1]	16	2 (100%)					2 (100%)			
		17	7 (78%)	2 (22%)				7 (78%)	2 (22%)		
		18	2 (100%)					2 (100%)			
		19	1 (100%)					1 (100%)			
		- Total -	12	2	0	0		12	2		

[1] S = Susceptible, R = Resistant. A patient can have multiple Zone Diameter values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_US_ALL_ZONE_SAUR_122 Program: \td-6424\hap\micro_analysis\programs\t_micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASrv SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 122

Tables 41 through 44 summarize the MIC and zone diameter results versus microbiological eradication rates for isolates of *S. pneumoniae* recovered in the combined clinical trials (global and US results, ME population). No *S. pneumoniae* isolate was recovered with an MIC greater than 0.03 mcg/ml. The disk diffusion range for isolates of *S. pneumoniae* recovered in the combined clinical trials was 18 – 23 mm.

Table 41: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin MIC Value Value: Global (ME Population)

			Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
			Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV mic (ug/mL)										
S. PNEUMONIAE	0.008		2 (100%)				2 (100%)			
	0.015		9 (90%)	1 (10%)			10 (100%)			
	0.03		5 (100%)				5 (100%)			
	Missing		2 (67%)	1 (33%)			2 (67%)	1 (33%)		
	- Total -		18	2	0	0	19	1		

[1] S = Susceptible, R = Resistant. A patient can have multiple mic values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_GLOBAL_ALL_MIC_SPHE_133 Program: \td-6424\hap\micro_analysis\programs\t_micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASrv SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 133

Table 42: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by

Baseline Telavancin MIC Value: US Patients (ME Population)

			Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
			Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV mic (ug/mL)										
S.	PNEUMONIAE	0.03	1 (100%)				1 (100%)			
		Missing	1 (100%)				1 (100%)			
		- Total -	2	0	0	0	2			

[1] S = Susceptible, R = Resistant. A patient can have multiple mic values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_US_ALL_MIC_SPHE_135 Program: \td-6424\hap\micro_analysis\programs\it_micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASRV SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 135

Table 43: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin Zone Diameter Value: Global (ME Population)

			Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
			Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV Zone Diameter (mm)										
S.	PNEUMONIAE	18	2 (100%)				2 (100%)			
		19	4 (100%)				4 (100%)			
		20	3 (100%)				3 (100%)			
		21	6 (100%)				6 (100%)			
		22		1 (100%)			1 (100%)			
		23	1 (100%)				1 (100%)			
		Missing	2 (67%)	1 (33%)			2 (67%)	1 (33%)		
		- Total -	18	2	0	0	19	1		

[1] S = Susceptible, R = Resistant. A patient can have multiple Zone Diameter values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_GLOBAL_ALL_ZONE_SPHE_139 Program: \td-6424\hap\micro_analysis\programs\it_micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASRV SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 139

Table 44: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by

Baseline Telavancin Zone Diameter Value: US Patients (ME Population)

			Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
			Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV Zone Diameter (mm)										
S.	PNEUMONIAE	21	1 (100%)				1 (100%)			
		Missing	1 (100%)				1 (100%)			
		- Total -	2	0	0	0	2			

[1] S = Susceptible, R = Resistant. A patient can have multiple Zone Diameter values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_US_ALL_ZONE_SPHE_140 Program: \td-6424\hapi\micro_analysis\programs\it_micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASRV SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 140

Tables 45 through 48 summarize the MIC and zone diameter results versus microbiological eradication rates for isolates of *E. faecalis* recovered in the combined clinical trials (global results and US results, ME population). One isolate of *E. faecalis* initially displayed an MIC result of 2 mcg/ml, but on re-testing (in duplicate), an MIC result of 1 mcg/ml was determined. The disk diffusion results for all isolates of *E. faecalis* recovered in the clinical trials were with a narrow range, 16-18mm.

Table 45: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin MIC Value: Global (ME Population)

			Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
			Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV mic (ug/mL)										
E.	FAECALIS	0.25	1 (100%)				1 (100%)			
		0.5	1 (25%)	3 (75%)			1 (25%)	3 (75%)		
		1	3 (100%)				3 (100%)			
		- Total -	5	3	0	0	5	3		

[1] S = Susceptible, R = Resistant. A patient can have multiple mic values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_GLOBAL_ALL_MIC_EFAE_151 Program: \td-6424\hapi\micro_analysis\programs\it_micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASRV SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 151

Table 46: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin MIC Value: US Patients (ME Population)

		Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
		Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV mic (ug/mL)									
E. FAECALIS	1	1 (100%)				1 (100%)			
	- Total -	1	0	0	0	1			

[1] S = Susceptible, R = Resistant. A patient can have multiple mic values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_US_ALL_MIC_EFAE_153 Program: \td-6424\hap\micro_analysis\programs\micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASRV SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 153

Table 47: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin Zone Diameter Value: Global (ME Population)

		Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
		Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV Zone Diameter (mm)									
E. FAECALIS	16	1 (100%)				1 (100%)			
	17	3 (60%)	2 (40%)			3 (60%)	2 (40%)		
	18	1 (50%)	1 (50%)			1 (50%)	1 (50%)		
	- Total -	5	3	0	0	5	3		

[1] S = Susceptible, R = Resistant. A patient can have multiple Zone Diameter values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_GLOBAL_ALL_ZONE_EFAE_157 Program: \td-6424\hap\micro_analysis\programs\micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASRV SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 157

Table 47: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin Zone Diameter Value: US Patients (ME Population)

		Clinical Outcome at Test-of-Cure Visit				Microbiological Outcome at Test-of-Cure Visit			
		Cured N [%][2]	Not Cured N [%][2]	Indeterminate	Missing	Eradicated[3] N [%][4]	Not Eradicated [5] N [%][4]	Indeterminate	Missing
Baseline TLV Zone Diameter (mm)									
E. FAECALIS	16	1 (100%)				1 (100%)			
	- Total -	1	0	0	0	1			

[1] S = Susceptible, R = Resistant. A patient can have multiple Zone Diameter values as a result of multiple baseline pathogens.

[2] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.

[3] Documented Eradication, Presumed Eradication

[4] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.

[5] Documented Persistence, Presumed Persistence

Source: Dataset(s): MICRO1_0015_0019, MICRO2_0015_0019, MICRO3_0015_0019. OUTPUT: T_MICRO_TLV_ME_US_ALL_ZONE_EFAE_158 Program: \td-6424\hap\micro_analysis\programs\micro.sas Run Date: 04AUG08/11:22 by pliu on NET_ASRV SASv9.1

Source: This submission; Microbiological Summary, Supplemental Table 158

Using the proposed telavancin breakpoints for *S. aureus* (including methicillin-resistant isolates), streptococcal species (including *S. pneumoniae*), and *E. faecalis* (vancomycin-susceptible isolates), no non-susceptible isolates of the principle Gram-positive respiratory pathogens (sought in the proposed indications) were recovered in the two Phase 3 clinical trials

With the exception of *S. aureus* isolates resistant to oxacillin (MRSA), there were no Gram-positive respiratory pathogens identified in the clinical trials with phenotypes commonly

considered "drug-resistant" or "multi-drug resistant", i.e. no isolates of *S. pneumoniae* were identified as penicillin-resistant and no isolates of *S. aureus* were identified as vancomycin non-susceptible. Vancomycin-resistant enterococci were excluded from the trial by design.

Development of resistance during the trials was defined as an increase of 2 or more doubling dilutions in the MIC values of isolates obtained at EOT or TOC, compared to the MIC at Baseline. No isolates collected from subjects in the telavancin-treatment arm met this criteria. Molecular methods (e.g. pulsed field gel electrophoresis) were not employed to characterize and compare isolates obtained at various time-points in the trial. This resulted in the inability of the Applicant to adequately characterize one *S. aureus* isolate, collected from a subject in the vancomycin arm, which may have displayed a 4-fold (2 doubling dilutions) increase in MIC to telavancin. Two *S. aureus* isolates were collected from the subject at baseline, one from respiratory secretions (telavancin MIC = 0.25 mcg/ml), and the other from blood (telavancin MIC = 1 mcg/ml). The isolate recovered at EOT had an MIC of 1 mcg/ml.

