# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-110**

# MICROBIOLOGY REVIEW(S)

# Division of Anti-Infective and Ophthalmology Products
# Clinical Microbiology Review

**NDA: 22-110**

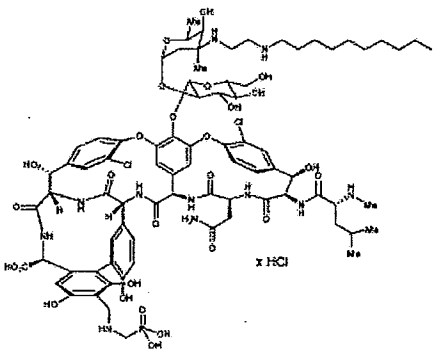
Date Company Submitted: 21 January 2008
Date received by CDER: 21 January 2008
Date Assigned: 21 January 2008
Date Completed: 25 February 2009
Reviewer: Kerry Snow

**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 | 10 mg/kg every 48 hours |

b(4)

**DISPENSED:**
Rx

**PROPOSED INDICATION:**
Treatment of complicated skin and skin structure infections (cSSSI) caused by *Staphylococcus aureus* (methicillin-resistant and –susceptible strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius* and *S. constellatus*), and *Enterococcus faecalis* (vancomycin-susceptible isolates only).

b(4)

**RELATED DOCUMENTS:**

**TYPE OF SUBMISSION:**
New Drug Application

**REMARKS:**

The Applicant submitted a response (21 January 2008) to an Action Letter dated 19 October 2008. The Action Letter included a comment (Comment 4) regarding the in vitro activity of telavancin against isolates of *Staphylococcus aureus* and *Enterococcus* sp., relative to the activity of vancomycin:

APPLICANT'S RESPONSE

> *"Figure 8 from 5.3.5.4.1 of the December 6, 2006, submission displayed below appears to identify S. aureus isolates which are sensitive to telavancin and resistant to vancomycin, recognizing that the breakpoints included in this table will be revised. Figure 9 from 5.3.5.4.1 of the December 6, 2006, submission displayed below appears to identify Enterococcal spp. isolates which are sensitive to telavancin and resistant to vancomycin, recognizing that the breakpoints included in this table will be revised.*
>
> *a. Please confirm whether you have identified any S. aureus or Enterococcal spp. isolates (particularly Enterococcus faecium and Enterococcus faecalis) which are sensitive to vancomycin and resistant to telavancin.*
>
> *b. Please identify the clinical disease from which there were vancomycin resistant (MIC of >16 mcg/mL)/telavancin sensitive S. aureus or Enterococcal spp. (particularly Enterococcus faecium and Enterococcus faecalis) isolates.*
>
> *c. If there are clinically relevant isolates (any bacterial organism) which are sensitive to*

*telavancin (MIC = 1 mcg/mL) and resistant to vancomycin, please identify them along with the clinical condition from which they were isolated."*

In its response to Comment 4a, The Applicant has stated that in combined studies used to support the development of telavancin (6,564 isolates from prospective global surveillance and clinical studies, retrospective surveillance studies, and pivotal clinical trials), five isolates of *S. aureus* were identified with MIC values of 2 mcg/ml against both telavancin and vancomycin. No *S. aureus* isolates were identified with an MIC greater than 2 mcg/ml. In clinical trials, no enterococcal isolates (89 isolates of vancomycin-susceptible *E. faecalis*) were identified with MICs higher than 1 mcg/ml. In surveillance studies (both prospective and retrospective) 2186 enterococcal isolates were tested, and 47 (2%) were susceptible to vancomycin (MIC ≤ 4 mcg/ml) and nonsusceptible to telavancin (MIC > 1 mcg/ml). Of the 47 telavancin-nonsusceptible enterococcal isolates (including *E. faecalis* and *E. faecium*) analyzed in these surveillance studies, 43 had a telavancin MIC of 2 mcg/ml, 3 had a telavancin MIC of 4 mcg/ml, and 1 had a telavancin MIC of 8 mcg/ml. The proposed breakpoint for telavancin against *S. aureus* (including methicillin-resistant isolates) and vancomycin-susceptible *Enterococcus faecalis* is 1 mcg/ml. The Applicant contends that PK/PD studies, Monte Carlo modeling, and animal studies support a higher breakpoint for telavancin susceptibility, and that no evidence indicates that *S. aureus* or enterococcal isolates are nonsusceptible to telavancin at 2 mcg/ml and 8 mcg/ml, respectively.

In its response to Comment 4b, the Applicant has provided a table, listing all enterococcal isolates identified as "vancomycin resistant (MIC > 16 mcg/ml)/telavancin sensitive." Of the 45 isolates listed, 24 were from skin and skin structures or wound infections. The remainder were from blood.

In its response to Comment 4c, the Applicant has provided a table of staphylococcal isolates identified as "vancomycin-intermediate" (vancomycin MIC: 4-8 mcg/ml), susceptible to telavancin (MIC ≤ 1 mcg/ml). One isolate was from a respiratory source, two from skin and skin structure sources, and twelve from blood. In addition to these (and isolates identified in the response to Comment 4b), the Applicant has identified 99 isolates analyzed from surveillance studies and reported in NDA 22-110, meeting the criteria of "sensitive to telavancin (MIC ≤ 1 mcg/ml) and resistant to vancomycin." The source of these isolates is not known. They included 1 *E. avium*, 19 *E. faecalis*, 59 *E. faecium*, 6 *S. anginosus*, 1 *S. bovis*, 5 *S. constellatus*, 6 *S. intermedius*, and 2 *S. pyogenes*.

The Applicant's responses to Agency Comments are complete. However, in their response to 4b they state in their last sentence that there is no evidence that indicates that *S. aureus* or enterococcal isolates are nonsusceptible to telavancin at 2 mcg/mL and 8 mcg/Ml. There also is no evidence that these organisms are susceptible as determined by clinical use of telavancin. In addition, these analyses were conducted at the time when the vancomycin interpretive criteria were ≤4 mcg/mL = susceptible, 8 mcg/mL = intermediate and ≥16 mcg/mL = resistant. Since that time the vancomycin interpretive criteria for *S. aureus* has changed to ≤2 mcg/mL = susceptible, 4 mcg/mL = intermediate, and ≥8 mcg/mL = resistant.

Fred Marsik, Ph.D.
Micro TL/HFD-520
10 Mar 09 FIN FJM

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/s/

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Kerry Snow
3/10/2009 10:04:48 AM
MICROBIOLOGIST

Frederic Marsik
3/10/2009 10:20:19 AM
MICROBIOLOGIST

# Product Quality Microbiology Review

**14 January 2009**

| | |
|---|---|
| **NDA:** | 22-110/N-000 BL<br>IR Response |
| **Drug Product Name** | |
| **Proprietary:** | VIBATIV™ |
| **Non-proprietary:** | Telavancin for Injection |
| **Drug Product Priority Classification:** | N/A. |
| **Review Number:** | 1 |

**Dates of Submission(s) Covered by this Review**

| Letter | Stamp | Review Request | Assigned to Reviewer |
|---|---|---|---|
| 30 OCT 2008 | 31 OCT 2008 | N/A | N/A |

| | |
|---|---|
| **Applicant/Sponsor** | |
| **Name:** | Theravance, Inc. |
| **Address:** | 901 Gateway Boulevard<br>South San Francisco, CA 94080 |
| **Representative:** | Rebecca Coleman |
| **Telephone:** | 650-808-6076 |
| **Name of Reviewer:** | John W. Metcalfe, Ph.D. |
| **Conclusion:** | Approvable. |

# Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** Applicant response to Information Request.

2. **SUBMISSION PROVIDES FOR:** Data to support a post constitution hold time of 12 hours at room temperature and 72 hours at refrigerated temperature.

3. **MANUFACTURING SITE:**
Boehringer Ingelheim
Ben Venue Laboratories, Inc. (BVL)
300 North Field Rd. P.O. Box 46568
Bedford, OH 44146

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:** b(4)
aseptic processing.

6. **PHARMACOLOGICAL CATEGORY:** Antibiotic.

B. **SUPPORTING/RELATED DOCUMENTS:** Microbiology Review of NDA 22-110/N-000 dated 18 June 2007.

C. **REMARKS:**
The subject submission is a response to an information request. Specifically, the submission contains data and a rationale for the post constitution in-use time periods.

**File Name:** N022110BLR1.doc

# Executive Summary

## I. Recommendations

**A. Recommendation on Approvability** – NDA 22-110/N-000 BL is approvable pending the applicant's adequate response to the microbiology comment on Page 7 of this review.

**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 solution is sterilized by [redacted] b(4)

**B. Brief Description of Microbiology Deficiencies** – The data submitted in the subject submission do not support the applicant's request to increase the post constitution room temperature holding time.

**C. Assessment of Risk Due to Microbiology Deficiencies** – A post constitution room temperature holding time of [redacted] may pose a risk to the microbiological quality of the final drug product. b(4)

## III. Administrative

**A. Reviewer's Signature** _____
John W. Metcalfe, Ph.D.

**B. Endorsement Block** _____
Stephen Langille, Ph.D.

**C. CC Block**
In DFS

# 4 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Microbiology-* 1

# Division of Anti-Infective and Ophthalmology Products
# Clinical Microbiology Review

**NDA:** 22-110, Telavancin for injection

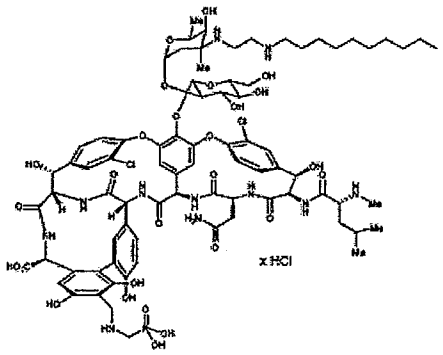
Date Company Submitted: December 6, 2006
Date received by CDER: December 6, 2006
Date Assigned: December 19, 2006
Date Completed:
Reviewer: Kerry Snow MS

**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:**
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**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 ( ) | 10 mg/kg every 48 hours |

b(4)

**DISPENSED:**
Rx

**PROPOSED INDICATION:**
Treatment of complicated skin and skin structure infections (cSSSI) caused by *Staphylococcus aureus* (methicillin-resistant and –susceptible strains) ( *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius* and *S. constellatus*), and *Enterococcus faecalis* (vancomycin-susceptible isolates only).

b(4)

**RELATED DOCUMENTS:**
IND 60,237

**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 complicated skin and skin-structure infections. 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:**

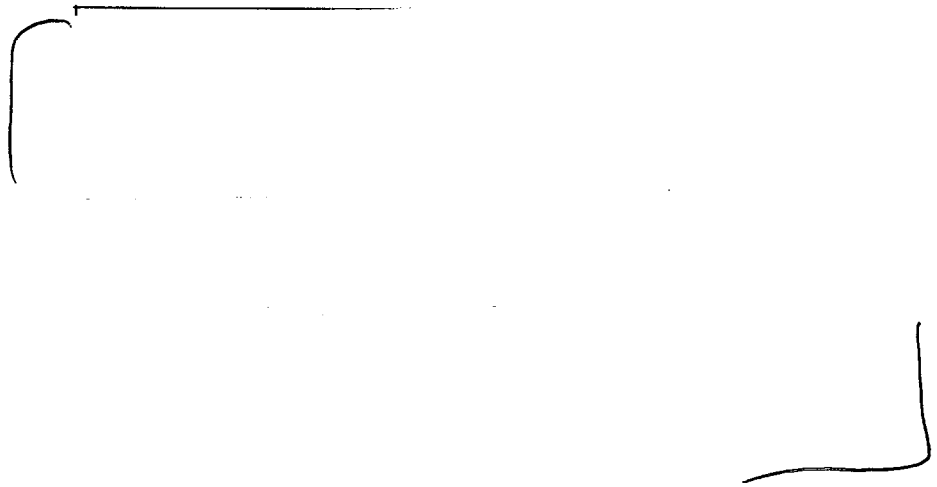
This review incorporates information from the original NDA submission (06 December 2006) and subsequent communications, including "Summary of Phase 2 Clinical Isolate MIC Re-test Data" (21 February 2007), "Telavancin Activity Against *Staphylococcus aureus* With Suspected Vancomycin Hetero-Resistance" (09 May 2007), and "A Preliminary Investigation of Telavancin Heteroresistance in Staphylococcus aureus" (24 May 2007).

**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 (below).

2) From the clinical microbiology perspective, the data provided by the Applicant do not support the Applicant's proposed breakpoints for the susceptibility breakpoints for listed indications (Table 1). Based on the reported in vitro activity of telavancin in large surveillance studies, pharmacokinetic/pharmacodynamic data, and clinical outcome information, the Agency proposes the following susceptibility breakpoints (summarized in Table 2):

Table 1: Susceptibility Breakpoints Proposed by the Applicant



b(4)

Table 2: Susceptibility Breakpoints Proposed by the Agency

| Pathogen | Susceptibility Interpretive Criteria | | | | | |
|---|---|---|---|---|---|---|
| | MIC (µg/ml) | | | Zone Diameter (mm) | | |
| | S | I | R | S | I | R |
| *Staphylococcus aureus* including methicillin-resistant isolates) | ≤1 | -- | -- | | -- | -- |
| *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus anginosus* group (*S. anginosus*, *S. intermedius*, *S. constellatus*) | ≤0.012 | -- | -- | | -- | -- |
| *Enterococcus faecalis* (vancomycin-susceptible only) | ≤1 | -- | -- | | -- | -- |

3) The Agency agrees with the Applicant's proposed in vitro susceptibility test quality control parameters as indicated in Table 3.

Table 3: CLSI Approved Quality Control Ranges

| QC Strain | Approved MIC Range (µg/ml) | Approved Disk Diffusion Range (mm) |
|---|---|---|
| S. aureus ATCC 29213 | 0.12-1 | n/a |
| S. aureus ATCC 25923 | n/a | 16-20 |
| E. faecalis ATCC 29212 | 0.12-0.5 | n/a |
| S. pneumoniae ATCC 49619 | 0.004-0.03 | 17-24 |

4) From the clinical microbiology perspective, submitted data and analysis supports the inclusion of the following organisms in the CLINICAL INDICATIONS section for telavancin:

*Staphylococcus aureus* (methicillin-resistant strains)
*Streptococcus pyogenes*
*Enterococcus faecalis* (vancomycin-susceptible isolates only)
*Streptococcus agalactiae*
*Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*)

5) From the clinical microbiology perspective, and based on the data presented by the Applicant, the Agency recommends the exclusion of the following organisms from the second list, for the reasons stated below.

b(4)

b(4)

## TABLE OF CONTENTS

## 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 peptidoglycan (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). While the second proposed mechanism of action, disruption of the microbial cell membrane, appears to play a role in the bactericidal activity of telavancin, it is unclear that this mechanism is 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 provided sufficient 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. While this second mechanism may contribute to a wider spectrum of activity and greater antimicrobial activity, compared to vancomycin and other glycopeptides (as proposed) data differentiating the contribution of each mechanism is modest.

### ANTIMICROBIAL SPECTRUM OF ACTIVITY

Data submitted from large prospective surveillance studies and other investigations of in vitro activity support the applicant's claim of activity against the pathogens generally associated with complicated skin and skin structure infections, including the organisms listed in the proposed indication for telavancin. MIC values for all tested strains of *S. aureus* (including strains resistant to other classes of antimicrobials, and strains with specific virulence profiles), *S. pyogenes*, *S. agalactiae*, *S. anginosus*, *S. constellatus*, *S. intermedius*, and vancomycin-susceptible *E. faecalis* were all below the attainable drug levels, discussed elsewhere in this review (see discussions of protein binding and human/animal PK/PD data). Telavancin MICs against vancomycin-intermediate *S. aureus* (VISA), heteroresistant vancomycin-intermediate *S. aureus* (hVISA), and vancomycin-resistant *S. aureus* (VRSA), in these studies, were lower than vancomycin and other comparator MICs. The clinical significance of this is not known.