"Potential superinfection" was defined by the Applicant as "isolation from post-treatment cultures of a pathogen that was not present at Baseline", with the term "potential" used to indicate the inability to distinguish colonization versus infection. The predominant isolate identified as a causative agent of potential superinfection was *Pseudomonas aeruginosa*, with incidence rates of 9% and 7% in the telavancin-treated subjects and vancomycin-treated subjects, respectively (ME population). Overall rates of potential superinfection were notably higher in the telavancin arm, with 33% incidence, compared to 22% incidence in the vancomycin arm.

QUALITY CONTROL PROCEDURES DURING CLINICAL STUDIES

All bacterial isolates collected in the Phase 3 clinical trials were shipped to (b) (4) for confirmation of identification and for susceptibility testing. Isolates originating in Europe, Russia, and South Africa were tested at the (b) (4) facility in (b) (4). All other isolates were tested at the (b) (4) facility in (b) (4).

MIC susceptibility testing was performed using frozen microbroth dilution panels supplied by (b) (4), according to procedures approved by CLSI. The Applicant has provided plate lot numbers and complete plate configurations in the study report, "Telavancin MIC and Disk Diffusion Quality Control Results for Phase 3 Clinical Studies 0015 and 0019" (Report 08-6424-MCB-03) and are summarized in Table 43. Isolates were subcultured to trypticase-soy agar + 5% sheep blood 12-24 hours prior to testing. Isolates were suspended in demineralized water or cation adjusted Mueller-Hinton broth to an approximate concentration of 10^8 CFU/ml. This suspension was diluted with demineralized water (without Tween), to a concentration of 5×10^4 CFU/ml, which was delivered to the microtiter wells. Plates were incubated in ambient air at 35°C for 16-20 hours (streptococcal isolates were incubated for 20-24 hours) and read manually.

Disk diffusion susceptibility testing was performed using the Kirby-Bauer method approved by CLSI. Mueller-Hinton agar plates were swabbed with a bacterial suspension of approximately 10^8 CFU/ml (5% sheep blood was added to the Mueller-Hinton agar when streptococci were tested). Streptococcal isolates were incubated at 35°C in 5-7% CO₂ for 20-24 hours. Staphylococci and enterococci were incubated at 35°C in ambient air for 16-18 hours. Telavancin disk diffusion was performed using a 30 mcg disk manufactured by BBL (Becton Dickinson, Sparks, MD).

Quality control was performed on each day of testing. Quality control ranges (reviewed in the NDA 22110 submission) were based on CLSI M23 studies, and approved by CLSI for testing of telavancin. Results were reported only when all QC results were within ranges approved by CLSI. The quality control organisms tested are listed in Table 44.

Table 43: MIC Frozen Panel Summary

Panel (part number)	Concentration Range (µg/mL)		Growth Media	Lot Numbers Used at Study Site	
	Telavancin	Vancomycin		(b) (4)	
CML1FSTA	0.015-16	0.25-32	CAMHB ¹	5484, 6351 and 7141	5484, 6351 and 7141
CML3FENC	0.015-32	0.5-512	CAMHB ¹	4433 and 4452	4452
CML2FSRP	0.001-2	0.06-1	CAMHB +2.5% LHB ²	4431 and 7021	4454 and 7021

¹Cation Adjusted Mueller-Hinton Broth prepared according to CLSI M7-A7 (2)

²Lysed Horse Blood

Source: This submission; Report 08-6424-MCB-03, Table 1

Table 44: Quality Control Strains and CLSI Approved Ranges

Strain	CLSI Approved MIC range (µg/mL) ¹	
	Telavancin	Vancomycin
<i>Staphylococcus aureus</i> ATCC 29213	0.12-1	0.5-2
<i>Enterococcus faecalis</i> ATCC 29212	0.12-0.5	1-4
<i>Streptococcus pneumoniae</i> ATCC 49619	0.004-0.03 ²	0.12-0.5
Strain	CLSI Approved Telavancin Disk range (mm) ¹	
<i>Staphylococcus aureus</i> ATCC 25923	16-20	
<i>Streptococcus pneumoniae</i> ATCC 49619	17-24	

¹From CLSI M100-S17 (1)

²From CLSI M100-S17 (tentative) (1)

Source: This submission; Report 08-6424-MCB-03, Table 2

Quality control results for MIC tests are summarized in Table 45 through 47. There was no noted site-to-site or frozen panel lot-to-lot variation.

For *S. aureus*, all vancomycin tests were within established control range. Telavancin results were within the tentative range on 172 of 173 tests (99.4%).

Table 45: *S. aureus* ATCC 29213 – Number of Results at Each MIC from HAP Clinical Studies 0015 and 0019

Telavancin				Vancomycin			
MIC (µg/mL)	(b) (4)		Both Sites	MIC (µg/mL)	(b) (4)		Both Sites
0.12	1	1	2	≤ 0.5	15	36	51
0.25	51	58	109	0.5	32	48	80
0.5	21	36	57	1	26	16	42
1		4	4	2			
2		1	1				
- Total -	73	100	173	- Total -	73	100	173

Shaded area indicates CLSI approved ranges

Source: This submission, Section 5.3.5.4.1.10.2, Table 1

For *E. faecalis*, all vancomycin tests were within established control range. Telavancin results were within the tentative range on 167 of 171 tests (98.2%).

Table 46: *E. faecalis* ATCC 29212 – Number of Results at Each MIC from HAP Clinical Studies 0015 and 0019

Telavancin				Vancomycin			
MIC (µg/mL)	(b) (4)		Both Sites	MIC (µg/mL)	(b) (4)		Both Sites
0.06		1	1				
0.12	2		2	1	1	3	4
0.25	64	62	126	2	70	94	164
0.5	7	32	39	4	2	1	3
1		3	3				
- Total -	73	98	171	- Total -	73	98	171

Shaded area indicates CLSI approved ranges

Source: This submission, Section 5.3.5.4.1.10.2, Table 2

For *S. pneumoniae*, all vancomycin tests were within established control range. All telavancin results were within the tentative range.

Table 47: *S. pneumoniae* ATCC 49619 – Number of Results at Each MIC from HAP Clinical Studies 0015 and 0019

Telavancin				Vancomycin			
MIC (µg/mL)	(b) (4)		Both Sites	MIC (µg/mL)	(b) (4)		Both Sites
0.004				0.12	21	1	22
0.008	5		5	0.25	11	11	22
0.015	22	14	36	0.5	1	2	3
0.03	6		6				
- Total -	33	14	47	- Total -	33	14	47

Shaded area indicates CLSI approved ranges

Source: This submission, Section 5.3.5.4.1.10.2, Table 3

Quality control results for disk diffusion susceptibility testing are summarized in Table 48. All vancomycin and telavancin results were within ranges approved by CLSI.

Table 48: Telavancin Disk Diffusion Results for *S. aureus* ATCC 25923 and *S. pneumoniae* ATCC 49619 – Number of Results at Each Inhibition Zone from HAP Clinical Study 0015 and Study 0019 Combined

Zone (mm)	<i>S. aureus</i> ATCC 25923			Zone (mm)	<i>S. pneumoniae</i> ATCC 49619		
	(b) (4)		Both Sites		(b) (4)		Both Sites
16	9	8	17	16			
17	20	30	50	17			
18	24	22	46	18	3	2	5
19	7	5	12	19	4	5	9
20	4		4	20	16	3	19
21				21	22	3	25
22				22	14	1	15
23				23	4		4
24				24	1		1
- Total -	64	65	129	- Total -	64	14	78

Shaded area indicates CLSI approved ranges

Source: This submission, Section 5.3.5.4.1.10.2, Table 6

Clinical Studies ~ Conclusions:

Data from the two Phase 3 clinical trials indicate that telavancin is effective against the pathogens in the proposed indications. Specimen types, subject demographics, subject co-morbidities, and bacterial isolates were similar between the telavancin and vancomycin arms of the trials. The majority of principle pathogens were recovered from non-invasive specimens (sputum and endotracheal aspiration), and a majority of specimens yielded a single Gram-positive pathogen. Methicillin-resistant *S. aureus* was the predominant pathogen isolated. Using breakpoints proposed in this Application, no telavancin-nonsusceptible isolates were recovered in the clinical trials. No development of telavancin resistance was observed during the trials.