### RESISTANCE STUDIES

The in vitro investigations, described above, indicate a low potential for the development of resistance to telavancin in selected species of the Gram positive pathogens sought in the indication for this application, either in terms of spontaneous emergence or as a result of selective pressure. One strain of Van A-type *E. faecalis* (MGH-01) appeared to demonstrate stable reduced susceptibility to telavancin, following selection on solid media. No isolates of *Streptococcus anginosus* group (*S. anginosus*, *S. intermedius*, and *S. constellatus*) were tested in

the in vitro studies of emergence of resistance to telavancin. In the pivotal clinical studies, no emergence of resistance to telavancin was noted.

The Applicant has provided sufficient 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 (only vancomycin-susceptible *E. faecalis* is listed), the data from resistance studies suggest a possible role for this resistance mechanism in staphylococcal species (e.g. vancomycin-resistant *S. aureus*). It is noted that resistant VanA-type enterococcal mutants were developed in passage studies. Since Van-A resistance is known to be transmissible via mobile elements, and vancomycin-resistant *S. aureus* (VRSA) possess the Van-A gene cluster, this data suggests a potential mechanism for the development of telavancin resistance in *S. aureus*.

Surveillance, regarding the development and spread of this resistance mechanism is warranted. *S. aureus* heteroresistance to telavancin was not observed in population analysis profile (PAP) investigations. The Agency requests a four-year surveillance study, as a Phase 4 commitment, designed to investigate the emergence of resistance of Gram positive pathogens to telavancin. Details of this investigation may be reported as a component of the annual report from the Applicant.

**ANTIMICROBIAL INTERACTION STUDIES**

The applicant has submitted date from time-kill studies, conducted to investigate the modest synergy observed in the checkerboard microdilution studies. No synergy between either telavancin and imipenem, or telavancin and cefepime, was observed against strains of MRSA and MSSA (ATCC 33591 and ATC 29213, respectively), in the time-kill studies. No antagonism was noted in any of the drug interaction investigations.

**EFFECTS OF MISCELLANEOUS FACTORS ON ACTIVITY**

Submitted data from 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. Human serum albumin), bactericidal activity consistently remains, at telavancin concentrations exceeding 4x MIC, against tested strains of Gram positive pathogens (*S. aureus* and *E. faecalis* strains).

Sufficient data was provided 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.

An investigation of a biofilm model was performed, designed to demonstrate the activity of telavancin against non-planktonic bacterial communities. The provided data supports 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 glycopeptide and some non-glycopeptide comparators in both respects.

The Applicant has 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. In addition, a prolonged PAE was demonstrated against *S. pyogenes* and *S. agalactiae*. PAE against strains of enterococcus was diminished, compared to the other tested pathogens, but vancomycin-sensitive E. faecalis demonstrated notable PAE (1.1 hours).

**BACTERICIDAL ACTIVITY**

The Applicant has provided data to support the claim of consistent bactericidal activity against the organisms included in the proposed indication, with the exception of vancomycin-susceptible *Enterococcus faecalis*. Bactericidal activity against enterococcal species did not meet the established criteria for bactericidal activity (MBC:MIC ratio of ≤ 4), but MBC values for these strains were superior to glycopeptide comparators and indicated some bactericidal activity.

Data from time-kill kinetic studies support a claim of rapid, bactericidal activity of telavancin against a variety of strains of *S. aureus*, including strains susceptible and non-susceptible to methicillin, and strains 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 strains of ß-hemolytic streptococci (*S. pyogenes* and *S. agalactiae*) was also demonstrated, but at low fixed concentrations activity was variable (i.e. concentrations representing $C_{min}$ for vancomycin in healthy adults dosed at 10 mg/kg).
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 $AUC_{(0\text{-}24)}$/MIC as the best PK/PD predictor of antimicrobial efficacy. Comparison of data from the mouse neutropenic thigh model and the mouse subcutaneous infection model suggest that immune status may play a minor role in telavancin efficacy.

### PHARMACOKINETIC / PHARMACODYNAMIC STUDIES

The applicant has provided data from a variety of studies to support the proposed pharmacokinetic parameters. Levels of telavancin measured in skin blister studies, including trough levels, are higher than the applicant's proposed telavancin susceptible breakpoint for all indicated organisms (*S. aureus*, vancomycin-susceptible *E. faecalis*, and Streptococcus spp. other than *S. pneumoniae*). 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).

## III. CLINICAL TRIALS

Data from post-amendment clinical trials indicate that telavancin is efficacious in infections involving pathogens in the proposed indication. 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 clinical trials, was low.

## IV. SUSCEPTIBILITY TEST METHODS

Broth microdilution methods were used for the determination of telavancin in vitro activity in all pivotal clinical studies, and surveillance studies. This data was the primary source of information in the development of provisional interpretive criteria and proposed quality control ranges. Correlation of microbroth dilution methods and disk diffusion methods are discussed elsewhere in this review. Investigations by the applicant suggest the correlation of microbroth dilution methods do not correlate reliably with agar dilution methods.

Alterations in standard testing parameters, employed in CLSI-approved microbroth dilution MIC testing, produced minimal changes in telavancin MIC for pathogens claimed in the proposed indication (*S. aureus*, *S. pyogenes*, *S. agalactiae*, *S. intermedius* group, and vancomycin-susceptible *E. faecalis*). Studied parameters included incubation time, $Ca^{2+}$ concentration, pH, inoculum size, and incubation in the presence of 5% $CO_2$. Investigations of multiple lots of Mueller-Hinton broth media suggested no significant performance differences. Similar investigations of Mueller-Hinton agar media suggested notable differences (particularly with regard to coagulase-negative staphylococcal species, *E. faecium*, and *S. pneumoniae*). No significant differences were noted in the comparison of telavancin disk lots, prepared by two separate manufacturers (BBL and Hardy). The use of solid media to test telavancin activity (e.g. disk diffusion method, agar dilution method) appears problematic and will require additional investigation. b(4)

Studies of the effect of Tween-80 in susceptibility testing methods suggest that the inclusion of the surfactant in microbroth techniques (e.g. methods using polystyrene plates) may reduce telavancin MIC values. Surfactants were not used in the investigations that support the provisional interpretive criteria and quality control ranges.

Data submitted by the applicant does not support the testing of vancomycin as a class-representative surrogate for telavancin.

Telavancin MIC distributions from clinical trials and survey studies are unimodal for *S. aureus* (both methicillin-susceptible and methicillin-resistant strains), the ß-hemolytic streptococci (*S. pyogenes* and *S. agalactiae*), and the *Streptococcus anginosus* group. Distributions derived from clinical studies, for these pathogens, are similar to those derived from survey studies. The upper range of MICs, from pathogens isolated during clinical studies, are 1-2 doubling dilutions less than the proposed susceptible breakpoints for *S. aureus*, *S. pyogenes*, *S. agalactiae*, and the *S. anginosus* group. $MIC_{range}$ values for isolates of these pathogens, tested in survey studies, also support susceptibility breakpoints 1-2 dilutions lower than proposed.

Based on in vitro data, pharmacokinetic/pharmacodynamic data, and data from clinical studies, the Agency recommends the following susceptibility breakpoints:

- *Staphylococcus aureus* (including methicillin-resistant isolates): ≤ 1 µg/ml
- *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus anginosus* group (*S. anginosus*, *S. intermedius*, *S. constellatus*): ≤ 0.012 µg/ml
- *Enterococcus faecalis* (vancomycin-susceptible only): ≤ 1 µg/ml

# 5 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Pharm/Tox-* 1A

## 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.

**COMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS (cSSSI)**

The principle pathogens associated with complicated skin and skin-structure infections (cSSSI) are *Staphylococcus aureus*, *Streptococcus pyogenes* (Group A ß-hemolytic streptococci), and *Streptococcus agalactiae* (Group B ß-hemolytic streptococci), but polymicrobial infections are not uncommon, especially in patients with an underlying comorbidity. These may include multidrug-resistant aerobic and anaerobic Gram positive and Gram negative bacteria. Skin and skin-structure infections have been defined as "complicated" when surgical intervention is required, the infectious process involves deeper soft tissue, and/or the patient suffers from a complicating condition (Nichols 1999).

Selection of appropriate empirical therapy is complicated by the emergence of drug-resistant pathogens, including both hospital-acquired and community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA), and macrolide-resistant *S. pyogenes*. Inappropriate therapy may lead to the development of resistant strains, and to clinical failure. Glycopeptides, once reserved as drugs of last resort, are now regularly administered in cases where MRSA is suspected or diagnosed. The more widespread use of glycopeptides has probably contributed to the emergence and spread of resistance in enterococci and to the appearance of vancomycin-resistant *S. aureus* and to strains demonstrating intermediate levels of glycopeptide susceptibility (both glycopeptide-intermediate *S. aureus* (GISA) and heteroresistant vancomycin-resistant *S. aureus* (hVISA)).

Treatment failures rates, related to vancomycin therapy, have been rising. This has been attributed to the slow bactericidal activity of vancomycin against *S. aureus* and to the development of heteroresistance (strains that test as susceptible in routine laboratory assays, but include resistant subpopulations) (Woods 2004). Recognition of the problems associated with vancomycin therapy have prompted research into semisynthetic glycopeptide and lipoglycopeptide derivates, including dalbavancin, oritavancin, and telavancin, as well as other antimicrobial classes with activity against resistant Gram positive pathogens (e.g. quinupristin-dalfopristin, linezolid, tigecycline, and ceftobiprole).

## *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).

The applicant conducted several studies to determine and characterize the antimicrobial mechanism of action of telavancin. Therapeutically relevant concentrations of the drug were considered in the design of these studies. The applicant asserts that relevant concentrations exist in the range between free concentrations (97 ± 14 µg/ml, peak, and 9.1 ± 3.4 µg/ml, trough, based on 10 mg/kg/day dosing) and protein-bound concentrations (telavancin is approximately 90% protein bound in human plasma). This assertion is based on *in vitro* data showing that the inhibitory and bactericidal activity of telavancin is only moderately affected by protein concentration, and that serum protein concentrations exceed those found in interstitial fluid (a relevant determination, with regard to the indications sought in this application).

*Reviewer's Note:* The *in vitro* data relevant to protein binding of telavancin and its effect on antimicrobial activity are discussed at length, elsewhere in this review, as are pharmacokinetic/pharmacodynamic data regarding telavancin activity in skin blister fluid. Data discussed in those sections support the Applicant's assertion that relevant therapeutic concentrations are greater than calculated free drug levels, in both serum and other body fluids. Although some of the data presented in those discussions indicate relatively low levels of available drug (e.g. trough free fraction of telavancin in skin blister fluid of 0.6 µg/ml [Study 107a; this submission]), this reviewer finds the concentrations tested in mechanism-of-action studies relevant and satisfactory for the purpose, based on conclusions of the studies in question, and comparisons to similar determinations with regard to parent compounds (e.g. vancomycin) and other lipoglycopeptides.

In an investigation of the effect of telavancin on peptidoglycan (PG) biosynthesis (Report 06-6424-MCB-01:this submission, Higgins 2005), inhibition of PG synthesis was demonstrated in all tested strains of *S. aureus*, including methicillin-susceptible (MSSA) and methicillin-resistant (MRSA) reference strains, and a glycopeptide-intermediately susceptible (GISA) isolate. Inhibition was also demonstrated in vancomycin-susceptible strains of *Enterococcus faecalis*. Telavancin was shown to inhibit PG biosynthesis at low concentrations and demonstrated 10-fold greater potency than vancomycin. At tested concentrations, telavancin demonstrated less than 25% inhibition of other macromolecular synthetic processes. Table 1 summarizes the results of testing against a strain of methicillin-resistant *Staphylococcus aureus* (ATCC 33591). Similar results were demonstrated with methicillin-susceptible *Staphylococcus aureus* and vancomycin-susceptible enterococcus species.

TABLE 1: Inhibition of Macromolecular Synthesis in *S. aureus*

| Antibiotic | MIC (µg/mL) | $IC_{50}$ (µg/mL) vs. Indicated Macromolecular Pathway† | | | |
|---|---|---|---|---|---|
| | | Peptidoglycan | Fatty Acid | RNA | Protein |
| Telavancin | 0.25 | 0.26 | > 2 | > 2 | > 2 |
| Vancomycin | 1 | 3.0 | > 32 | > 32 | 25.4 |
| Triclosan | 0.06 | > 1 | < 0.125 | > 1 | 0.63 |
| Rifampin | 0.015 | > 0.25 | > 0.25 | 0.015 | 0.14 |
| Linezolid | 2 | > 16 | > 16 | > 16 | 7.7 |

†*S. aureus* ATCC 33591

Source: 5.3.5.4.1.2 Table 1, this submission

Substrate-dependent inhibition of transglycosylase activity was demonstrated by measuring conversion of radiolabeled lipid II into trichloroacetic acid (TCA)-insoluble material in mid-exponential growth culture phases, in a variety of species and phenotypes (Table 2). Antimicrobial activity was measured in parallel. Comparative $IC_{50}$ values correlated well with MIC determinations. Telavancin inhibited PG biosynthesis in all species tested, with greater inhibition than both comparators (vancomycin and teicoplanin).

TABLE 2: Peptidoglycan Biosynthesis and Antibacterial Inhibitory Activities of Telavancin and Comparator Glycopeptides Against *S. aureus* and *E. faecalis*

| Organism | Relevant Genotype | Strain ID | telavancin | | vancomycin | | teicoplanin | |
|---|---|---|---|---|---|---|---|---|
| | | | $IC_{50}$† | MIC† | $IC_{50}$† | MIC† | $IC_{50}$† | MIC† |
| *S. aureus* | MSSA | ATCC 29213 | 0.12 | 0.25 | 1.9 | 1 | 1.0 | 0.5 |
| *S. aureus* | MRSA | ATCC 33591 | 0.26 | 0.25 | 3.0 | 1 | 2.4 | 0.5 |
| *S. aureus* | VISA | HIP 5836 | 2.4 | 1 | 21.1 | 4 | 48.1 | 4 |
| *E. faecalis* | VSE | BM4110* | 0.19 | 0.5 | 3.0 | 1 | 1.9 | 1 |
| *E. faecalis* | VRE-VanB | BM4323* | 9.0 | 8 | >64 | >64 | >64 | >64 |

†Units are µg/mL; $IC_{50}$s for PG synthesis are the geometric means from at least three experiments
*BM4323 is a constitutive expressing VanB strain derived from BM4110 (16).

Source: 5.3.5.4.1.2 Table 2, this submission

A substrate-dependent mechanism for telavancin was further supported by investigations involving antagonism of the drug's PG biosynthesis inhibition and antimicrobial activity by molar excess of the substrate analog N,N'-diacetyl-L-lysyl-D-alanyl-D-alanine (dKAA). In PG synthesis assays and cell-free assays for transglycosylase activity, increasing concentrations of dKAA inhibited the biosynthetic activity and antimicrobial potency of telavancin and vancomycin (Higgins 2005).

Hexapeptide derivatives of synthetic glycopeptides have been used in mechanism of action studies to demonstrate comparative affinities for proposed target residues (Allen 2002). The Applicant prepared THRX-881620, a des-*N*-methylleucyl (hexapeptide) derivative of telavancin to assess the contribution of the intact carboxylate binding pocket to telavancin activity and antimicrobial activity. In interactions with D-Ala-D-Ala cell wall precursors, THRX-881620 is incapable of forming one key hydrogen bond, relative to telavancin. Binding affinities of telavancin, vancomycin, and THRX-881620 for dKAA were determined by electrospray ionization mass spectrometry (ESI-MS) and affinity capillary electrophoresis (ACE) (Higgins 2005). The results are summarized in Table 3. The results are consistent with previously reported values for vancomycin (Allen 2002), and there is general agreement between methods. No formation of a

THRX-881620 – dKAA complex was detected by ACE. Vancomycin demonstrated approximately four- to six-fold greater affinity for the soluble cell wall surrogate than telavancin. Telavancin demonstrated approximately 25-fold greater affinity than THRX-881620.

TABLE 3: Solution Phase Binding Affinities of Telavancin and Comparators for dKAA

| Glycopeptide | $K_A$ ($M^{-1}$) Determined by Two Techniques[†] | |
|---|---|---|
| | ACE[a] | ESI-MS[b] |
| Vancomycin | $5.2 \times 10^5$ | $13.5 \times 10^5$ |
| Telavancin | $0.96 \times 10^5$ | $3.2 \times 10^5$ |
| THRX-881620 | BLQ[c] | $0.13 \times 10^5$ |

[†]Values shown are the means from three separate determinations.
[a]ACE, affinity capillary electrophoresis
[b]ESI-MS, electrospray ionization mass spectrometry
[c]BLQ, below the limit of quantitation

Source: 5.3.5.4.1.2 Table 3, this submission

In partitioning studies (Higgins 2005), telavancin was shown to preferentially associate with the cell membrane, relative to vancomycin (which preferentially associated with the bacterial cell wall peptidoglycan). The association is D-ala-D-ala-dependent (inhibited by the addition of molar excess of kKAA). The applicant has hypothesized that membrane targeting of telavancin may be associated with the lipophilic substitutions. The results are summarized in Table 4.

TABLE 4: Binding and Distribution of [$H^3$]-Telavancin and [$H^3$]-Vancomycin in MRSA Cellular Fractions

| Compound | dKAA (mM) | Nanograms Recovered[†] (% of Total) | % of Recovered Radioactivity Associated With Cellular Fractions | |
|---|---|---|---|---|
| | | | Peptidoglycan | Protoplasts |
| Telavancin | 0.0 | 30 (8%) | 23 | 77 |
| | 0.4 | 2.8 (0.7%) | 29 | 71 |
| Vancomycin | 0.0 | 13 (3.5%) | 95 | 5 |
| | 0.4 | 0.32 (0.09%) | 94 | 6 |

MRSA, *S. aureus* ATCC 33591

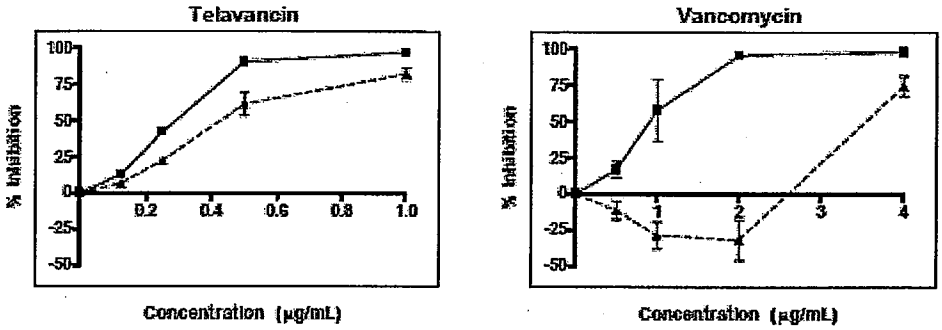
[†]Amount of compound recovered in the combined peptidoglycan and protoplast fractions derived from 75 mL of culture incubated with 375 ng radiolabeled compound.

Source: 5.3.5.4.1.2 Table 4, this submission

Membrane-associated partitioning of telavancin was further supported by investigations that demonstrated the binding affinity of telavancin to membrane anchored lipid II (Breukink 2006). Investigators demonstrated that telavancin has a 35-fold greater affinity for membrane anchored lipid II than for the soluble version. This differs from vancomycin, which has approximately equal binding affinity for both membrane-bound and soluble lipid II.

Telavancin inhibition of transglycosylase and transpeptidase activity was demonstrated in relevant bacterial species (including MSSA, MRSA, and VSE), and the level of activity was compared to that of vancomycin and teicoplanin (Report 06-6424-MCB-02: this submission, Debabov 2006). Telavancin was found to inhibit formation of both immature PG (nascent glycan strands) and mature PG (cross-linked PG), with approximately 10-fold greater potency than comparators. Comparison of the inhibition profiles of telavancin and vancomycin (Figure 1) demonstrated a significant difference in the inhibitory activities of the antimicrobials, with telavancin comparatively more active than vancomycin in the inhibition of immature PG biosynthesis.

Figure 1: Inhibition Patterns of Telavancin and Vancomycin in Assays for Transglycosylase and Transpeptidase Activity in *S. aureus*




*S. aureus* ATCC 29213. The solid lines indicate inhibition of synthesis of mature, cross-linked peptidoglycan and the broken lines indicate inhibition of synthesis of immature, uncross-linked peptidoglycan

Source: 5.3.5.4.1.2 Figure 5, this submission

The possibility of direct interaction of telavancin with transglycosylases (in the absence of the d-Ala-d-Ala substrate) was investigated. The investigators demonstrated that in the presence of alternative substrates (e.g. UDP-MurNac-L-Ala-D-Glu-L-Lys-D-Ala-D-Lac or UDP-MurNac-L-Ala-D-Glu-L-Lys-D-Ala), telavancin lacked inhibitory activity (Report 06-6424-MCB-03: this submission).

In addition to the inhibitory activities with regard to cell wall biosynthesis (described above), telavancin appears to demonstrate a second, separate mechanism of action involving disruption of the bacterial plasma membrane. The applicant investigated this proposed mechanism in a set of experiments designed to demonstrate: 1) increases in plasma membrane permeability, 2) membrane depolarization, and 3) ultrastructural modifications, all resulting from exposure to telavancin.

Propidium iodide staining was used to demonstrate telavancin activity on cell membrane permeability, in *S. aureus* ATCC 33591 cells. Permeability changes occurred in a dose- and time-dependent manner, with activity observed initially at telavancin concentrations of 2-16 µg/ml, and nearly complete permeabilization occurring with 64 µg/ml telavancin (at 30 minutes exposure). In these experiments, vancomycin caused no changes in *S. aureus* membrane permeability.

Changes in cell membrane potential, caused by exposure to telavancin, were investigated (Renelli 2006, Report 06-6424-MCB-06: this submission). Movement of a negatively charged oxonyl dye (bis-(1,30dibutylbarbituric acid) tremethine oxonol) was used to measure membrane depolarization. Depolarization was observed, following exposure of methicillin-resistant *S. aureus* cells, at 2-16 µg/ml telavancin, with concentrations of 64 µg/ml resulting in greater than 80% depolarization (at 30 minutes). Vancomycin-treated cells exhibited approximately 10% depolarization, following treatment with 64 µg/ml drug concentration. The telavancin-induced depolarization of bacterial cell membranes was shown to be both dose- and time-dependent.

Transmission electron microscopy (TEM) was used to determine the ultrastructural effects of telavancin treatment on methicillin-resistant *S. aureus* and vancomycin-resistant *E. faecalis* cells

(studies by MicroTEM, Inc. 2005; this submission). After treatment with either vancomycin or telavancin, cell wall defects were observed in both species. These defects, including abnormal septation, occurred after exposure to concentrations near MIC values for the species tested.

*Reviewer's note:* The original data indicate that although morphologic changes were seen in vancomycin-resistant *E. faecalis* (VRE) at 1 µg/ml (near MIC), severe morphologic changes for vancomycin-sensitive E. faecalis (VSE) were not seen at this concentration (the only tested concentration). Similarly, with regard to experiments involving methicillin-resistant *S. aureus* (MRSA), the researchers concluded that "In this preliminary study, it was apparent that severe morphologic effects were not occurring at the lowest TLV concentrations and the earliest (15 min) time points so the membrane intrusions and septal thickening were not always observed." Since treatment of VRE infections is not among the proposed indications for telavancin, and data for both MRSA and VSE appear inconclusive, TEM data will not be considered as supportive for the application.

*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). While the second proposed mechanism of action, disruption of the microbial cell membrane, appears to play a role in the bactericidal activity of telavancin, it is unclear that this mechanism is 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).

*Mechanism of Action Studies ~ Conclusions:*
The applicant has provided sufficient 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. While this second mechanism may contribute to a wider spectrum of activity and greater antimicrobial activity, compared to vancomycin and other glycopeptides (as proposed) data differentiating the contribution of each mechanism is modest.

## ANTIMICROBIAL SPECTRUM OF ACTIVITY

Telavancin is active against a broad range of Gram positive bacteria, including all pathogens sought in the proposed indication. The applicant has assembled data from nineteen studies, including two large, prospective surveys. The results for indicated pathogens are summarized in the tables and figures below.

The in vitro activity of telavancin was assessed against more than 12,000 clinical isolates, from 165 centers worldwide. The majority (> 11,000) of tested isolated were Gram positive pathogens (including > 5,000 S. aureus, > 800 ß-hemolytic streptococci, and > 300 viridans group streptococci). The applicant has provided tabulated data, listing isolates by organism class and geographic region. Isolates in retrospective surveillance studies included challenge strains of specific interest (e.g. methicillin-resistant *S. aureus*, vancomycin-intermediate *S. aureus*, vancomycin-resistant *S. aureus*, vancomycin-resistant enterococci, and MRSA strains positive for

the Panton-Valentine leukocidin toxin). Surveillance studies also included studies of specific genotypes, including defined staphylococcal strains (e.g. macrolide-resistant *ermA* and *ermC*, and linezolid-nonsusceptible strains with 23S rRNA mutations) and enterococcal strains (e.g. VanA-, B-, C1-, C2/3-, D-, E-, and G-type resistance).

Studies included isolates from various sources, including bloodstream, respiratory, skin and skin structure, and wound (Table 1). Most isolates, assayed in the retrospective studies, were taken from stocks of relatively recent collection (from 1999 or more recent).

The majority of relevant isolates were tested using broth microdilution methods, according to CLSI-approved methodology. Stock solutions of telavancin were prepared with either low initial concentrations of water or using acidified 50% aqueous DMSO as a solvent, due to the low solubility of telavancin in water. In solutions utilizing DMSO, the final concentration of solvent was <1% in media containing ≤ 16 µg/ml telavancin. Assays conducted in the two large prospective surveys, and in Phase 2 and Phase 3 clinical trials, employed frozen panels manufactured by TREK Diagnostics (Cleveland, Ohio). Frozen panels were also used in the development of MIC quality control parameters. MIC and disk diffusion methodologies, as well as the development of quality control procedures for both assays, are discussed in greater detail elsewhere in this review.

*Reviewer's note:* In a communication dated 9 March, 20007, the Applicant informed the agency that, contrary to information included in the original application, a wetting agent (polysorbate 80) was added to the inoculating water, used in the preparation of the frozen panel assays reported in Phase 2 studies. In early studies of telavancin in vitro activity, addition of the wetting agent was determined to have minimal impact on MIC values, and a decision was made to perform MIC testing without such an agent (CLSI methods advise against using wetting agents). Broth microdilution testing in Phase 3 clinical studies, prospective and retrospective surveillance studies, and MIC quality control studies were performed without polysorbate 80 (P80) added to the inoculating water. In the assays in which P80 was mistakenly added (two Phase 2 clinical studies), susceptibility tests were repeated, using frozen panels inoculated without the addition of P80. With regard to the repeated tests, only data from the assays performed without the addition of P80 are considered in this review.

Table 1: Specimen Sources of Clinical Isolates in Two Prospective Surveys of Telavancin Activity

| Organism | Body Site | US Surveillance[1] N | US Surveillance[1] % | Europe Surveillance[2] N | Europe Surveillance[2] % |
|---|---|---|---|---|---|
| *S. aureus* | Bloodstream | 405 | 17.6 | 402 | 22.5 |
| | Respiratory | 518 | 22.5 | 379 | 21.2 |
| | Skin and Skin Structure | 422 | 18.4 | 479 | 26.8 |
| | Wound[3] | 891 | 38.8 | 489 | 27.4 |
| | Other/Unknown | 63 | 2.7 | 36 | 2.0 |
| | Total | 2,299 | | 1,785 | |
| CoNS | Bloodstream | 359 | 96.5 | 200 | 84.7 |
| | Skin and Skin Structure | 5 | 1.3 | 13 | 5.5 |
| | Wound | 0 | 0 | 12 | 5.1 |
| | Other/Unknown | 8 | 2.2 | 11 | 4.7 |
| | Total | 372 | | 236 | |
| β-hemolytic streptococci | Bloodstream | 60 | 41.7 | 34 | 26.8 |
| | Skin and Skin Structure | 30 | 20.8 | 46 | 36.2 |
| | Wound | 53 | 36.8 | 36 | 28.3 |
| | Other/Unknown | 1 | 0.7 | 11 | 8.7 |
| | Total | 144 | | 127 | |
| Viridans group streptococci | Bloodstream | 69 | 67.6 | 40 | 59.7 |
| | Skin and Skin Structure | 10 | 9.8 | 19 | 28.4 |
| | Wound | 18 | 17.6 | 8 | 11.9 |
| | Other/Unknown | 5 | 4.9 | 0 | 0.0 |
| | Total | 102 | | 67 | |
| *S. pneumoniae* | Bloodstream | 106 | 38.4 | 58 | 32.4 |
| | Respiratory | 155 | 56.2 | 103 | 57.5 |
| | Other/Unknown | 15 | 5.4 | 18 | 10.1 |
| | Total | 276 | | 179 | |
| *Enterococcus* spp. | Bloodstream | 472 | 59.4 | 354 | 43.6 |
| | Skin and Skin Structure | 117 | 14.7 | 211 | 26 |
| | Wound | 190 | 23.9 | 225 | 27.7 |
| | Other/Unknown | 16 | 2.0 | 22 | 2.7 |
| | Total | 795 | | 812 | |
| Total | | 3,988 | | 3,206 | |

[1] 2004-2005 US Surveillance (75)
[2] 2004-2005 EU Surveillance (72)
[3] Wounds may include SSSI and other sites of infection

Source: 5.3.5.4.1.4 Table 6, this submission

Tables 2 through 6 summarize the in vitro activity (pooled data) of telavancin against organisms claimed in the proposed indication. MIC values, in all cases, are normally distributed and the majority of isolates fall within a narrow range of values.

Telavancin was active against all tested staphylococcal species (Tables 2 and 3). $MIC_{90}$ values were generally within one doubling dilution of $MIC_{50}$ values. Against all comparators (e.g. vancomycin, teicoplanin, linezolid, daptomycin, quinupristin/dalfopristin, trimethoprim/sulfamethoxazole, gentamicin) telavancin was generally more active (data not shown). No geographic differences were noted in the two large prospective studies (one performed on isolates collected in the United States, the other performed on isolates collected in Europe and Israel). Histograms, compiled from pooled data, suggest normal distribution MIC values for *S. aureus* isolates, including all pooled isolates as well as the subset of methicillin-resistant *S. aureus*, with similar distributions for both groups (Figure 1). More than 90% of the MIC values obtained for *S. aureus* isolates are in the range ( ) µg/ml. b(4)

In tests of vancomycin non-susceptible *S. aureus* isolates (n = 101), MIC values for vancomycin-intermediate *S. aureus* (VISA) ranged from / µg/ml. Greater than 95% of isolates demonstrated MICs of 2 µg/ml or less (Figure 2). Three vancomycin-resistant S. aureus (VRSA) were tested multiple times by various investigators. MIC values for VRSA ranged from / µg/ml. No data is available with regard to hetero-vancomycin-intermediate *S. aureus* in vitro activity (see Review's Note under **RESISTANCE STUDIES**, below). b(4)

Investigations of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) demonstrated activity of telavancin against USA 300 strains (PVL+ and SCC*mec* Type IV) and other CA-MRSA strains (PVL- and SCC*mec* Type II, IV, or Nontypeable) (data not shown). In these studies, MIC values ranged from 0.25 to 1 µg/ml, with $MIC_{50}$ and $MIC_{90}$ values ≤ 1 µg/ml.