SUSCEPTIBILITY TEST METHODS

VALIDATION STUDIES

In NDA 22-110, the Applicant provided data from studies designed to investigate the effect of altered conditions (temperature, pH, incubation time, calcium ion concentration, incubation atmosphere, and inoculum size) in the susceptibility testing of telavancin against isolates of *S. aureus*, *E. faecalis*, *E. faecium*, and *S. pneumoniae*. While most parameters had little or no effect on outcome (MIC values within 1 doubling dilution, compared to testing under standard conditions), isolates of *S. pneumoniae* demonstrated dramatic differences in MIC values with changes in pH and inoculum size. Disk diffusion results for isolates of *S. pneumoniae*, *E. faecium*, and *S. epidermidis* were affected by differences in solid media lots and manufacturers. No additional studies of this type have been submitted in this Application.

The NDA 22-110 submission also included data from studies comparing broth dilution to agar dilution for the determination of telavancin MIC values. These studies generally demonstrated equivalence between the two methods, when testing staphylococcal and enterococcal isolates. Significant disparities were noted, however, when streptococcal isolates (including *S. pneumoniae*) were tested, with notably higher results obtained by the agar dilution method (> 1 doubling dilution). No additional studies, comparing agar dilution to broth dilution techniques have been submitted in this Application.

BROTH DILUTION METHODS

MIC data from all *S. aureus* isolates tested in studies submitted in support of this Application is summarized in Figure 24. The distribution of all tested isolates is unimodal, ranging from 0.03 mcg/ml to 1 mcg/ml (0.03 – 1 mcg/ml for the 11965 isolates tested in the survey studies, 0.06 – 1 mcg/ml for the 650 isolates tested in the clinical studies). The MIC₉₀ for the isolates tested in the clinical studies was 0.5 mcg/ml, and 0.25 mcg/ml for isolates tested in the survey studies. The MIC_{range} and MIC₉₀ values for methicillin-resistant *S. aureus* (Figure 25) were identical to those of methicillin-susceptible *S. aureus* (0.06 – 1 mcg/ml and 0.5 mcg/ml, respectively, for isolates collected in the clinical trials). With a breakpoint of 1 mcg/ml (proposed for both NDA 22110 and this Application), 100% of *S. aureus* isolates analyzed in both the survey studies and clinical studies are susceptible. No vancomycin non-susceptible *S. aureus* isolates were recovered in the clinical trials. The highest telavancin MIC against *S. aureus*, at which clinical efficacy was demonstrated in the HAP clinical studies was 1 mcg/ml.

Figure 24: Frequency Distribution of Telavancin MIC Values for *Staphylococcus aureus* from HAP Clinical Studies (N = 650, all baseline isolates) and Survey Studies (N = 11,965)

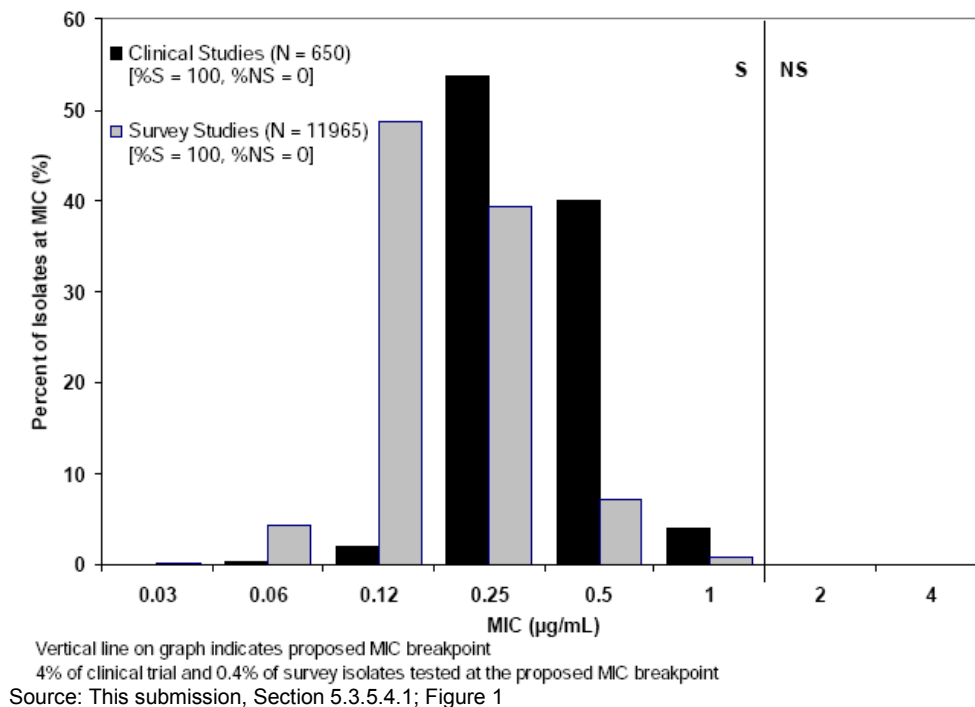
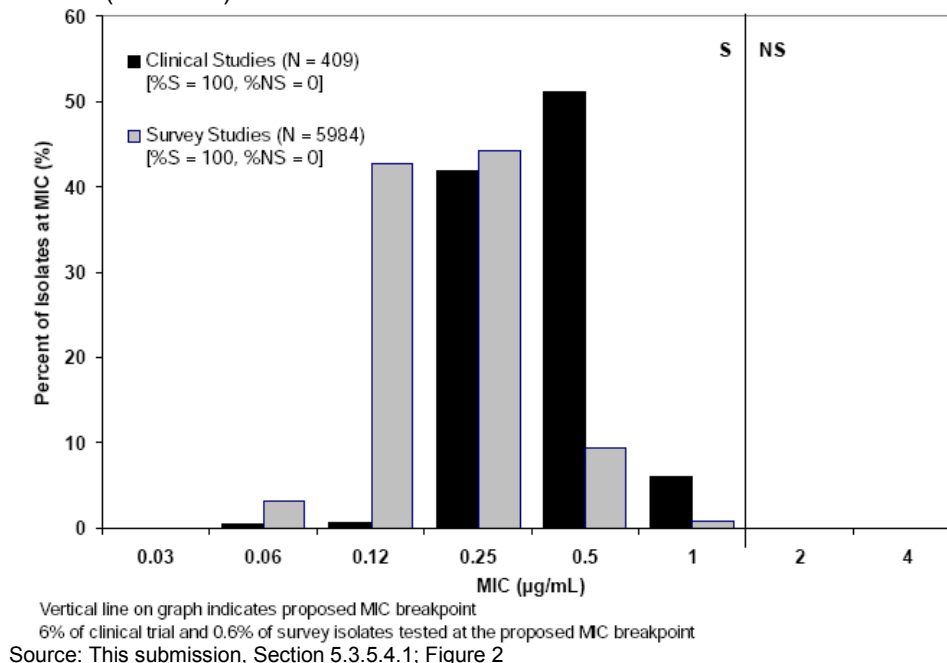