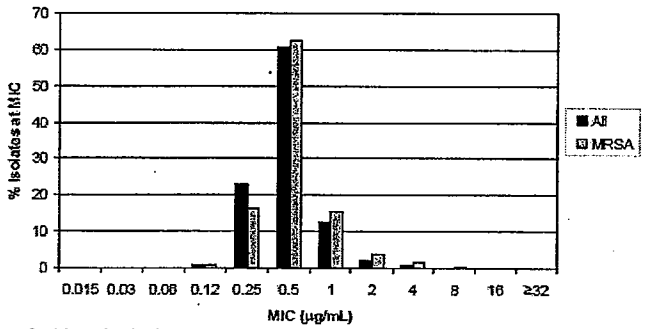
Table 2: Summary of Telavancin In Vitro Susceptibility Data for Claimed Organisms

| Organism (Phenotype[1]) | Study No. | N | No. of isolates inhibited at Concentration (µg/mL) | | | | | | | | | | | | MIC[2] (µg/mL) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | ≤0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | ≥ 32 | Range[3] | 50%[4] | 90%[5] |
| *Staphylococcus aureus* (All)[6] | 1 | 517 | | | | 21 | 435 | 51 | 8 | | 2 | | | | | 0.25 | 0.5 |
| | 2 | 2209 | | 1 | 10 | 462 | 1536 | 262 | 28 | | | | | | | 0.25 | 0.5 |
| | 3 | 1785 | 3 | 1 | 4 | 607 | 970 | 176 | 24 | | | | | | | 0.25 | 0.5 |
| | 6 | 80 | | | | 2 | 20 | 33 | 5 | | | | | | | 0.5 | 0.5 |
| | 7 | 75 | | | | 1 | 35 | 37 | 2 | | | | | | | 0.5 | 0.5 |
| | 9 | 52 | | | | 7 | 32 | 8 | 2 | 1 | 2 | | | | | 0.25 | 0.5 |
| | 10 | 75 | | | | | 4 | 11 | 22 | 37 | | 1 | | | | 2 | 2 |
| | 12 | 100 | | | 2 | 37 | 58 | 3 | | | | | | | | 0.25 | 0.25 |
| | 14 | 88 | | | 29 | 42 | 11 | 1 | | | 2 | | 1 | | | 0.12 | 0.25 |
| | 15 | 39 | | | | 1 | 8 | 18 | 9 | 2 | 1 | | | | | 0.5 | 1 |
| | 16 | 60 | | | | | 15 | 43 | 2 | | | | | | | 0.5 | 0.5 |
| | Total | 5,148 | 3 | 2 | 45 | 1,190 | 3,124 | 643 | 102 | 40 | 7 | 1 | 1 | | | 0.25 | 0.5 |
| *Staphylococcus aureus* (Methicillin-S) | 1 | 275 | | | | 13 | 233 | 26 | 3 | | | | | | | 0.25 | 0.5 |
| | 2 | 1217 | | 1 | 6 | 268 | 782 | 172 | 10 | | | | | | | 0.25 | 0.5 |
| | 3 | 1238 | 3 | 1 | 3 | 491 | 689 | 83 | 8 | | | | | | | 0.25 | 0.25 |
| | 6 | 30 | | | | | 3 | 25 | 2 | | | | | | | 0.5 | 0.5 |
| | 7 | 33 | | | | 1 | 19 | 12 | 1 | | | | | | | 0.25 | 0.5 |
| | 9 | 17 | | | | 4 | 13 | | | | | | | | | 0.25 | 0.25 |
| | 10 | 13 | | | | | 1 | 3 | 1 | 8 | | | | | | 2 | 2 |
| | 12 | 60 | | | 1 | 28 | 30 | 1 | | | | | | | | 0.25 | 0.25 |
| | 14 | 37 | | | 15 | 17 | 4 | 1 | | | | | | | | 0.12 | 0.25 |
| | Total | 2,920 | 3 | 2 | 25 | 820 | 1,734 | 303 | 25 | 8 | | | | | | 0.25 | 0.5 |
| *Staphylococcus aureus* (Methicillin-R)[6] | 1 | 242 | | | | 8 | 202 | 25 | 5 | | 2 | | | | | 0.25 | 0.5 |
| | 2 | 1082 | | | 4 | 196 | 774 | 90 | 18 | | | | | | | 0.25 | 0.25 |
| | 3 | 547 | | | 1 | 118 | 301 | 113 | 16 | | | | | | | 0.25 | 0.5 |
| | 6 | 30 | | | | 2 | 17 | 8 | 3 | | | | | | | 0.25 | 0.5 |
| | 7 | 42 | | | | | 16 | 25 | 1 | | | | | | | 0.5 | 0.5 |
| | 9 | 35 | | | | 3 | 19 | 8 | 2 | 1 | 2 | | | | | 0.25 | 1 |
| | 10 | 62 | | | | | 3 | 8 | 21 | 29 | | 1 | | | | 1 | 2 |
| | 12 | 40 | | | 1 | 9 | 28 | 2 | | | | | | | | 0.25 | 0.25 |
| | 14 | 49 | | | 14 | 25 | 7 | | | | 2 | | 1 | | | 0.12 | 0.25 |
| | 15 | 39 | | | | 1 | 8 | 18 | 9 | 2 | 1 | | | | | 0.5 | 1 |
| | 16 | 60 | | | | | 15 | 43 | 2 | | | | | | | 0.5 | 0.5 |
| | Total | 2,228 | | | 20 | 360 | 1,380 | 340 | 77 | 32 | 7 | 1 | 1 | | | 0.25 | 0.5 |

Source: 5.3.5.4.1.4 Table 18, this submission

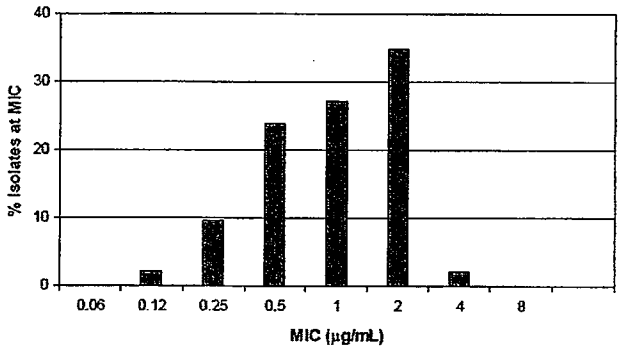
b(4)

Figure 1: Telavancin MIC Distributions for All *S. aureus* (n = 5,148) and MRSA (n = 2,228) Survey Isolates




Source: 5.3.5.4.1.4 Figure 2, this submission

Figure 2: Telavancin MIC Distributions for 92 VISA Isolates (Vancomycin MIC Values = 4 – 8 µg/ml)




Source: 5.3.5.4.1.4 Figure 1, this submission

The applicant has submitted an analysis of putative heteroresistant vancomycin-intermediate *S. aureus* (hVISA) included in the Telavancin Combined Database, to describe telavancin activity against that specific sub-population. Twenty-six hVISA isolates, obtained from the repository of the Network on Antimicrobial Resistance in *S. aureus* (NARSA) were included in the analysis. All 26 were identified as methicillin-resistant *S. aureus* (MRSA). Eight of the 26 identified isolates tested as VISA by investigators reporting MIC values in surveillance studies. The two populations (hVISA n=26, hVISA n=18) were analyzed separately. The results are summarized in Table 6.

Table 6: Summary of the In Vitro Activity of Telavancin against hVISA and MRSA Isolates

| Organism (no. tested) | Agent | MIC (µg/mL) | | | |
|---|---|---|---|---|---|
| | | Range | Mode | 50% | 90% |
| hVISA (26) | Telavancin | ( | 0.5 | 0.5 | 1 |
| | Vancomycin | | 4 | 4 | 8 |
| hVISA (18) | Telavancin | | 0.5 | 0.5 | 1 |
| | Vancomycin | | 4 | 4 | 4 |
| MRSA (1082)[a] | Telavancin | | 0.25 | 0.25 | 0.25 |
| | Vancomycin | ) | 1 | 1 | 1 |

b(4)

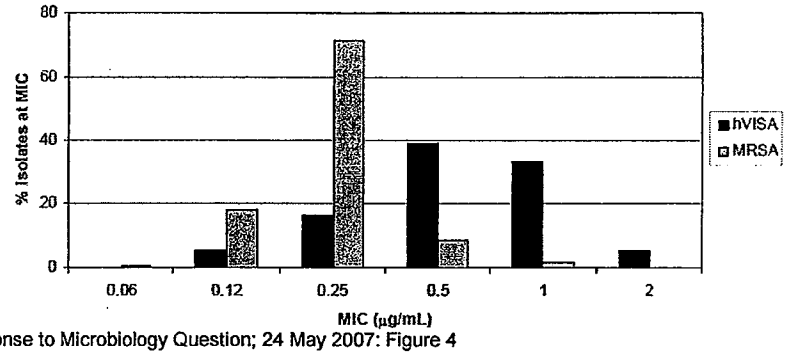
[a] 2004-2005 Telavancin US Surveillance

Source: Response to Microbiology Question; 24 May 2007: Table 2

The $MIC_{range}$ of telavancin against 18 strains identified as hVISA was ( ) µg/ml, similar to the $MIC_{range}$ for all MRSA, but shifted approximately 1 doubling dilution to the right (decreased susceptibility) (Figure 1). The data suggests greater potency than vancomycin against identified hVISA isolates, but reduced potency, compared to pooled data for all MRSA isolates.

b(4)

Figure 1: Telavancin MIC Population Distributions for NARSA hVISA (n = 18) and MRSA (n = 1082) Isolates




Source: Response to Microbiology Question; 24 May 2007: Figure 4

In investigations of in vitro activity against species of coagulase-negative staphylococci (CoNS) (Table 3), telavancin was highly active against strains of *S. epidermidis* and *S. haemolyticus*. No difference in MIC values was noted for methicillin-resistant S. epidermidis, compared to all tested isolates ($MIC_{50}$ and $MIC_{90}$ = 0.5 µg/ml). Vancomycin-intermediate CoNS were investigated in two studies, with telavancin MIC values ranging from ( \ µg/ml (n = 10). Species of CoNS are not claimed as a primary indication in this application. b(4)

Table 3: Summary of Telavancin In Vitro Susceptibility Data for Claimed Organisms (cont'd)

| Organism (Phenotype[1]) | Study No. | N | No. of Isolates Inhibited at Concentration (µg/mL) | | | | | | | | | | | | MIC[2] (µg/mL) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | ≤0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | ≥32 | Range[3] | 50%[4] | 90%[5] |
| *Staphylococcus epidermidis* (All)[6] | 1 | 98 | | | | 2 | 42 | 43 | 7 | 2 | | | | | | 0.5 | 0.5 |
| | 2 | 214 | | | 1 | 9 | 151 | 50 | 3 | | | | | | | 0.25 | 0.5 |
| | 3 | 130 | | | 1 | 24 | 92 | 10 | 2 | 1 | | | | | | 0.25 | 0.25 |
| | 6 | 60 | | | | 5 | 24 | 25 | 4 | 2 | | | | | | 0.5 | 0.5 |
| | 7 | 38 | | | | | 9 | 24 | 3 | | | | | | | 0.5 | 0.5 |
| | 9 | 41 | | | 1 | 6 | 33 | 1 | | | | | | | | 0.25 | 0.25 |
| | 14 | 6 | | | 1 | 5 | | | | | | | | | | ND[7] | ND |
| | 15 | 7 | | | | | 2 | 4 | | 1 | | | | | | ND | ND |
| | 19 | 93 | | | | | 11 | 65 | 18 | 2 | | | | | | 0.5 | 1 |
| | Total | 686 | | | 4 | 51 | 364 | 222 | 37 | 8 | | | | | | 0.25 | 0.5 |
| *Staphylococcus epidermidis* (Methicillin-R)[8] | 1 | 51 | | | | | 22 | 22 | 5 | 2 | | | | | | 0.5 | 1 |
| | 2 | 171 | | | | 3 | 127 | 39 | 2 | | | | | | | 0.25 | 0.5 |
| | 3 | 103 | | | 1 | 18 | 72 | 10 | 2 | | | | | | | 0.25 | 0.5 |
| | 6 | 30 | | | | | 15 | 11 | 2 | 2 | | | | | | 0.25 | 1 |
| | 7 | 25 | | | | | 7 | 15 | 3 | | | | | | | 0.5 | 1 |
| | 9 | 27 | | | 1 | 4 | 22 | | | | | | | | | 0.25 | 0.25 |
| | 14 | 6 | | | 1 | 5 | | | | | | | | | | ND | ND |
| | 15 | 7 | | | | | 2 | 4 | | 1 | | | | | | ND | ND |
| | 19 | 74 | | | | | 7 | 50 | 15 | 2 | | | | | | 0.5 | 1 |
| | Total | 494 | | | 3 | 30 | 274 | 151 | 29 | 7 | | | | | | 0.25 | 0.5 |
| *Staphylococcus haemolyticus* (All) | 1 | 2 | | | | | 2 | | | | | | | | | ND | ND |
| | 2 | 14 | | | | 2 | 8 | 4 | | | | | | | | 0.25 | 0.5 |
| | 3 | 25 | | | | 6 | 15 | 3 | | 1 | | | | | | 0.25 | 0.5 |
| | 6 | 25 | | | | | 6 | 18 | 1 | | | | | | | 0.5 | 0.5 |
| | 7 | 16 | | | | 1 | 4 | 11 | | | | | | | | 0.5 | 0.5 |
| | 9 | 12 | | | | 2 | 6 | 3 | 1 | | | | | | | 0.25 | 0.5 |
| | 14 | 2 | | | | 2 | | | | | | | | | | ND | ND |
| | 15 | 5 | | | | | 2 | 3 | | | | | | | | ND | ND |
| | 19 | 6 | | | 1 | | 1 | 3 | 1 | | | | | | | ND | ND |
| | Total | 107 | | | 1 | 13 | 44 | 45 | 3 | 1 | | | | | | 0.25 | 0.5 |

b(4)

Source: 5.3.5.4.1.4 Table 18, this submission

Data from investigations of the in vitro activity of telavancin against streptococcal species is summarized in Tables 4 and 5. Against all streptococcal species, telavancin $MIC_{90}$ values ranged from 0.06 - 0.12 µg/ml. Activity against streptococcal isolates (including *S. pyogenes*, *S. agalactiae*, and the *S. anginosus* group) exceeded that of vancomycin, daptomycin, linezolid, and levofloxacin (data not shown). Histograms of MIC distributions for ß-hemolytic streptococci (*S. pyogenes* in Figure 3, and *S. agalactiae* in Figure 4) show unimodal, normal distributions. The histogram for the combined data from investigations of isolates in the *S. anginosus* group suggests bimodal distribution but the total number of tested isolates is small (n = 57). Intrinsic or acquired glycopeptide resistance mechanisms have not been described in this group.

In the two large, prospective studies, telavancin demonstrated a high level of activity against *Streptococcus pneumoniae*, with an overall $MIC_{90}$ of 0.03 µg/ml (exceeding most comparators, including vancomycin, daptomycin, linezolid, and levofloxacin). The measured activity was independent of susceptibility to penicillin. *Streptococcus pneumoniae* is not included in the primary indications in this application.

Table 4: Summary of Telavancin In Vitro Susceptibility Data for Claimed Organisms (cont'd)

| Organism (Phenotype[1]) | Study No. | N | No. of Isolates Inhibited at Concentration (µg/mL) | | | | | | | | | | | MIC[2] (µg/mL) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | ≤ 0.008 | 0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | Range[3] | 50%[4] | 90%[5] |
| *Streptococcus pyogenes* (All) | 1 | 30 | | 4 | 23 | 3 | | | | | | | | | 0.03 | 0.03 |
| | 2 | 68 | | 8 | 49 | 9 | 2 | | | | | | | | 0.03 | 0.06 |
| | 3 | 54 | | 8 | 41 | 4 | 1 | | | | | | | | 0.03 | 0.03 |
| | 6 | 42 | | | 4 | 15 | 23 | | | | | | | | 0.12 | 0.12 |
| | 7 | 35 | | 5 | 20 | 9 | 1 | | | | | | | | 0.03 | 0.06 |
| | 12 | 60 | | | 50 | 10 | | | | | | | | | 0.03 | 0.06 |
| | 14 | 1 | | | | 1 | | | | | | | | | ND | ND |
| | 19 | 122 | 10 | 9 | 74 | 22 | 7 | | | | | | | | 0.03 | 0.06 |
| | Total | 412 | 10 | 34 | 261 | 73 | 34 | | | | | | | | 0.03 | 0.06 |
| *Streptococcus agalactiae* (All) | 1 | 44 | | | 6 | 38 | | | | | | | | | 0.06 | 0.06 |
| | 2 | 45 | | | 11 | 33 | 1 | | | | | | | | 0.06 | 0.06 |
| | 3 | 48 | 1 | | 7 | 38 | 2 | | | | | | | | 0.06 | 0.06 |
| | 6 | 30 | | | | | 30 | | | | | | | | 0.12 | 0.12 |
| | 7 | 30 | | | | 20 | 10 | | | | | | | | 0.06 | 0.12 |
| | 12 | 60 | | | 2 | 56 | 2 | | | | | | | | 0.06 | 0.06 |
| | 14 | 1 | | | | 1 | | | | | | | | | ND | ND |
| | 19 | 81 | | | 7 | 73 | 1 | | | | | | | | 0.06 | 0.06 |
| | Total | 339 | 1 | | 33 | 259 | 46 | | | | | | | | 0.06 | 0.12 |
| *Streptococcus anginosus* (All) | 3 | 1 | | | 1 | | | | | | | | | | ND | ND |
| | 7 | 4 | | | 4 | | | | | | | | | | ND | ND |
| | 20 | 7 | | | | | 7 | | | | | | | | ND | ND |
| | Total | 12 | | | 5 | | 7 | | | | | | | | 0.12 | 0.12 |
| *Streptococcus constellatus* (All) | 1 | 5 | | | 4 | 1 | | | | | | | | | ND | ND |
| | 19 | 1 | | | | 1 | | | | | | | | | ND | ND |
| | 20 | 9 | | | | | 9 | | | | | | | | ND | ND |
| | Total | 15 | | | 4 | 2 | 9 | | | | | | | | 0.12 | 0.12 |

Source: 5.3.5.4.1.4 Table 18, this submission

b(4)

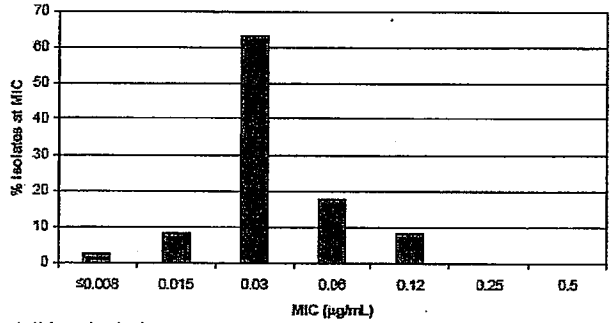
Table 5: Summary of Telavancin In Vitro Susceptibility Data for Claimed Organisms (cont'd)

| Organism (Phenotype[1]) | Study No. | N | No. of Isolates Inhibited at Concentration (µg/mL) | | | | | | | | | | | MIC[2] (µg/mL) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | ≤0.008 | 0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | Range[3] | 50%[4] | 90%[5] |
| *Streptococcus intermedius* (All) | 1 | 16 | | | 11 | 4 | 1 | | | | | | | | 0.03 | 0.06 |
| | 2 | 2 | | | 1 | 1 | | | | | | | | | ND | ND |
| | 7 | 1 | | | 1 | | | | | | | | | | ND | ND |
| | 19 | 2 | | | 2 | | | | | | | | | | ND | ND |
| | 20 | 9 | | | | | 8 | 1 | | | | | | | ND | ND |
| | Total | 30 | | | 15 | 5 | 9 | 1 | | | | | | | 0.03 | 0.12 |
| *Streptococcus dysgalactiae* (All) | 1 | 1 | | | | 1 | | | | | | | | | ND | ND |
| | 2 | 10 | | | 8 | 2 | | | | | | | | | 0.03 | 0.6 |
| | 3 | 9 | 1 | | 7 | | 1 | | | | | | | | ND | ND |
| | 6 | 5 | | | | 1 | 4 | | | | | | | | ND | ND |
| | 14 | 1 | | | 1 | | | | | | | | | | ND | ND |
| | Total | 26 | 1 | | 16 | 4 | 5 | | | | | | | | 0.03 | 0.12 |
| *Streptococcus mitis* (All) | 1 | 1 | | | | 1 | | | | | | | | | ND | ND |
| | 2 | 1 | | | | | 1 | | | | | | | | ND | ND |
| | 7 | 10 | 1 | 1 | 2 | 5 | 1 | | | | | | | | 0.06 | 0.06 |
| | 19 | 3 | | 1 | 1 | 1 | | | | | | | | | ND | ND |
| | 20 | 6 | | | | | 6 | | | | | | | | ND | ND |
| | Total | 21 | 1 | 2 | 3 | 7 | 8 | | | | | | | | 0.06 | 0.12 |
| *Streptococcus oralis* (All) | 1 | 1 | | | 1 | | | | | | | | | | ND | ND |
| | 7 | 9 | | 1 | 1 | 6 | 1 | | | | | | | | ND | ND |
| | 19 | 1 | | | | 1 | | | | | | | | | ND | ND |
| | Total | 11 | | 1 | 2 | 7 | 1 | | | | | | | | 0.06 | 0.06 |
| *Streptococcus* spp. Group G (All) | 1 | 1 | | | | 1 | | | | | | | | | ND | ND |
| | 2 | 16 | | | 8 | 8 | 1 | 1 | | | | | | | 0.06 | 0.12 |
| | 3 | 15 | | | 9 | 5 | | 1 | | | | | | | 0.03 | 0.06 |
| | 6 | 5 | | | | 2 | 3 | | | | | | | | ND | ND |
| | Total | 39 | | | 17 | 16 | 4 | 2 | | | | | | | 0.06 | 0.12 |

Source: 5.3.5.4.1.4 Table 18, this submission

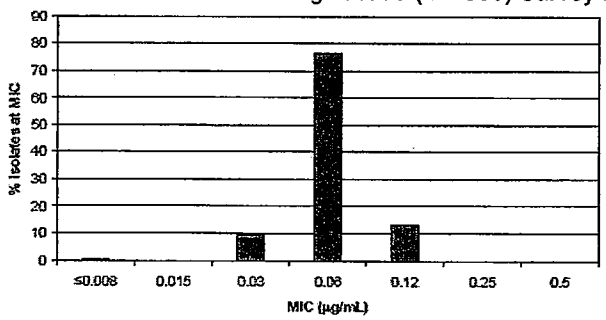
b(4)

Figure 3: Telavancin MIC Distributions for All *S. pyogenes* (n = 412) Survey Isolates



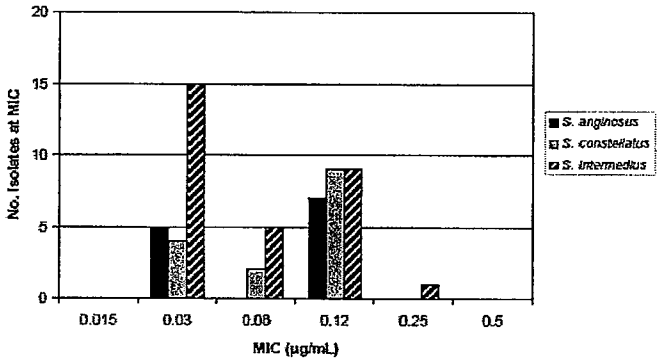

Source: 5.3.5.4.1.4 Figure 4, this submission

Figure 4: Telavancin MIC Distributions for All *S. agalactiae* (n = 339) Survey Isolates




Source: 5.3.5.4.1.4 Figure 5, this submission

Figure 5: Telavancin MIC Distributions for Survey Isolates of Principal Species within the *S. anginosus* Group (n = 57)




Source: 5.3.5.4.1.4 Figure 9, this submission

The proposed indication for telavancin includes vancomycin-susceptible isolates of *Enterococcus faecalis*. Data from investigations of telavancin in vitro activity against enterococcal species is summarized in Table 6. Data from surveillance studies include results for a substantial number of glycopeptide-resistant *Enterococcus* species (*E. faecium* and *E. faecalis*), tested to determine the activity of telavancin against resistant enterococcal phenotypes. The inclusion of these isolates explains the relatively high number of isolates with MIC values ≥ 4 µg/ml in Table 6. MICs of ls *E. faecalis* isolates, tested during clinical trails (discussed below), did not exceed 1 µg/ml.

Table 6: Summary of Telavancin In Vitro Susceptibility Data for Claimed Organisms (cont'd)

| Organism (Phenotype[1]) | Study No. | N | No. of Isolates Inhibited at Concentration (µg/mL) | | | | | | | | | | | | | MIC[2] (µg/mL) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 0.008 | 0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | ≥32 | Range[3] | 50%[4] | 90%[5] |
| *Enterococcus faecalis* (All) | 1 | 152 | | | | | | 29 | 87 | 10 | 2 | 3 | 18 | 3 | | [redacted] | 0.5 | 8 |
| | 2 | 458 | | | | | 7 | 87 | 256 | 102 | 4 | 5 | 14 | 3 | | | 0.5 | 1 |
| | 3 | 450 | | | | 4 | 41 | 121 | 234 | 18 | 6 | 6 | 20 | | | | 0.5 | 1 |
| | 6 | 50 | | | | 1 | 2 | 11 | 19 | 5 | 7 | 5 | | | | | 0.5 | 2 |
| | 7 | 30 | | | | | | 6 | 10 | 13 | | 1 | | | | | 0.5 | 1 |
| | 10 | 62 | | | | | | 3 | 5 | 19 | 17 | 1 | 7 | 8 | 2 | | 2 | 16 |
| | 12 | 80 | | 1 | 1 | 1 | 4 | 44 | 25 | | | 3 | 1 | | | | 0.25 | 0.5 |
| | 14 | 11 | | | | 3 | 1 | 5 | | 1 | 1 | | | | | | 0.25 | 1 |
| | 19 | 119 | | | | | | 4 | 10 | 73 | 10 | 2 | 12 | 7 | 1 | | 1 | 8 |
| | Total | 1,412 | | 1 | 1 | 9 | 55 | 280 | 646 | 241 | 47 | 26 | 72 | 21 | 3 | | 0.5 | 2 |
| *Enterococcus faecalis* (Vancomycin-S) | 1 | 117 | | | | | | 28 | 79 | 8 | 2 | | | | | | 0.5 | 0.5 |
| | 2 | 429 | | | | | 7 | 66 | 253 | 99 | 4 | | | | | | 0.5 | 1 |
| | 3 | 426 | | | | 4 | 41 | 121 | 233 | 18 | 6 | 3 | | | | | 0.5 | 0.5 |
| | 6 | 30 | | | | 1 | 2 | 10 | 13 | 4 | | | | | | | 0.5 | 1 |
| | 7 | 28 | | | | | | 5 | 10 | 13 | | | | | | | 0.5 | 1 |
| | 10 | 31 | | | | | | 3 | 5 | 14 | 9 | | | | | | 1 | 2 |
| | 12 | 73 | | 1 | 1 | 1 | 4 | 43 | 23 | | | | | | | | 0.25 | 0.5 |
| | 14 | 6 | | | | 3 | 1 | 2 | | | | | | | | | ND | ND |
| | 19 | 90 | | | | | | 2 | 10 | 68 | 10 | | | | | | 1 | 2 |
| | Total | 1,230 | | 1 | 1 | 9 | 55 | 280 | 626 | 224 | 31 | 3 | | | | | 0.5 | 1 |
| *Enterococcus faecium* (All) | 1 | 153 | | | 2 | 10 | 28 | 18 | 5 | 1 | 9 | 51 | 32 | 1 | | | 4 | 8 |
| | 2 | 337 | | 2 | 1 | 11 | 51 | 34 | 7 | 7 | 16 | 107 | 94 | 7 | | | 4 | 8 |
| | 3 | 382 | | | 8 | 67 | 142 | 49 | 7 | 9 | 29 | 46 | 6 | | | | 0.12 | 4 |
| | 6 | 50 | | | | 2 | 7 | 15 | 5 | 2 | 11 | 7 | 1 | | | | 0.5 | 4 |
| | 7 | 32 | | | | 2 | 6 | 12 | 7 | | 2 | 2 | | 1 | | | 0.25 | 2 |
| | 10 | 90 | | | | 2 | 13 | 10 | 7 | | 2 | 3 | 40 | 12 | 1 | | 8 | 16 |
| | 12 | 80 | | | 1 | 8 | 43 | 7 | 5 | 7 | 7 | 1 | 1 | | | | 0.12 | 2 |
| | 14 | 5 | | | 1 | | 1 | | 1 | | 1 | | 1 | | | | 0.5 | 8 |
| | 19 | 204 | | | | 1 | 2 | 16 | 10 | 11 | 7 | 21 | 112 | 24 | | | 8 | 16 |
| | Total | 1,313 | | 2 | 13 | 103 | 291 | 159 | 54 | 36 | 84 | 238 | 287 | 45 | 1 | | 1 | 8 |

| Organism (Phenotype[1]) | Study No. | N | No. of Isolates Inhibited at Concentration (µg/mL)[2] | | | | | | | | | | | | MIC[2] (µg/mL) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 0.008 | 0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | ≥32 | Range[3] | 50%[4] | 90%[5] |
| *Enterococcus faecium* (Vancomycin-S) | 1 | 52 | | | 2 | 8 | 23 | 16 | 3 | | | | | | | [redacted] | 0.12 | 0.25 |
| | 2 | 92 | | 1 | 1 | 11 | 42 | 32 | 5 | | | | | | | | 0.12 | 0.25 |
| | 3 | 276 | | | 8 | 67 | 137 | 48 | 5 | 3 | 8 | | | | | | 0.12 | 0.25 |
| | 6 | 28 | | | | 2 | 7 | 15 | 4 | | | | | | | | 0.25 | 0.5 |
| | 7 | 24 | | | | 2 | 5 | 10 | 7 | | | | | | | | 0.25 | 0.5 |
| | 10 | 15 | | | | | 3 | 5 | 6 | | 1 | | | | | | 0.25 | 0.5 |
| | 12 | 59 | | | 1 | 8 | 41 | 7 | 2 | | | | | | | | 0.12 | 0.25 |
| | 14 | 1 | | | 1 | | | | | | | | | | | | ND | ND |
| | 19 | 16 | | | | | | 7 | 5 | 4 | | | | | | | 0.5 | 1 |
| | Total | 563 | | 1 | 13 | 98 | 258 | 140 | 37 | 7 | 9 | | | | | | 0.12 | 0.25 |