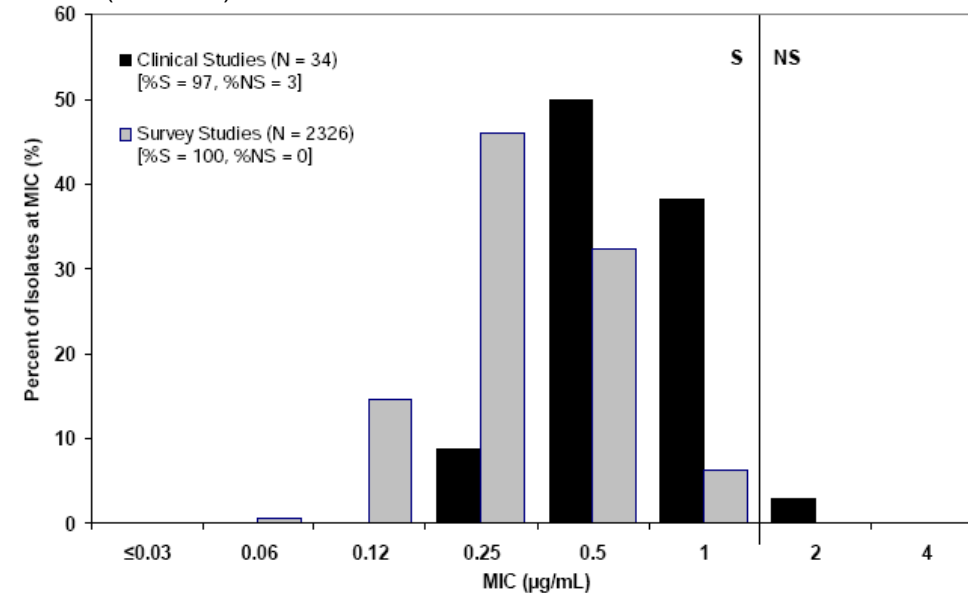
Figure 25: Frequency Distribution of Telavancin MIC Values for Methicillin-Resistant *Staphylococcus aureus* from HAP Clinical Studies (N = 409, all baseline isolates) and Survey Studies (N = 5984)



The distribution of all *Enterococcus faecalis* isolates tested in support of this Application (34 from clinical trials, 2325 from survey studies) is unimodal, ranging from ≤ 0.03 – 2 mcg/ml (Figure 26). The MIC_{range} and MIC₉₀ for the isolates recovered in clinical trials were 0.25 – 2 mcg/ml and 1 mcg/ml, respectively (compared to ≤ 0.03 – 1 mcg/ml and 1 mcg/ml for isolates tested in survey studies). At the proposed breakpoint of 1 mcg/ml, 100% of survey isolates and 97% (33 of 34)

clinical trial isolates were susceptible to telavancin. The one clinical trial isolate with an MIC value of 2 mcg/ml was retested, with a value of 1 mcg/ml reported from duplicate analyses. The highest telavancin MIC against *E. faecalis*, at which clinical efficacy was demonstrated in the HAP clinical studies was 1 mcg/ml.

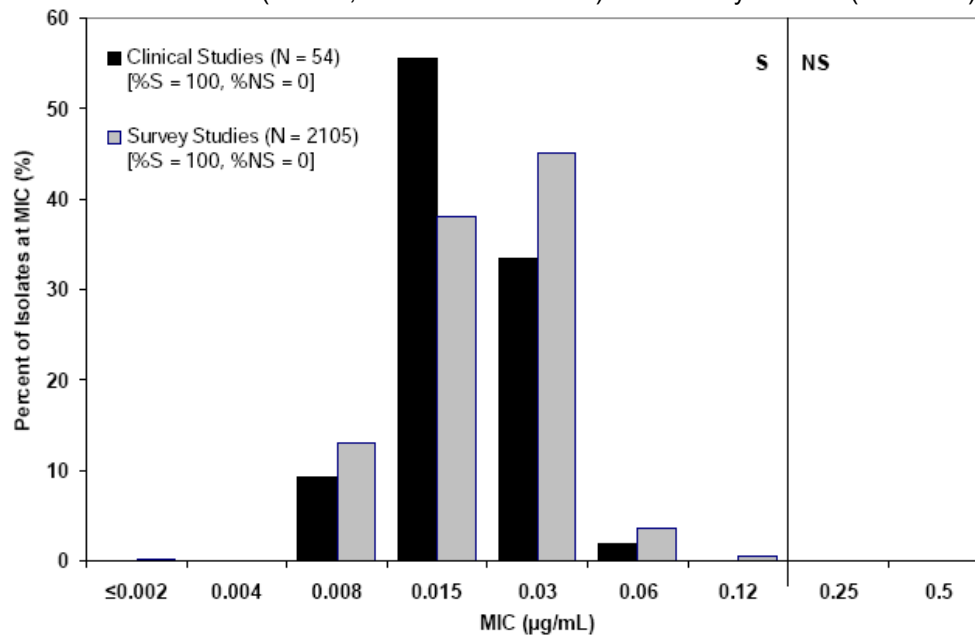
Figure 26: Frequency Distribution of Telavancin MIC Values for Vancomycin-susceptible *Enterococcus faecalis* from HAP Clinical Studies (N = 34, all baseline isolates) and Survey Studies (N = 2326)



Vertical line on graph indicates proposed MIC breakpoint
38% of clinical trial and 6% of survey isolates tested at the proposed MIC breakpoint
Source: This submission, Section 5.3.5.4.1; Figure 3

The distribution of all *Streptococcus pneumoniae* isolates tested in support of this Application (54 from clinical trials, 2105 from survey studies) is unimodal, ranging from ≤ 0.002 – 0.12 mcg/ml (Figure 27). The MIC_{range} and MIC₉₀ for the isolates recovered in clinical trials were 0.008 – 0.06 mcg/ml and 0.03 mcg/ml, respectively (compared to ≤ 0.002 – 0.12 mcg/ml and 0.03 mcg/ml for isolates tested in survey studies). At the proposed breakpoint of 0.12 mcg/ml, 100% of survey isolates and clinical trial isolates were susceptible to telavancin. The highest telavancin MIC for *S. pneumoniae*, at which clinical efficacy was demonstrated in the HAP clinical studies was 0.03 mcg/ml.

Figure 27: Frequency Distribution of Telavancin MIC Values for *Streptococcus pneumoniae* from HAP Clinical Studies (N = 54, all baseline isolates) and Survey Studies (N = 2105)



Vertical line on graph indicates proposed MIC breakpoint
0% of clinical trial and 0.1% of survey isolates tested at the proposed MIC breakpoint

Source: This submission, Section 5.3.5.4.1; Figure 3

Table 49 summarizes clinical cure rates versus MIC values for isolates collected in the combined HAP clinical trials. Table 50 summarizes microbial eradication rates versus MIC values for the same set of organisms. The *E. faecalis* row includes the one isolate initially reported with an MIC value of 2 mcg/ml (re-tested twice, and reported here as 1 mcg/ml).

Table 49: Global Results for the Combined HAP Clinical Studies, ME Population, Telavancin Treatment Arm, Telavancin MIC versus Clinical Cure, n/N (%)

MIC (µg/mL)	<i>S. aureus</i> (All)	MRSA	MSSA	<i>S. pneumoniae</i>	<i>E. faecalis</i>
0.008	-- ^a	--	--	2/2 (100)	--
0.015	--	--	--	9/10 (90)	--
0.03	--	--	--	5/5 (100)	--
0.06	--	--	--	--	--
0.12	4/4 (100)	1/1 (100)	3/3 (100)	--	--
0.25	89/118 (75)	43/60 (72)	46/58 (79)	--	1/1 (100)
0.5	58/71 (82)	44/ 56 (79)	14/15 (93)	--	1/4 (25)
1	4/5 (80)	4/5 (80)	--	--	3/3 (100)
- Total -	155/198 (78)	92/122 (75)	63/76 (83)	16/17 (94)	5/8 (63)

^a Data not available

Source: This submission, Section 5.3.5.4.1.11; Table 3

Table 50: Global Results for the Combined HAP Clinical Studies, ME Population, Telavancin Treatment Arm, Telavancin MIC versus Microbiological Eradication, n/N (%)