[1] Phenotype: All, all isolates tested; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; VSE, vancomycin-susceptible *E. faecalis*; VRE, vancomycin-resistant *E. faecalis*
[2] MIC: Minimal Inhibitory Concentration
[3] Range: Range of telavancin MIC values
[4] 50%: Lowest telavancin concentration required to inhibit 50% of the test isolates
[5] 90%: Lowest telavancin concentration required to inhibit 90% of the test isolates
[6] Includes VISA (n = 92 determinations) and VRSA (n = 11 determinations) isolates
[7] ND, not determined (MIC$_{50}$ and MIC$_{90}$ values not calculated for N < 10 isolates)
[8] Includes 7 vancomycin-intermediate isolates and 39 teicoplanin-nonsusceptible isolates

Source: 5.3.5.4.1.4 Table 18, this submission

b(4)

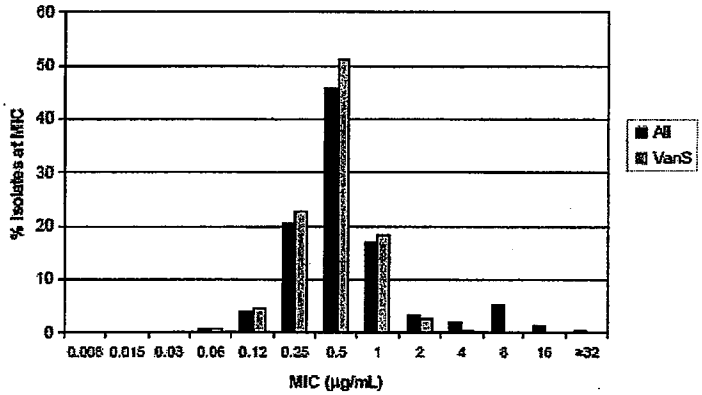
b(4)

The overall telavancin MIC$_{90}$ for vancomycin-susceptible isolates of *E. faecalis* (n = 1230) was determined to be 1 µg/ml (MIC$_{50}$ = 0.5 µg/ml, MIC$_{range}$ = [redacted] µg/ml). The MIC$_{90}$ for all tested isolates of *E. faecalis* was 2.0 µg/ml (n = 1412). Telavancin also demonstrated activity against vancomycin-susceptible strains of *E. faecium* (overall MIC$_{90}$ = 0.25 µg/ml). Activity against VanA-type vancomycin-resistant enterococci was diminished (MIC$_{range}$ = [redacted] µg/ml), but superior to other glycopeptide comparators (vancomycin and teicoplanin). Telavancin demonstrated modest activity against VanB-type vancomycin-resistant enterococci (MIC$_{range}$ = [redacted] µg/ml).

b(4)

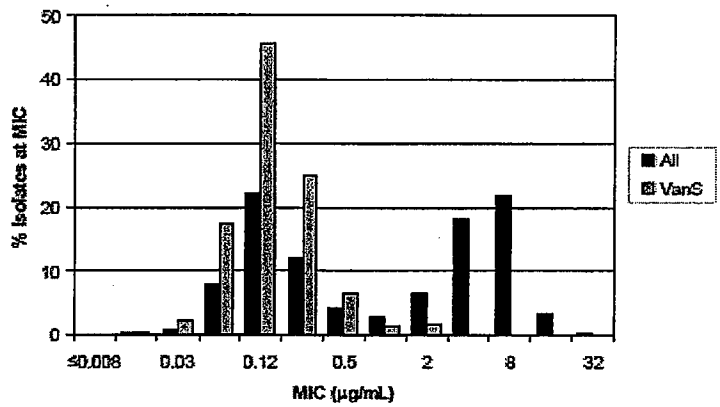
Histograms for MIC distributions of telavancin activity against vancomycin-susceptible *E. faecalis* (Figure 6) show a normal, unimodal distribution.

Figure 6: Telavancin MIC Distributions for All *E. faecalis* (n = 1,412) and Vancomycin-susceptible (VanS; n = 1,230) *E. faecalis* Survey isolates




Source: 5.3.5.4.1.4 Figure 11, this submission

Figure 7: Telavancin MIC Distributions for All *E. faecium* (n = 1,313) and Vancomycin-susceptible (VanS; n = 563) *E. faecium* Survey isolates




Source: 5.3.5.4.1.4 Figure 12, this submission

In addition to the in vitro data relevant to the principle pathogens involved in cSSSI (those claimed in the proposed indication), the applicant has submitted data describing telavancin activity against other Gram positive pathogens, including both aerobic species (*Corynebacterium* spp., *Bacillus anthracis*, and *Listeria monocytogenes*), and anaerobic species (*Peptostreptococcus* spp., *Clostridium* spp., and *Lactobacillus* spp.). Notable activity was demonstrated against *C. perfringens* ($MIC_{range}$ = ( / µg/ml; n = 12), *Peptostreptococcus* spp. ($MIC_{range}$ = ≤ ( ) µg/ml) and *Lactobacillus* spp. ($MIC_{range}$ = ( ) µg/ml). Telavancin was also active against aerobic Gram positive rods. The $MIC_{range}$ of telavancin against all tested *Corynebacterium* spp. (including eleven isolates of *C. jeikeium*) was ≤ ( )µg/ml (n = 31). The MIC of telavancin against *L. monocytogenes* (n = 10) was 0.12 µg/ml (King 2004). Activity against B. anthracis ($MIC_{range}$ = ( ) µg/ml) was greater than other glycopeptide comparators (vancomycin and daptomycin) but less than ciprofloxacin and doxycycline (data not shown).

b(4)

In studies of telavancin activity against Gram negative bacterial pathogens, the drug was inactive. MICs for *Citrobacter freundii*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Acinetobacter* spp., and *Pseudomonas aeruginosa* were all ≥ 128 µg/ml. Similar

results were obtained with anaerobic isolates (including *Bacteroides fragilis*, *Prevotella* spp., and *Porphyromonas asaccharolytica*). Telavancin was also inactive against *Chlamydia pneumoniae* and *Legionella pneumophila*.

*Antimicrobial Spectrum of Activity ~ Conclusions:*
Data submitted from large prospective surveillance studies and other investigations of in vitro activity support the applicant's claim of activity against the pathogens generally associated with complicated skin and skin structure infections, including the organisms listed in the proposed indication for telavancin. MIC values for all tested strains of *S. aureus* (including strains resistant to other classes of antimicrobials, and stains 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, discussed elsewhere in this review (see discussions of protein binding and human/animal PK/PD data). Telavancin activity against vancomycin-intermediate *S. aureus* (VISA), heteroresistant vancomycin-intermediate *S. aureus*, and vancomycin-resistant *S. aureus* (VRSA), in these studies, was superior to vancomycin.

**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 [Leclerq 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 µg/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 µg/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.

The Applicant has investigated the emergence of resistance to telavancin, using a variety of pathogenic strains (listed in the appropriate tables, below), in both serial passage studies and single-step selection studies. The applicant also monitored the emergence of telavancin resistance during the Phase 2 and Phase 3 clinical programs, associated with this application. In a study of spontaneous mutation to telavancin, a variety of resistance phenotypes at high inocula were exposed to multiples of the MIC ( 2x, 4x, and 8x) for 24 hours. Chosen phenotypes included representative isolates from species associated with cSSSI. The results are summarized in Table 1. The observed potential for selection of resistant mutants was similar to comparators (vancomycin, teicoplanin, and daptomycin; data not shown). The spontaneous mutation frequency for telavancin ranged between $<2.7 \times 10^{-10}$ and $<2.4 \times 10^{-9}$. No stable mutants were detected.
In a second study of spontaneous mutation, two strains of *S. aureus* (MRSA and GISA) and five

strains of enterococcus were exposed to 1x, 2x, and 3x MIC of telavancin. Reduced susceptibility for telavancin was observed in one strain of vancomycin-resistant *E. faecalis*, but in no other tested strains (results summarized in Tables 2 and 3). Vancomycin-resistant Enterococcus species (VRE) is not sought as an indication for telavancin.

In a study designed to determine the effect of drug selective pressure on strains of VRE (VanA), utilizing solid agar plates with increasing concentrations of telavancin, moderate resistance frequency ($10^{-7}$) was observed. No mutants were stable in the absence of selective pressure [Krause 2003]. In the same study, low spontaneous frequency of resistance was noted for tested strains of *S. aureus* and vancomycin-sensitive Enterococcus species.

TABLE 1: Spontaneous Resistance Frequency to Telavancin

| Strain | Phenotype | Isolate ID | Frequency |
|---|---|---|---|
| Staphylococci | | | |
| *S. aureus* | MSSA | 1345076 | $<3.4 \times 10^{-10}$ |
| | MRSA | 1345084 | $<2.4 \times 10^{-9}$ |
| | MRSA | 1345080 | $<9.4 \times 10^{-10}$ |
| | MRSA; Dap-NS[a] | 1345074 | $<2.7 \times 10^{-10}$ |
| | GISA (Mu50) | 1345081 | $<5.5 \times 10^{-10}$ |
| | VRSA-MI | 1345078 | $<6.1 \times 10^{-10}$ |
| | VRSA-PA | 1345079 | $<7.8 \times 10^{-10}$ |
| *S. epidermidis* | MRSE[b] | 1345087 | $<2.2 \times 10^{-9}$ |
| Enterococci | | | |
| *E. faecium* | VSE[c] | 1345088 | $<1.4 \times 10^{-9}$ |
| | VRE (VanA) | 1345082 | $<1.9 \times 10^{-9}$ |
| | VRE (VanB) | 1345083 | $<1.6 \times 10^{-9}$ |
| Streptococci | | | |
| *S. pneumoniae* | Multi-resistant | 1345089 | $<1.3 \times 10^{-9}$ |
| *S. pyogenes* | ERY-R[d] | 1345086 | $<1.4 \times 10^{-9}$ |
| *S. agalactiae* | ERY-R[d] | 1345085 | $<5.4 \times 10^{-10}$ |

[a] Dap-NS: Daptomycin non-susceptible
[b] MRSE: Methicillin-resistant *S. epidermidis*
[c] VSE: Vancomycin-susceptible enterococci
[d] ERY-R: Erythromycin-resistant

Source: 5.3.5.4.1.3 Table 4, this submission

TABLE 2: Determination of Telavancin Frequency of Resistance

| Strain | Phenotype | Isolate ID | Frequency |
|---|---|---|---|
| Staphylococci | | | |
| *S. aureus* | MRSA | ATCC 33591 | $<4.4 \times 10^{-10}$ |
| | GISA | HIP-5836 | $<6.4 \times 10^{-10}$ |
| Enterococci | | | |
| *E. faecalis* | VSE | E6 | $<9.2 \times 10^{-9}$ |
| | VRE (VanA) | A256 | $<6.5 \times 10^{-9}$ |
| | VRE (VanA) | MGH-01 | $4.6 \times 10^{-7}$ |
| *E. faecium* | VRE (VanA) | CDC-01 | $<3.9 \times 10^{-9}$ |
| | VRE (VanA) | KPB-01 | $<1.4 \times 10^{-9}$ |

Source: 5.3.5.4.1.3 Table 5, this submission

TABLE 3: Telavancin MIC Values for *E. faecalis* MHG-01 Isolates Selected on Telavancin Containing Agar Plates

| Strains | MIC determination (µg/mL) (N=1/N=2) | | | | | |
|---|---|---|---|---|---|---|
| | Parent | Isolate 1 | Isolate 2 | Isolate 3 | Isolate 4 | Isolate 5 |
| *E. faecalis* | | | | | | |
| MGH-01 (VanA) | 6.25/6.25 | 25/25 | 25/25 | 25/25 | 25/25 | 25/25 |

Source: 5.3.5.4.1.3 Table 6, this submission

Two separate laboratories were commissioned to perform serial passage studies. In the first study, isolates were passaged for 10 successive days. Results (summarized in Table 4) indicate that no true mutants developed in the course of the study. The final MICs, in all tested strains, were equivalent to or within one doubling dilution of the initial MIC.

TABLE 4: MIC Values after 10 Days of Serial Passage in the Presence of Telavancin

| Strain[a] | Phenotype | Isolate ID | Initial MIC (µg/mL) | Final MIC (µg/mL) | Passage (Days) |
|---|---|---|---|---|---|
| Staphylococci | | | | | |
| *S. aureus* | MSSA | 1345076 | 0.5 | 1 | 10 |
| | MRSA | 1345084 | 0.5 | 1 | 10 |
| | MRSA | 1345080 | 0.5 | 1 | 10 |
| | MRSA Dap-NS[b] | 1345074 | 0.5 | 0.5 | 10 |
| | GISA (Mu50) | 1345081 | 1 | 1 | 10 |
| | VRSA-MI | 1345078 | 4 | 8 | 10 |
| | VRSA-PA | 1345079 | 2 | 4 | 10 |
| *S. epidermidis* | MRSE[c] | 1345087 | 0.5 | 0.5 | 10 |
| Enterococci | | | | | |
| *E. faecium* | VSE[d] | 1345088 | 0.12 | 0.25 | 10 |
| | VRE (VanA) | 1345082 | 4 | 8 | 10 |
| | VRE (VanB) | 1345083 | 0.12 | 0.25 | 10 |
| Streptococci | | | | | |
| *S. pneumoniae* | Multi-resistant | 1345089 | 0.015 | 0.03 | 10 |
| *S. pyogenes* | ERY-R[e] | 1345086 | 0.03 | 0.06 | 10 |
| *S. agalactiae* | ERY-R[e] | 1345085 | 0.12 | 0.12 | 10 |

[a] Data source: Focus Bio-Inova (74)
[b] Dap-NS: Daptomycin non-susceptible
[c] MRSE: Methicillin-resistant *S. epidermidis*
[d] VSE: Vancomycin-susceptible enterococci
[e] ERY-R: Erythromycin-resistant

Source: 5.3.5.4.1.3 Table 7, this submission

In a second investigation of development of resistance, employing serial passage of reference strains, isolates were exposed to sub-MIC concentrations of telavancin, and passaged for 20 days. The results are summarized in Table 5. During the course of the investigation, telavancin failed to select for mutants with MICs greater than four-fold the initial MIC. The stability of mutants was investigated, with varying results. Specific strains (*E. faecium* KPB-01) partially reverted to the parental level, while other strains (*E. faecalis* MGH-01) appeared stable. Additionally, stable mutants of specific strains (*E. faecalis* MGH-01) were selected in broth cultures, over the 20-day investigation, while only unstable mutants were observed when the identical strain was passaged on solid media.

TABLE 5: In vitro Activity of Telavancin against *S. aureus*, *E. faecalis*, and *E. faecium* Following Serial Passage for 20 Days

| Strain[a] | Phenotype | Isolate ID | Initial MIC (µg/mL) | Final MIC (µg/mL) | Passage (Days) |
|---|---|---|---|---|---|
| Staphylococci | | | | | |
| *S. aureus* | MRSA | ATCC 33591 | 0.5 | 0.25 | 20 |
| | MRSA | MCJ-10 | 0.25 | 1 | 20 |
| | MRSA | MED 121 | 0.25 | 1 | 20 |
| Enterococci | | | | | |
| *E. faecalis* | VSE | ATCC 29212 | 0.25 | 1 | 20 |
| | VRE (VanA) | MGH-01 | 4 | 16 | 20 |
| | VRE (VanB) | BM4323 | 16 | 32 | 20 |
| *E. faecium* | VRE (VanA) | CDC-01 | 16 | 16 | 20 |
| | VRE (VanA) | KPB-01 | 4 | 32 | 20 |

[a] Data source: Krause, 2005 (119)

Source: 5.3.5.4.1.3 Table 8, this submission

*Reviewer's note:* The Applicant has presented data suggesting a low potential for the development of telavancin resistance in all strains of *S. aureus*, including isolates resistant to vancomycin. It is noted, however, that resistant VanA-type enterococcal mutants were developed in passage studies. Since Van-A resistance is known to be transmissible via mobile elements, and vancomycin-resistant *S. aureus* (VRSA) possess the Van-A gene cluster, this data suggests a potential mechanism for the development of telavancin resistance in *S. aureus*.

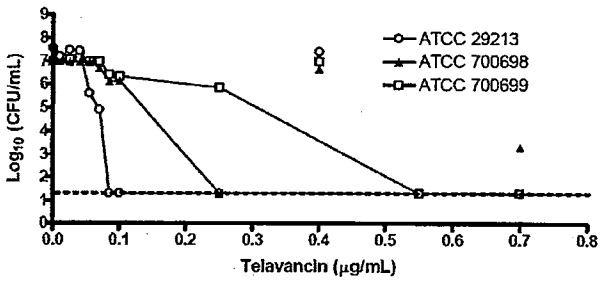
The Applicant conducted a preliminary study of S. aureus heteroresistance to telavancin. A modified population analysis profiling (PAP) method, developed by Wooten and Howe (Wooten 2001) was used in the investigation. Tested strains included *S. aureus* ATCC 29213 (VSSA), *S. aureus* ATCC 700698 (hVISA Mu3), and *S. aureus* ATCC 700699 (VISA Mu50). Results of the investigation are summarized in Table 6 and Figure 1.

Table 6: In Vitro Activities of Telavancin and Vancomycin

| Isolate | MIC (µg/mL) | |
|---|---|---|
| | Telavancin | Vancomycin |
| ATCC 29213 | 0.12 | 1 |
| ATCC 700698 | 0.25 | 2 |
| ATCC 700699 | 0.5 | 8 |

Source: "A Preliminary Investigation of Telavancin Heteroresistance in Staphylococcus aureus": 24 May 2007; Table 2

Figure 1: Telavancin Population Analysis Profiles for VSSA (ATTC 29213), hVISA (ATCC 700698) and VISA (ATCC 700699 Isolates




Source: "A Preliminary Investigation of Telavancin Heteroresistance in Staphylococcus aureus": 24 May 2007; Figure 2

Determination of defined telavancin heteroresistance (i.e. the presence of resistant subpopulations in isolates that test susceptible by standard in vitro methods) is dependent on the approved susceptible breakpoint for telavancin. Using the Applicant's proposed susceptible breakpoint ( ) µg/ml); telavancin heteroresistance was not observed in the three *S. aureus* strains, although reduced potency was observed in both hVISA and VISA strains, relative to the vancomycin-susceptible strain. b(4)

*Resistance Studies ~ Summary:*
The in vitro investigations, described above, indicate a low potential for the development of resistance to telavancin in selected species of the Gram positive pathogens sought in the indication for this application, either in terms of spontaneous emergence or as a result of selective pressure. One strain of Van A-type *E. faecalis* (MGH-01) appeared to demonstrate stable reduced susceptibility to telavancin, following selection on solid media. No isolates of *Streptococcus anginosus* group (*S. anginosus*, *S. intermedius*, and *S. constellatus*) were tested in the in vitro studies of emergence of resistance to telavancin. In the pivotal clinical studies, no emergence of resistance to telavancin was noted. In PAP investigations, *S. aureus* heteroresistance to telavancin, at or near the proposed susceptible breakpoint, was not observed.

*Resistance Studies ~ Conclusions:*
The Applicant has provided sufficient 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 (only vancomycin-susceptible *E. faecalis* is listed), 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. The Agency requests a four-year surveillance study, as a Phase 4 commitment, designed to investigate the emergence of resistance of Gram positive pathogens to telavancin. Details of this investigation may be reported as a component of the annual report from the Applicant.

**ANTIMICROBIAL INTERACTION STUDIES**

The applicant has 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.

In checkerboard microdilution studies, seventeen Gram-positive challenge isolates were tested against telavancin in combination with amikacin, aztreonam, cefepime, ciprofloxacin, imipenem,

piperacillin/tazobactam, rifampin, and trimethoprim/sulfamethoxazole. In the first study,

conducted by Focus Bio-Inova, the fractional inhibitory concentration index (FICI) was determined using the lowest inhibitory concentration of each drug. Researchers in the second study, conducted by Theravance Inc., determined the FICI by testing telavancin at 0.25X MIC, in combination with the lowest inhibitory concentration of the comparator agents. In both studies, a standard method was employed to calculate the FICA (Lorian 2005).

The results of the Theravance study are summarized in Table 1, and the results from the Focus study are summarized in Table 2. No antagonism was demonstrated in either study. Although some synergy was noted in specific determinations, synergy with a single agent was not evident against all strains of a particular species.

Most drug combinations resulted in no interaction (NI) in both studies. In the Focus study, synergy was observed with telavancin in combination with cefepime, imipenem, piperacillin/tazobactam against a vancomycin-resistant *S. aureus* strain (Michigan isolate), and in combination with imipenem and piperacillin/tazobactam against a vancomycin-intermediate *S. aureus* strain (Mu50). In the Theravance study, significant synergy was noted with telavancin in combination with imipenem against an MRSA strain (ATCC 33591), and with telavancin in combination with rifampin against a VSE strain (ATCC 29212).

TABLE 1: Telavancin Activity Alone and in Combination with Other Antibiotics

| Organism | Isolate ID | Phenotype[1] | Telavancin MIC (µg/mL) | FICI Interpretation[2] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | CIP | FEP | IPM | PTZ | RIF | SXT | AMK | AZT |
| *S. aureus* | ATCC 29213 | MSSA | 1 | S | S | S | NI | NI | NI | NI | ND |
| | ATCC 33591 | MRSA | 0.5 | S | S | S | NI | NI | NI | NI | ND |
| | B422933 | MRSA | 0.5 | S | —[3] | S | S | NI | NI | NI | ND |
| | ATCC 4330 | MRSA | 0.25 | — | S | S | — | — | — | — | — |
| | B419179 | MRSA | 0.5 | — | NI | NI | — | — | — | — | — |
| | B422944 | MRSA | 0.25 | — | S | S | — | — | — | — | — |
| | B380937 | MRSA | 0.25 | — | S | S | — | — | — | — | — |
| | Mu50 | VISA | 1 | NI | — | S | ND | ND | NI | NI | ND |
| *E. faecalis* | ATCC 29212 | VSE | 0.5 | NI | — | NI | S | S | NI | NI | ND |
| | MGH-01 | VRE | 8 | NI | — | NI | NI | NI | NI | NI | ND |
| *S. pneumoniae* | SU-10 | PRSP | 0.03 | NI | — | NI | NI | NI | NI | NI | ND |
| | ATCC 49619 | PSSP | 0.03 | NI | — | NI | NI | NI | NI | NI | ND |

Data from Theravance (192)
[1]MSSA, methicillin-sensitive *S. aureus*; MRSA, methicillin-resistant *S. aureus*; VISA, vancomycin-intermediate *S. aureus*; VSE, vancomycin-sensitive *Enterococcus*, VRE, vancomycin-resistant *Enterococcus* (VanA); PRSP, penicillin-resistant *Streptococcus pneumoniae*; PSSP, penicillin-sensitive *S. pneumoniae*.
[2]S, Synergistic interaction; NI, No interaction; ND, Data could not be interpreted because one agent was inactive against the strain tested.
[3]—, Not determined
CIP, ciprofloxacin; FEP, cefepime; IPM, imipenem; PTZ, piperacillin/tazobactam; RIF, rifampin; SXT, trimethoprim/sulfamethoxazole; AMK, amikacin; AZT, aztreonam.

Source: 5.3.5.4.1.7 Table 1, this submission

TABLE 2: MIC and FIC Index Determination Between Telavancin and Comparator Antibiotics

| Organism | Focus Bio-Inova Isolate ID | Phenotype[1] | Telavancin MIC (µg/mL) | FICI Interpretation[2] | | | |
|---|---|---|---|---|---|---|---|
| | | | | CIP | FEP | IPM | PTZ |
| *S. aureus* | 1345084 | MRSA | 0.25 | NI | NI | NI | NI |
| | 1345074 | MRSA; Dap-NS | 0.25 | NI | NI | NI | NI |
| | 1345081 | VISA Mu50 | 0.5 | NI | NI | S | S |
| | 1345078 | VRSA-MI | 4 | NI | S | S | S |
| *E. faecalis* | 1443444 | VSE | 1 | NI | NI | NI | NI |
| *E. faecium* | 1345082 | VRE | 4 | NI | NI | NI | NI |
| *S. agalactiae* | 1443443 | Ery-R | 0.125 | NI | NI | NI | NI |
| *S. pyogenes* | 1443442 | Ery-R | 0.03 | NI | NI | NI | NI |
| | 1273289 | Ery-R | 0.03 | NI | NI | NI | NI |

Data from Focus Bio-Inova, Inc. (76, 164)
[1]MRSA, methicillin-resistant *S. aureus*; Dap-NS, daptomycin non-susceptible; VRSA, vancomycin-resistant *S. aureus* (VanA); VISA, vancomycin-intermediate *S. aureus*; VSE, vancomycin-sensitive *Enterococcus*; VRE, vancomycin-resistant *Enterococcus* (VanA); Ery-R, erythromycin-resistant.
[2]S, Synergistic interaction; NI, No interaction.
CIP, ciprofloxacin; FEP, cefepime; IPM, imipenem; PTZ, piperacillin/tazobactam

Source: 5.3.5.4.1.7 Table 2, this submission

*Antimicrobial Interaction Studies ~ Conclusions:*
The applicant has submitted data from time-kill studies, conducted to investigate the modest synergy observed in the checkerboard microdilution studies. No synergy between either telavancin and imipenem, or telavancin and cefepime, was observed against strains of MRSA and MSSA (ATCC 33591 and ATC 29213, respectively), in the time-kill studies. No antagonism was noted in any of the drug interaction investigations.

## EFFECTS OF MISCELLANEOUS FACTORS ON ACTIVITY

### I. PROTEIN BINDING

Telavancin is highly protein-bound (~90%) in human serum, principally to human 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 levels of protein binding (85.5% at a concentration of 100 µg/ml). Hepatic or renal insufficiency did not markedly alter levels of serum protein binding.

The effect of protein binding on in the vitro activity of telavancin against *S. aureus* and *E. faecalis* (including vancomycin-resistant and vancomycin-sensitive strains) was investigated.

In one study, six strains of *S. aureus* (including methicillin-sensitive, methicillin-resistant, and vancomycin-intermediate strains) were tested against varying concentrations of telavancin in time-kill studies (Table 1). In this study, a parabolic relationship of drug activity to serum concentration was observed. Reduction in antimicrobial activity was noted at high concentrations of serum (50-70%) and low concentrations of telavancin. The decreased activity was attributed to protein binding and reduced concentrations of free drug.

In a separate study (Leuthner 2006), the effect of human serum on telavancin activity was examined against isolates of glycopeptide non-susceptible *S. aureus* (including glycopeptide-intermediate staphylococcal species (GISS), heteroresistant GISS (hGISS), and vancomycin-

resistant *S. aureus*). Using time-kill methods, the investigators demonstrated concentration-

dependent bactericidal activity of telavancin against all strains tested. Telavancin activity was diminished in the presence of human serum, with MICs increased 2-fold, on average, but bactericidal activity was maintained, in the presence of human serum, at telavancin concentrations ≥ 4x MIC. The results of the study are summarized in Table 2.

Table 1: Effect of Human Serum on the Bactericidal Activity of Telavancin against Six Strains of *S. aureus* at 24 Hours

| Strain | % serum | MIC (µg/mL) | $Log_{10}$ Change in CFU/mL at Fold-MIC | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | GC | 0.5XMIC[a] | 1XMIC | 2XMIC | 4XMIC | 8XMIC | 10XMIC | 20XMIC |
| ATCC 25923 MSSA | 0 | 0.25 | 4.25 | 3.48 | 2.43 | 1.20 | -1.26 | NS | -3.09 | -3.62 |
| | 10 | | 3.05 | -2.61 | -2.36 | -2.14 | -2.37 | -3.01 | -2.97 | -3.35 |
| | 30 | | 3.36 | 2.94 | -2.36 | -3.49 | -3.64 | -3.63 | -3.67 | -3.77 |
| | 50 | | 3.05 | 2.97 | 2.24 | -2.37 | -3.14 | -3.37 | -3.39 | -3.53 |
| | 70 | | 2.36 | 2.41 | 2.12 | 0.04 | -2.80 | -3.60 | -3.70 | -3.83 |
| ATCC 29213 MSSA | 0 | 0.25 | 3.64 | 2.11 | -1.20 | -1.71 | -2.27 | -2.33 | -2.53 | -3.75 |
| | 10 | | 3.47 | -3.17 | -3.78 | -4.12 | -4.12 | -4.12 | -4.12 | -4.12 |
| | 30 | | 3.22 | 2.12 | -3.86 | -4.01 | -4.01 | -4.01 | -4.01 | -4.22 |
| | 50 | | 2.76 | 2.56 | 2.00 | -1.55 | -3.66 | -3.80 | -3.87 | -4.15 |
| | 70 | | 2.26 | 2.25 | 2.00 | .069 | -2.10 | -3.84 | -3.87 | -4.00 |
| MSSA S122 | 0 | 0.25 | 3.10 | 2.19 | -0.06 | -1.28 | -2.92 | -3.78 | -3.78 | -3.87 |
| | 10 | | 3.20 | -2.04 | -3.19 | -4.08 | -4.08 | -4.08 | -4.08 | -4.08 |
| | 30 | | 3.00 | 2.30 | -3.47 | -4.25 | -4.25 | -4.25 | -4.25 | -4.25 |
| | 50 | | 2.97 | 2.78 | 2.15 | -1.36 | -3.39 | -3.45 | -3.48 | -3.65 |
| | 70 | | 2.54 | 2.43 | 2.18 | -0.57 | -1.94 | -4.35 | -4.35 | -4.35 |
| MRSA S159 | 0 | 0.125 | 3.74 | 3.46 | 1.64 | -0.05 | -0.66 | -1.11 | -1.64 | -1.31 |
| | 10 | | 3.24 | 2.68 | -3.17 | -3.90 | -3.90 | -3.90 | -3.90 | -3.90 |
| | 30 | | 3.09 | 2.52 | 0.58 | -3.75 | -4.04 | -4.04 | -4.04 | -3.98 |
| | 50 | | 3.09 | 2.95 | 2.66 | 1.66 | -3.93 | -3.93 | -3.93 | -3.93 |
| | 70 | | 2.3 | 2.62 | 2.04 | 1.53 | 0.42 | -2.28 | -2.30 | -2.81 |
| MRSA S170 | 0 | 0.25 | 3.48 | 2.92 | -0.44 | -1.77 | -1.33 | -2.70 | -3.57 | -3.57 |
| | 10 | | 3.70 | 0.50 | -3.78 | -3.66 | -3.85 | -3.85 | -3.85 | -3.85 |
| | 30 | | 3.47 | 2.31 | -2.70 | -3.93 | -3.93 | -3.93 | -3.93 | NS |
| | 50 | | 3.29 | 2.96 | 2.89 | -1.61 | -3.62 | -3.62 | -3.62 | -3.62 |
| | 70 | | 3.11 | 2.92 | -0.44 | -1.77 | -1.33 | -2.70 | -3.57 | -3.57 |
| VISA S171 | 0 | 0.5 | 3.23 | 1.38 | 0.56 | -0.10 | -0.56 | -3.32 | -3.87 | -3.87 |
| | 10 | | 3.53 | -1.88 | -3.14 | -3.61 | -3.72 | -3.72 | -3.72 | -3.72 |
| | 30 | | 3.30 | -1.38 | -3.19 | -3.63 | -3.72 | -3.70 | -3.80 | -3.80 |
| | 50 | | 2.79 | 2.05 | -1.64 | -3.41 | -4.02 | -4.02 | -4.02 | -4.02 |
| | 70 | | NS | 2.18 | 1.19 | -0.56 | -2.58 | -3.00 | -3.07 | -3.36 |

Source Data (11)
[a]The $log_{10}$ increase or decrease in CFU/mL, a positive value indicates bacterial growth
GC, Growth Control
NS, No Sample

Source: 5.3.5.4.1.6 Table 1, this submission

Table 2: Effect of Human Serum on the Anti-staphylococcal Activity of Telavancin

| Strain (+/- 50% human serum) | $MIC_{50}$ µg/mL | $MIC_{90}$ µg/mL | MIC Range µg/mL | MBC Range µg/mL |
|---|---|---|---|---|
| GISS and hGISS[1] (- serum) | 0.5 | 1 | | |
| GISS and hGISS[1] (+ serum) | 2 | 4 | | |
| VRSA[2] (- serum) | ND[3] | ND | | |
| VRSA[2] (+ serum) | ND | ND | | |

b(4)

Source Data (124)
[1]Fifty GISS isolates
[2]Three VRSA isolates (VRSA-MI, VRSA-NY and VRSA-PA)
[3]ND, $MIC_{50}$ and $MIC_{90}$ values were not determined because <10 isolates were tested
Source: 5.3.5.4.1.6 Table 2, this submission

The effect of pooled human serum, human serum albumin (HSA) and $\alpha_1$-acid glycoprotein (AGP) on both telavancin and vancomycin activity was investigated by the applicant (Table 3). Three reference strains were tested against the two antimicrobials, supplemented with concentrations of HSA and AGP approximating physiologic levels (as well as HSA at 50% concentration) in Mueller-Hinton broth. Telavancin activity was not affected by the addition of AGP to the growth medium. The addition of PHS or HAS resulted in changes in telavancin activity ranging from 1 to 2 doubling-dilutions.