MIC (µg/mL)	<i>S. aureus</i> (All)	MRSA	MSSA	<i>S. pneumoniae</i>	<i>E. faecalis</i>
0.008	-- ^a	--	--	2/2 (100)	--
0.015	--	--	--	10/10 (100)	--
0.03	--	--	--	5/5 (100)	--
0.06	--	--	--	--	--
0.12	4/4 (100)	1/1 (100)	3/3 (100)	--	--
0.25	86/118 (73)	41/60 (68)	45/58 (78)	--	1/1 (100)
0.5	58/71 (82)	44/56 (79)	14/15 (93)	--	1/4 (25)
1	4/5 (80)	4/5 (80)	--	--	3/3 (100)
- Total -	152/198 (77)	90/122 (74)	62/76 (82)	17/17 (100)	5/8 (63)

^a Data not available

Source: This submission, Section 5.3.5.4.1.11; Figure 4

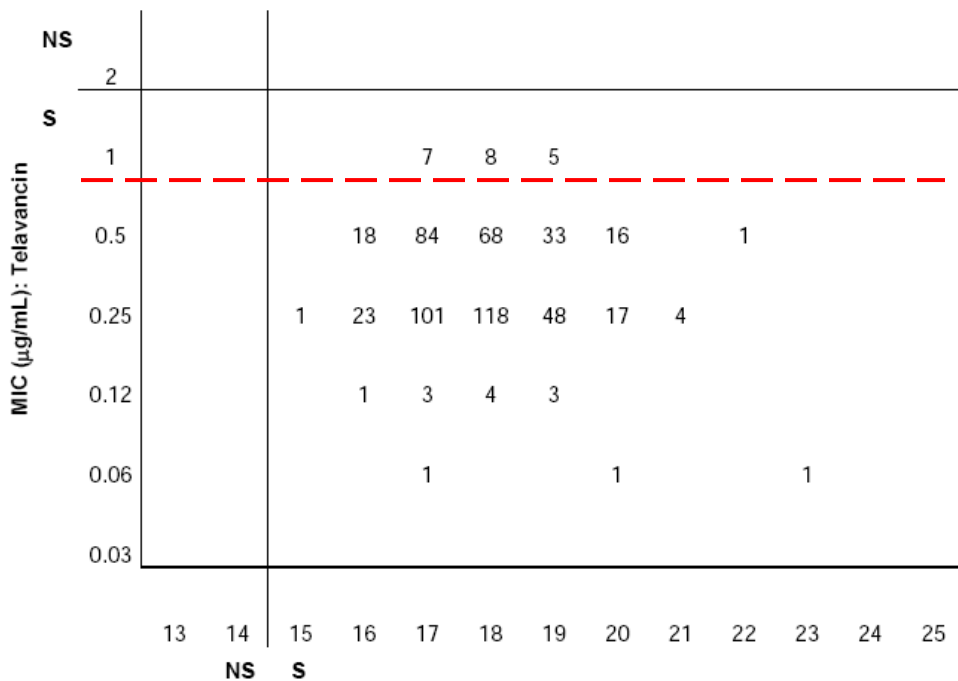
DISK DIFFUSION METHODS

Scatter plots, comparing MIC and disk diffusion results from isolates tested in the HAP clinical trials (ME population) are presented in Figures 29 through 32.

The scatter plot for *S. aureus* (n = 566), along with charted categorical errors, is presented in Figure 28. The scatter plot of methicillin-resistant isolates of *S. aureus* (n = 377), along with charted categorical errors, is presented in Figure 29.

Using data from the HAP clinical trials, and the Agency-proposed susceptible breakpoint of ≥ 0.05 µg/ml (susceptible zone size = 15mm), the very major error rate for *S. aureus* (methicillin-resistant and –susceptible) is 0%, as is the very major error rate for methicillin-resistant isolates, analyzed separately. The major error rates for both analysis groups (all *S. aureus* and MRSA) is also 0%. Breakpoints proposed by the Applicant are shown in non-hashed, black lines. Breakpoints proposed by the Agency are shown in hashed, red lines. Clinical outcome data, comparing cure rates during clinical trials to baseline telavancin susceptibility (disk diffusion method) is presented in Table 51.

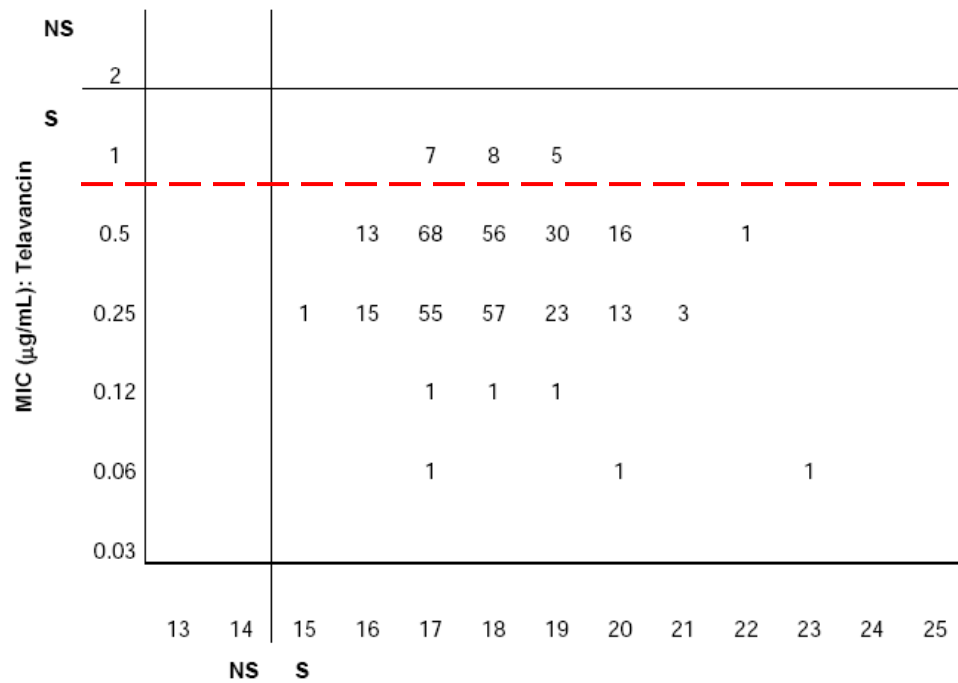
Figure 28: Telavancin Broth Microdilution MIC vs. Disk Diffusion Zone Diameter against *Staphylococcus aureus* from HAP Clinical Studies (Microbiologically Evaluable population, all treatment arms) (N = 566)



Zone Diameter (mm): Telavancin					
MIC Range	Total N	Very Major	% Very Major	Major	% Major
≥ R+1	0	0	0.0%	N/A	N/A
R+S	239	0	0.0%	0	0.0%
≤ S-1	327	N/A	N/A	0	0.0%
Total	566	0	0.0%	0	0.0%

Source: This submission, Section 5.3.5.4.1; Figure 5

Figure 29: Telavancin Broth Microdilution MIC vs. Disk Diffusion Zone Diameter against Methicillin-resistant *Staphylococcus aureus*, from HAP Clinical Studies (Microbiologically Evaluable population, all treatment arms) (N = 377)



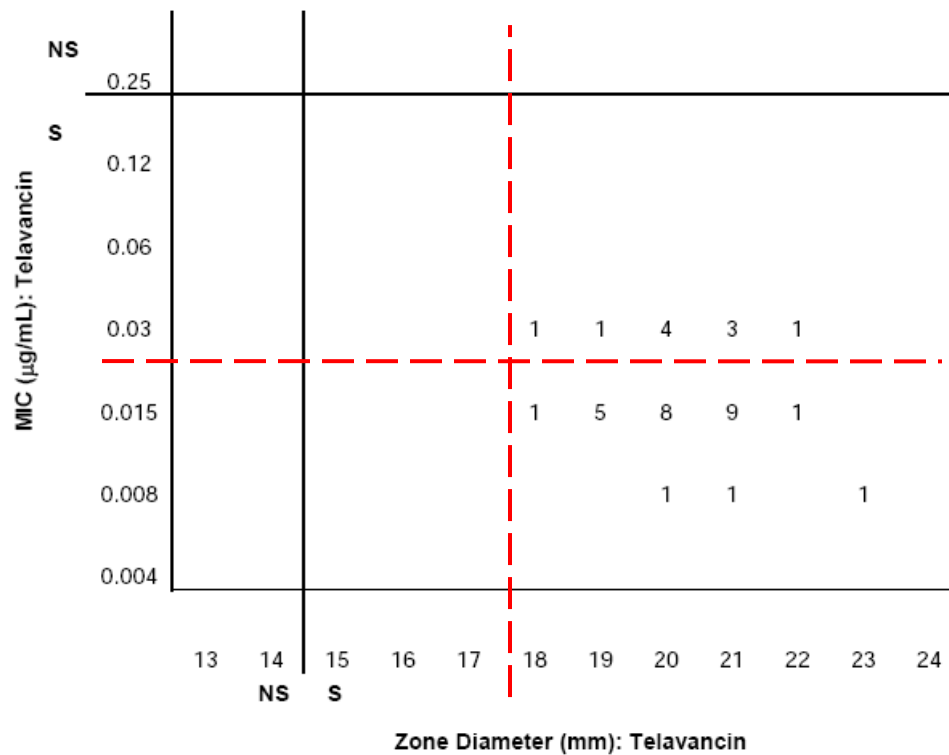
Zone Diameter (mm): Telavancin					
MIC Range	Total N	Very Major	% Very Major	Major	% Major
≥ R+1	0	0	0.0%	N/A	N/A
R+S	204	0	0.0%	0	0.0%
≤ S-1	173	N/A	N/A	0	0.0%
Total	377	0	0.0%	0	0.0%

Source: This submission, Section 5.3.5.4.1.11; Figure 6

The scatter plot for *S. pneumoniae* isolates collected in HAP clinical trials (n = 37), along with charted categorical errors, is presented in Figure 30. Since the number of isolates of *S. pneumoniae* that were collected in the clinical trials was relatively low, and since *S. pneumoniae* was not sought as an indication in NDA 22110 (and discussed in that review), a scatter plot of combined isolates of *S. pneumoniae* from clinical trials and survey studies (n = 137), along with charted categorical errors, is presented in Figure 31.

Using data from the HAP clinical trials only, the Agency-proposed susceptible breakpoint of ≥ 0.015 mcg/ml (susceptible zone size = 18 mm), the very major error rate and major error rate for *S. pneumoniae* is 0%. Breakpoints proposed by the Applicant are shown in non-hashed, black lines. Breakpoints proposed by the Agency are shown in hashed, red lines. Clinical outcome data, comparing cure rates during clinical trials to baseline telavancin susceptibility (disk diffusion method) is presented in Table 51.

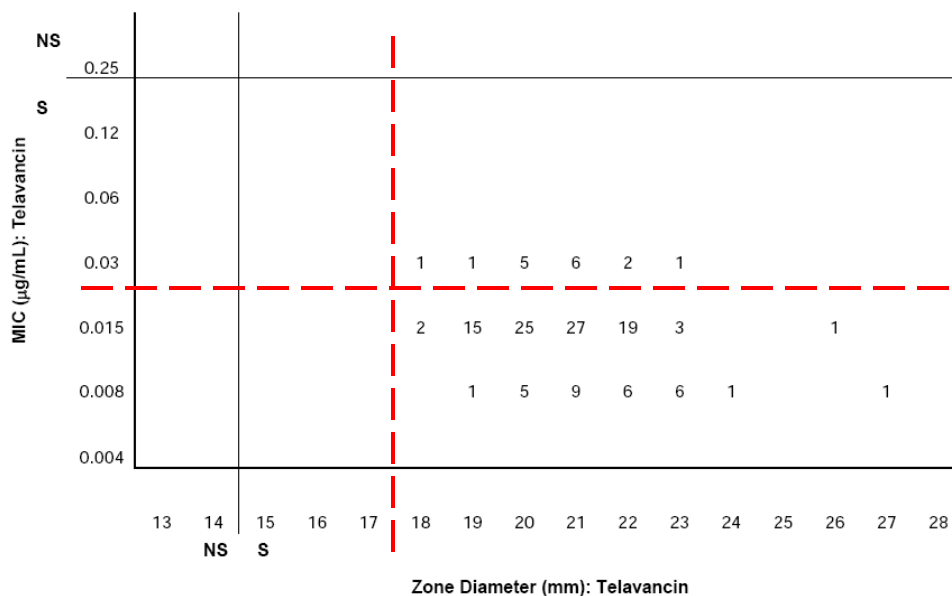
Figure 30: Telavancin Broth Microdilution MIC vs. Disk Diffusion Zone Diameter against *Streptococcus pneumoniae* from HAP Clinical Studies (Microbiologically Evaluable Population, N = 37)



MIC Range	Total N	Very Major	% Very Major	Major	% Major
$\geq R+1$	0	0	0.0%	N/A	N/A
R+S	34	0	0.0%	0	0.0%
$\leq S-1$	3	N/A	N/A	0	0.0%
Total	37	0	0.0%	0	0.0%

Source: This submission, Section 5.3.5.4.1.11; Figure 8

Figure 31: Telavancin Broth Microdilution MIC vs. Disk Diffusion Zone Diameter against *Streptococcus pneumoniae* from Combined HAP Clinical (Microbiologically Evaluable Population, N = 37) and Survey Studies (N = 100)



MIC Range	Total N	Very Major	% Very Major	Major	% Major
≥ R+1	0	0	0.0%	N/A	N/A
R+S	108	0	0.0%	0	0.0%
≤ S-1	29	N/A	N/A	0	0.0%
Total	137	0	0.0%	0	0.0%

Source: This submission, Section 5.3.5.4.1.11; Figure 7

Table 51: Global Results for the Combined HAP Clinical Studies, ME Population, Telavancin Treatment Arm, Zone Diameter versus Clinical Cure, n/N (%)

Zone (mm)	<i>S. aureus</i> (All)	MRSA	MSSA	<i>S. pneumoniae</i>	<i>E. faecalis</i>
23	-- ^a	--	--	1/1 (100)	--
22	--	--	--	0/1 (0)	--
21	2/2 (100)	1/1 (100)	1/1 (100)	6/6 (100)	--
20	10/12 (83)	8/10 (80)	2/2 (100)	3/3 (100)	--
19	28/34 (82)	17/21 (81)	11/13 (85)	4/4 (100)	--
18	50/67 (75)	32/43 (74)	18/24 (75)	2/2 (100)	1/2 (50)
17	52/68 (76)	27/38 (71)	25/30 (83)	--	3/5 (60)
16	13/15 (87)	7/9 (78)	6/6 (100)	--	1/1 (100)
15	--	--	--	--	--
- Total -	155/198 (78)	92/122 (75)	63/76 (83)	16/17 (94)	5/8 (63)

^a Data not available

Source: This submission, Section 5.3.5.4.1.11; Figure 5

Table 52: Global Results for the Combined HAP Clinical Studies, ME Population, Telavancin Treatment Arm, Zone Diameter versus Microbiological Eradication, n/N (%)

Zone (mm)	<i>S. aureus</i> (All)	MRSA	MSSA	<i>S. pneumoniae</i>	<i>E. faecalis</i>
23	-- ^b	--	--	1/1 (100)	--
22	--	--	--	1/1 (100)	--
21	1/2 (50)	0/1 (0)	1/1 (100)	6/6 (100)	--
20	10/12 (83)	8/10 (80)	2/2 (100)	3/3 (100)	--
19	28/34 (82)	17/21 (81)	11/13 (85)	4/4 (100)	--
18	50/67 (75)	32/43 (74)	18/24 (75)	2/2 (100)	1/2 (50)
17	50/68 (74)	26/39 (68)	24/30 (80)	--	3/5 (60)
16	13/15 (87)	7/9 (78)	6/6 (100)	--	1/1 (100)
15	--	--	--	--	--
- Total -	152/198 (77)	90/122 (74)	62/76 (82)	17/17 (100)	5/8 (63)

^b Data not available

Source: This submission, Section 5.3.5.4.1.11; Figure 6

Susceptibility Test Methods ~ Conclusions:

Telavancin MIC distributions from clinical trials and survey studies are unimodal for *S. aureus* (both methicillin-susceptible and methicillin-resistant strains), *E. faecalis*, and *S. pneumoniae*. Distributions derived from clinical studies, for these pathogens, are similar to those derived from survey studies, although the percentage of clinical isolates with higher telavancin MIC values

appears to trend higher, for isolates of *S. aureus* and *E. faecalis*, compared to survey isolates, particularly at higher MIC values. Since this may imply developing resistance among these pathogens, continued surveillance is warranted.

Correlation studies comparing the disk diffusion method of susceptibility testing with the minimum inhibitory concentration method support the zone size recommendations of the Applicant.

Data from reference laboratory reports, reviewed in NDA 22110, suggest that susceptibility testing of telavancin, using solid media techniques, may result in values that are difficult to reproduce or vary from acceptable quality control ranges. This may be due to the size of the telavancin molecule and its diffusion properties. Susceptibility testing by the agar diffusion method is not recommended. Data presented in this Application suggests that modest alterations in the pH of test media and inoculum size may result in unreliable telavancin susceptibility results for *S. pneumoniae*.

Data from quality control studies do not support vancomycin as a class-representative surrogate for telavancin susceptibility testing.

APPLICANT'S PROPOSED SUSCEPTIBILITY INTERPRETIVE CRITERIA

Table 53: Applicant-proposed Telavancin Susceptibility Breakpoints

Pathogen	Susceptibility Interpretive Criteria ^a					
	MIC (µg/mL)			Zone Diameter (mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i> (including methicillin-resistant strains)	≤ 1	--	--	≥ 15	--	--
<i>Streptococcus agalactiae</i> <i>Streptococcus anginosus</i> group <i>Streptococcus pneumoniae</i> <i>Streptococcus pyogenes</i>	≤ 0.12	--	--	≥ 15	--	--
<i>Enterococcus faecalis</i> (vancomycin-susceptible only)	≤ 1	--	--	≥ 15	--	--

^a The current absence of data on resistant isolates precludes defining any categories other than Susceptible (S). Isolates yielding results other than susceptible should be submitted to a reference laboratory for further testing.

Based on data from the Phase 3 clinical trials, in addition to in vitro studies of telavancin activity against the pathogens sought in the proposed indications, the Agency proposes the following susceptibility breakpoints (Table 54). Since streptococci other than *S. pneumoniae*, and *E. faecalis* (vancomycin-susceptible only) are not sought in the proposed indication, no breakpoints for those isolates are included.

Table 54: Agency-proposed Telavancin Susceptibility Breakpoints

Pathogen	Susceptibility Interpretive Criteria					
	MIC (mcg/ml)			Zone Diameter (mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i> (including methicillin-resistant isolates)	≤ 0.05	-	-	≥15	-	-
<i>Streptococcus pneumoniae</i>	≤0.015	-	-	≥18	-	-

APPLICANT'S PROPOSED SUBSECTION OF THE PACKAGE INSERT

Telavancin is a semisynthetic, lipoglycopeptide antibiotic. Telavancin exerts concentration-dependent, bactericidal activity against Gram-positive organisms *in vitro*, as demonstrated by time-kill assays and MBC/MIC ratios (minimum bactericidal concentration/minimum inhibitory concentration) using broth dilution methodology. *In vitro* studies demonstrated a telavancin post-antibiotic effect ranging from 1 to 6 hours against *S. aureus* and other Gram-positive pathogens.

Although telavancin is approximately 90% protein bound, the presence of human serum or human serum albumin has minimal impact on the *in vitro* activity of telavancin against staphylococci, streptococci, and vancomycin-susceptible enterococci.

Mechanism of Action:

Telavancin inhibits cell wall biosynthesis by binding to late-stage peptidoglycan precursors, including lipid II. Telavancin also binds to the bacterial membrane and disrupts membrane barrier function.

Interactions with Other Antibiotics:

In vitro investigations demonstrated no antagonism between telavancin and amikacin, aztreonam, cefepime, ceftriaxone, ciprofloxacin, gentamicin, imipenem, meropenem, oxacillin, piperacillin/tazobactam, rifampin, and trimethoprim/sulfamethoxazole, (b) (4)

(b) (4)

(b) (4)

Cross-Resistance:

Some vancomycin-resistant enterococci have reduced susceptibility to telavancin. There is no known cross-resistance between telavancin and other classes of (b) (4).

(b) (4)

Susceptibility Test Methods:

When available, the clinical microbiology laboratory should provide cumulative results of the *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution technique

Quantitative methods are used to determine antimicrobial MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure (b) (4). Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of telavancin powder. The MIC values should be interpreted according to the criteria provided in Table (b) (4).

Diffusion technique

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations (b) (4). This procedure uses paper disks impregnated with 30 µg of telavancin to test the susceptibility of microorganisms to telavancin. The disk diffusion interpretive criteria are provided in Table (b) (4).

Table (b) (4) Susceptibility Interpretive Criteria for Telavancin

	Susceptibility Interpretive Criteria ^a					
	Minimal Inhibitory Concentration (µg/mL)			Disk Diffusion Zone Diameter (mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i> (including methicillin-resistant isolates)	≤ 1	--	--	≥ 15	--	--
(b) (4) <i>Streptococcus pyogenes</i> <i>Streptococcus agalactiae</i> <i>Streptococcus anginosus</i> group	≤ 0.12	--	--	≥ 15	--	--
<i>Enterococcus faecalis</i> (vancomycin-susceptible isolates only)	≤ 1	--	--	≥ 15	--	--

a. The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding results other than susceptible should be subjected to additional testing.

A report of "Susceptible" indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control microorganisms to monitor the performance of the supplies and reagents used in the assay and the techniques of the individuals performing the test. Standard telavancin powder should provide the range of values noted in Table (b) (4).

Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within bacteria; the specific strains used for microbiological quality control are not clinically significant.

Table (b) (4) Acceptable Quality Control Ranges for Telavancin to be Used in Validation of Susceptibility Test Results

	Acceptable Quality Control Ranges	
	Minimal Inhibitory Concentration (µg/mL)	Disk Diffusion Zone Diameter (mm)
<i>Enterococcus faecalis</i> ATCC 29212	0.12-0.5	Not applicable

	Acceptable Quality Control Ranges	
<i>Staphylococcus aureus</i> ATCC 29213	0.12-1	Not applicable
<i>Staphylococcus aureus</i> ATCC 25923	Not applicable	16-20
<i>Streptococcus pneumoniae</i> ATCC 49619 ^a	0.004-0.03	17-24
^a This organism may be used for validation of susceptibility test results when testing <i>Streptococcus</i> spp. other than <i>S. pneumoniae</i> .		

CONCLUSIONS AND RECOMMENDATIONS

See page 3.

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Fred Marsik, Ph.D.
Micro TL/HFD-520
25 Sep 09 FIN FJM

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

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/s/

KERRY SNOW
09/29/2009

FREDERIC J MARSIK
09/30/2009

Product Quality Microbiology Review

27 July 2009

NDA: 22-407/N-000

Drug Product Name

Proprietary: VIBATIV.

Non-proprietary: Telavancin Hydrochloride.

Review Number: 1.

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
23 JAN 2009	26 JAN 2009	02 FEB 2009	05 FEB 2009

Applicant/Sponsor

Name: Theravance, Inc.

Address: 901 Gateway Boulevard
South San Francisco, CA 94080

Representative: Rebecca Coleman

Telephone: 650-438-0235

Name of Reviewer: John W. Metcalfe, Ph.D.

Conclusion: Approvable.

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Original NDA.
 2. **SUBMISSION PROVIDES FOR:** A drug product for a new indication.
 3. **MANUFACTURING SITE:**
 - Drug Product Manufacturing, release testing, packaging & labeling:
(b) (4)
 - Microbiological testing of stability samples:
(b) (4)
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - Sterile lyophilized powder for Injection.
 - Intravenous infusion.
 - 250 mg and 750 mg.
 5. **METHOD(S) OF STERILIZATION:** Sterile (b) (4)
 6. **PHARMACOLOGICAL CATEGORY:** Antibiotic.
- B. **SUPPORTING/RELATED DOCUMENTS:** Microbiology Review of NDA 22-110/N-000, dated 18 JUNE 2007.
- C. **REMARKS:**
The NDA is submitted electronically in the CTD format.
- The NDA references NDA 22-110 for Modules 3 (Quality) and 4 (Non-Clinical) on Page 1 of the cover letter.

File Name: N022407R1.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – NDA 22-407/N-000 is approvable pending resolution of the microbiology deficiencies.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – Not applicable.

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** - The bulk drug (b) (4)
(b) (4)
- B. Brief Description of Microbiology Deficiencies** – The applicant has not provided microbiological data supporting the statement in the draft label concerning the length of the maximum holding period following preparation of the final drug product.
- C. Assessment of Risk Due to Microbiology Deficiencies** – A long post constitution holding period may allow microbial growth in the final drug product which would put the patient at risk for infection following administration.

III. Administrative

- A. Reviewer's Signature** _____
John W. Metcalfe, Ph.D.
- B. Endorsement Block** _____
Stephen Langille, Ph.D.
- C. CC Block**
N/A

Product Quality Microbiology Assessment**1. REVIEW OF COMMON TECHNICAL DOCUMENT-
QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA**

The NDA references NDA 22-110 for Modules 3 (Quality) and 4 (Non-Clinical) on Page 1 of the cover letter.

Reviewer's Comments

1. A microbiology review of NDA 22-110 was completed on 18 June 2007. The review recommended approval of the NDA from the standpoint of product quality microbiology. Consequently, this reviewer finds that NDA 22-407 is adequate with regard to manufacturing processes related to the sterility assurance of the subject drug product.
2. A separate review of NDA 22-110 was performed on microbiological studies submitted by the applicant in support of information in the draft label concerning the recommended holding time following constitution of the product. The 14 January 2009 microbiology review resulted in a conclusion of "approvable". To date, additional studies in support of the NDA 22-110 post constitution holding time have not been submitted.

**2. REVIEW OF COMMON TECHNICAL DOCUMENT-
QUALITY (CTD-Q)
MODULE 1****A. PACKAGE INSERT**

The draft label states that the powder should be reconstituted with either 5% Dextrose, Sterile WFI or 0.9% Sodium Chloride. Subsequently, an additional dilution is made using either 5% Dextrose, 0.9% Sodium Chloride or Lactated Ringer's Injection.

The draft label states that the solutions which result from each of the above dilutions are

(b) (4)

(b) (4)

Reviewer's Comment

There are no microbiology data in the NDA to support the above claim regarding the maximum post constitution holding time.

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

The following comment and Information Request should be forwarded to the applicant:

The draft labeling states that the drug product will be diluted twice in one of three diluents. In addition, the labeling states (b) (4)

(b) (4) However, it is unknown as to whether the final solutions will support the growth of adventitious microorganisms which may contaminate the drug solution during final preparation.

Please amend the application with the following:

- Provide a risk assessment report summarizing studies that show adventitious microbial contamination does not grow under the storage and infusion conditions. Reference is made to *Guidance for Industry: ICH Q8 Pharmaceutical Development*, Section II.E and *Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products*, Section 2.2.7.

The report should describe test methods and results that employ a minimum countable inoculum to simulate potential microbial contamination that may occur during product dilution. It is generally accepted that growth is evident when the population increases more than 0.5 Log₁₀. The test should be run at the label's recommended storage conditions and be conducted for 2 to 3-times the holding period (the total time between initial vial penetration and the completion of patient infusion) and using the label-recommended fluids. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections.

In lieu of the risk assessment report, modify the draft label information stating that the final reconstituted product must be used within 4 hours of preparation when stored at room temperature and 24 hours when stored under refrigeration.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22407	----- ORIG 1	----- THERAVANCE INC	----- VIBATIV

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/s/

JOHN W METCALFE
07/27/2009

STEPHEN E LANGILLE
07/27/2009

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 22-407

Applicant: Theravance

Letter Date: 23 JAN 2009

Drug Name: Telavancin

NDA Type: Standard

Stamp Date: 26 JAN 2009

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		Preservative effectiveness is not applicable.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		
7	Has the applicant submitted the results of analytical method verification studies?	X		
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			This reviewer has no knowledge of any pre-submission information requests.
9	Is this NDA fileable? If not, then describe why.	X		

Additional Comments:

- The subject NDA references NDA 22-110 with regard to all CMC information.
- There are no comments for the applicant regarding issues pertaining to the microbiological quality of the subject drug product at this time.

John W. Metcalfe, Ph.D.

Date

Stephen Langille, Ph.D.

Date

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/s/

John Metcalfe
3/18/2009 08:13:32 AM
MICROBIOLOGIST

Stephen Langille
3/18/2009 09:32:56 AM
MICROBIOLOGIST

Clinical Microbiology: 45-Day Meeting Checklist NDA - Fileability
NDA 22-407: Telavancin for Hospital Acquired Pneumonia
Reviewer: Kerry Snow **Date Review completed: 10 March 2009**

On **initial** overview of the NDA application for RTF:

No.	Item	Yes	No	Comments
1	Is the clinical microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA organized in a manner to allow substantive review to begin?	✓		
2	Is the clinical microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA indexed, paginated, and/or linked in a manner to allow substantive review to begin?	✓		
3	Is the clinical microbiology information (preclinical/nonclinical and clinical) in different sections of the NDA legible so that substantive review can begin?	✓		
4	On its face, has the applicant <u>submitted</u> <i>in vitro</i> data in necessary quantity, using necessary clinical and non-clinical strains/ isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?	✓		
5	Has the applicant <u>submitted</u> draft provisional breakpoint and interpretive criteria, along with quality control (QC) parameters, if applicable, in a manner consistent with contemporary standards, which attempt to correlate criteria with clinical results of NDA studies, and in a manner to allow substantive review to begin?	✓		
6	Has the applicant <u>submitted</u> any required animal model studies necessary for approvability of the product based on the submitted draft labeling?	✓		
7	Has the applicant <u>submitted</u> all special/critical studies/data requested by the Division during pre-submission discussions?	✓		

Clinical Microbiology: 45-Day Meeting Checklist NDA - Fileability
NDA 22-407: Telavancin for Hospital Acquired Pneumonia
Reviewer: Kerry Snow **Date Review completed: 10 March 2009**

8	Has the applicant <u>submitted</u> the clinical microbiology datasets in a format which intends to correlate baseline pathogen with clinical and microbiologic outcomes exhibited by relevant pathogens isolated from test of cure or end of treatment?	✓		
9	Has the applicant <u>submitted</u> a clinical microbiology dataset in a format which intends to determine resistance development by correlating changes in the phenotype (such as <i>in vitro</i> susceptibility) and/or genotype (such as mutations) of the baseline relevant pathogen with clinical and microbiologic outcome as exhibited by relevant pathogens isolated from test of cure or end of treatment?	✓		
10	Has the applicant used standardized methods or if non-standardized methods were used has the applicant included full details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?	✓		
11	Is the clinical microbiology draft labeling consistent with 21 CFR Parts 201, 314, 601 and current Divisional policy.	✓		
12	FROM A CLINICAL MICROBIOLOGY PERSPECTIVE, IS THIS NDA FILEABLE? IF NO, GIVE REASONS BELOW.	✓		

Any Additional Clinical Microbiology Comments:

No additional comments.

Name Kerry Snow
Reviewing Clinical Microbiologist

Name Fred Marsik, Ph.D.
Team Leader Clinical Microbiology

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this page is the manifestation of the electronic signature.**

/s/

Kerry Snow
3/10/2009 01:37:50 PM
MICROBIOLOGIST

Frederic Marsik
3/10/2009 01:43:06 PM
MICROBIOLOGIST