Table 3: Comparative Effect of Human Serum and Serum Proteins on MIC and MBC Values for Telavancin and Vancomycin

| Strain | Phenotype[1] | Antibiotic | MIC (MBC) (µg/mL) | | |
|---|---|---|---|---|---|
| | | | MH Broth[2] | 50% PHS[2] | 40 mg/mL HSA[2] |
| *S. aureus* ATCC 33591 | MRSA | telavancin | 1 (1) | 2 (4) | 2 (2) |
| | | vancomycin | 2 (2) | 2 (2) | 2 (2) |
| *E. faecalis* ATCC 29212 | VSE | telavancin | 1 (16) | 2 (32) | 4 (4) |
| | | vancomycin | 2 (>256) | 8 (>256) | 4 (>256) |
| *E. faecalis* ATCC 51575 | VRE | telavancin | 1 (32) | 4 (16) | 4 (32) |
| | | vancomycin | >256 (>256) | >256 (>256) | >256 (>256) |

[1]MRSA, methicillin-resistant *S. aureus* ; VSE, vancomycin-susceptible *E. faecalis*; VRE, VanB-type *E. faecalis*;
[2]PHS, pooled human serum; HSA, human serum albumin; MH, Mueller-Hinton broth

Source: 5.3.5.4.1.6 Table 5, this submission

*Protein Binding Studies ~ Conclusions:*
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).

**II. INTRACELLULAR ACTIVITY**

Cellular uptake and intracellular concentration of telavancin was studied in murine J774 macrophages. Intracellular uptake displayed a linear dose-proportional relationship up to a concentration of 90 µg/ml (at 90 µg/ml extracellular $^{14}C$, intracellular $^{14}C \approx 20$ µg/ml). In a separate study (also using J774 macrophages), telavancin uptake and efflux kinetics were studied. Linear rates of uptake and efflux were noted (directly proportional to extracellular concentration), with uptake measured at 0.86 µg/ml and efflux measured at -0.25 µg/ml).

Sub-cellular localization of telavancin was determined in two studies that employed cell fractionation techniques and electron microscopy. Both studies suggested lysosomal localization of the drug. Activity of telavancin at pH 5.5 was investigated, to approximate the intra-lysosomal environment (Table 4). The activity of telavancin against reference strains of *S. aureus* (MSSA, MRSA, VISA, and VRSA) was not significantly altered in a reduced pH environment.

Table 3: Telavancin MIC values for *S. aureus* at pH 7.2 and pH 5.5

| Phenotype | Strain | MIC (µg/mL) | |
|---|---|---|---|
| | | pH 7.2 | pH 5.5 |
| MSSA | ATCC 25923 | 0.5 | 1 |
| | ATCC 29213 | 0.5 | 1 |
| MRSA | ATCC 33591 | 0.5 | 1 |
| | ATCC 43300 | 0.5 | 1 |
| VISA | NRS23[a] | 0.5 | 0.5 |
| | NRS52[b] | 0.5 | 0.5 |
| VRSA | VRS1[†c] | 4 | 4 |
| | VRS2[†d] | 2 | 2 |

Source Data (17)
[a]also known as HIP-08926
[b]also known as HIP-09737
[†]VRSA strains described by Centers for Disease Control and Prevention (35, 36)
[c]also known as HIP-11714 and VRSA-MI
[d]also known as HIP-11983 and VRSA-PA
Source: 5.3.5.4.1.6 Table 8, this submission

Intracellular activity of telavancin was studied in both murine (J774) and human (THP-1) macrophages. Intracellular killing was observed in both studies, and was equal or superior to comparators (vancomycin, linezolid, teicoplanin, nafcillin, and oxacillin). Intracellular bactericidal activity (> 2-$\log_{10}$ reduction in bacterial counts) was concentration-dependent.

*Intracellular Activity Studies ~ Conclusions:*
The applicant has provided sufficient 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.

## III. ACTIVITY AGAINST BIOFILMS

Telavancin activity against staphylococcal biofilms was investigated, using a modified Sorbarod model [Gander 2005]. Concentrations of test antibiotics (including telavancin, vancomycin, teicoplanin, linezolid, and moxifloxacin) were chosen to correspond to peak serum levels achievable in humans. The biofilms were exposed to exponentially decreasing levels of the antimicrobials, with rates of decrease corresponding to the drug's elimination half-life in humans. Results indicated that telavancin was active in reducing the number of cells in staphylococcal biofilms and that the activity was greater than glycopeptide comparators (moxifloxacin was more active in the Sorbarod model). Results are summarized in Table 4.

Table 4: Bacterial Indices of Telavancin and Comparator Antibiotics

| Strain[1] | Phenotype[2] | Bacterial Index (BI)[3] | | | | |
|---|---|---|---|---|---|---|
| | | Telavancin | Vancomycin | Teicoplanin | Linezolid | Moxifloxacin |
| *S. aureus* ATCC 29213 | MSSA | 2.22 | 0.65 | 0.73 | 1.31 | 6.35 |
| *S. aureus* ATCC 33591 | MRSA | 3.19 | 0.6 | 0.81 | 3.47 | 7.44 |
| *S. aureus* MS 01 | MSSA | 3.52 | 1.18 | 1.03 | 2.25 | 4.24 |
| *S. epidermidis* MS 501 | MSSE | 3.32 | 0.77 | 1.6 | 1.78 | 0.61 |
| *S. epidermidis* RP62A | MRSE | 3.87 | 1.28 | 1.16 | 2.52 | 7.15 |
| *S. aureus* Mu50 | GISA | 3.32 | 0.05 | 0.26 | 0.92 | 0.61 |
| *S. aureus* Mu3 | GISA | 1.92 | 0.32 | 0.07 | 0.14 | 0 |
| *S. aureus* HIP-5836 | GISA | 3.35 | 1.06 | 0.16 | 1.09 | 0 |

[1]Source Data (84)
[2]MSSA, methicillin-sensitive *S. aureus*; MRSA, methicillin-resistant *S. aureus*; MSSE, methicillin-sensitive *S. epidermidis*; GISA, glycopeptide-intermediate *S. aureus*
[3]The BI is the AUC of the $\log_{10}$ reduction in viable counts versus $\log_{10}$ time (hours)
Source: 5.3.5.4.1.6 Table 11, this submission

*Activity Against Biofilm Studies ~ Conclusions:*
The applicant has presented data from an investigation of a biofilm model, designed to demonstrate the activity of telavancin against non-planktonic bacterial communities. The provided data supports 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.

## IV. POSTANTIBIOTIC EFFECT

Postantibiotic effect (PAE) was determined for telavancin, vancomycin, teicoplanin, linezolid, and daptomycin against isolates of *S. aureus*, *E. faecium*, *E. faecalis*, *S. pyogenes*, and *S. agalactiae*. The results are summarized in Table 5. Isolates were exposed to antimicrobials at 4 or 8 µg/ml for 1 hour, and then diluted 1:1,000 in Mueller-Hinton broth. Assay tubes were sampled every hour, up to 8 hours. PAE was defined as "the difference between the time required for the test culture and the time required for the growth control culture to increase one log10 above the colony count immediately following dilution." Against *S. aureus* strains, telavancin demonstrated a PAE 1.6 to >5 hours.

Table 5: PAE of telavancin, vancomycin, teicoplanin, linezolid, and daptomycin against eight isolates of *S. aureus*, *E. faecium*, *E. faecalis*, *S. pyogenes*, and *S. agalactiae*

| Organism | Phenotype or Genotype | Isolate ID | PAE (hours) Telavancin (0.5 mIC) | | Vancomycin (1g/mL) | | Teicoplanin (1g/mL) | | Linezolid (1/2mIC) | | Daptomycin (1g/mL) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 |
| *S. aureus* | Dapto-NS; MR | 1345074 | 1.6 | 2.0 | 0.7 | 0.5 | 0.7 | 0.7 | 0.8 | 0.8 | 0.5 | 1.0 |
| *S. aureus* | MR-VRSA | 1345078 | 2.4 | 2.6 | 0.3 | 0.2 | 0.2 | 0.6 | 0.4 | 0.5 | 1.2 | 2.2 |
| *S. aureus* | VISA Mu50 | 1345081 | 5.0 | >5 | 1.8 | 1.9 | 1.1 | 1.9 | 1.3 | 1.3 | 1.2 | 2.1 |
| *S. aureus* | MRSA | 1345084 | 3.7 | 4.0 | 0.3 | 0.7 | 0.9 | 0.6 | 0.4 | 0.5 | 2.4 | 4.1 |
| *E. faecium* | Van-R/*vanA* | 1345082 | 0.5 | 0.6 | 0.2 | 0.3 | 0.0 | -0.1 | 0.7 | 0.7 | 4.3 | 2.7 |
| *E. faecalis* | Van-S | 1443444 | 1.1 | 1.1 | 0.3 | 0.5 | 1.0 | 1.1 | 0.6 | 0.8 | 1.8 | 3.3 |
| *S. pyogenes* | Ery-R | 1443442 | >6.5 | >6.5 | 2.3 | 1.9 | >6.5 | >6.5 | 0.3 | 0.2 | >6.5 | >6.5 |
| *S. agalactiae* | Ery-R | 1443443 | 1.6 | 2.6 | 0.8 | 0.7 | 0.7 | 1.1 | 0.3 | 0.4 | 1.9 | 4.2 |

Source: Table 2; Focus Bio-Inova Inc. Postantibiotic Effect of Telavancin against Staphylococci, Enterococci, and Streptococci. 2006 (this submission)

*Postantibiotic Effect Studies ~ Conclusions:*
The applicant has 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. In addition, a prolonged PAE was demonstrated against *S. pyogenes* and *S. agalactiae*. PAE against strains of enterococcus was diminished, compared to the other tested pathogens, but vancomycin-susceptible *E. faecalis* demonstrated notable PAE (1.1 hours).

*Reviewer's Note:*
In addition to the above miscellaneous properties of telavancin, the applicant has provided data regarding the activity of the effect of pulmonary surfactant 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. .

## BACTERICIDAL ACTIVITY

### I. Minimum Bactericidal Concentration Studies

The bactericidal activity of telavancin was studied in several independent laboratory investigations. For the purposes of this application, the Minimum Bactericidal Concentration (MBC) was defined as the lowest concentration of the antimicrobial (telavancin and comparators) that produced ≥ 99.9 % killing in 24 hours, compared to the starting inoculum. The term "bactericidal" was defined as an MBC:MIC ratio of ≤ 4.

The bactericidal activity of telavancin against *S. aureus* (including glycopeptide-nonsusceptible strains and strains identified as "community-acquired") was investigated in six studies. All of the investigations employed CLSI-approved microbroth dilution methods. Three of the studies used frozen panels supplied by TREK Diagnostic Systems, Inc. Three studies used panels prepared by the investigators. Quality control strains were tested in accordance with NCCLS (CLSI) M7-A6 (2003). Day-of-testing quality control strains included *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212.

Data from the six investigations support bactericidal activity of telavancin against all tested phenotypes of *S. aureus*, including vancomycin-resistant strains, with MBC:MIC ratios ≤ 4, and MBC values generally within 1-2 doubling dilutions of the MIC. The results of one study,

evaluating the bactericidal activity of telavancin against strains of *S. aureus* with reduced susceptibility to glycopeptides, is summarized in Table 1.

Table 1: Telavancin MBC Values for *S. aureus* Strains Including Isolates with Reduced Susceptibility to Methicillin, Daptomycin, Linezolid and Vancomycin

| Phenotype[a] | N | MIC (µg/mL) | | | MBC (µg/mL) | | |
|---|---|---|---|---|---|---|---|
| | | Range | $MIC_{50}$ | $MIC_{90}$ | Range | $MBC_{50}$ | $MBC_{90}$ |
| All isolates | 75 | | 2 | 2 | | 4 | 8 |
| MSSA | 13 | | 2 | 2 | | 4 | 8 |
| MRSA[b] | 62 | | 1 | 2 | | 4 | 8 |
| Daptomycin-NS | 37 | | 2 | 2 | | 4 | 8 |
| Linezolid-NS | 3 | | —[c] | — | | — | — |
| VISA[d] | 42 | | 2 | 2 | | 4 | 8 |
| VRSA | 2 | | — | — | | — | — |

[a] Daptomycin-NS: daptomycin-non-susceptible ; Linezolid-NS: linezolid-non-susceptible
[b] MRSA isolates also include Daptomycin-NS, Linezolid-NS, VISA and VRSA isolates
[c] $MIC_{50}$ and $MIC_{90}$ were not determined for <10 isolates
[d] VISA: Vancomycin MIC ≥4 µg/mL

b(4)

Source: 5.3.5.4.1.5 Table 3, this submission

Telavancin bactericidal activity was also investigated in strains of coagulase negative staphylococci (CNS). Assays were similar to those discussed above, and employed CLSI-approved broth microdilution methods. Isolates were not identified to species level. Six methicillin-susceptible and four methicillin-resistant strains were tested. The MIC and MBC for CNS were equivalent, indicating significant bactericidal activity of telavancin in the tested strains. Bactericidal activity as measured by MBC:MIC ratios, was comparable to that obtained from other glycopeptide comparators.

Telavancin MBC:MIC ratios for *S. agalactiae* (n = 5), *S. pyogenes* (n = 4), and *S. intermedius* (n = 5) were determined from the sponsor's Non-Clinical MBC Line Listing (Theravance 2006, this application). Bactericidal activity was suggested by data for both species of ß-hemolytic streptococci, with MBC:MIC ratios ≤ 4. MBC values for two isolates of *S. intermedius* were 0.5 and 1 µg/ml (MBC:MIC ratio = 16-32 and MIC =0.03 µg/ml).

Bactericidal activity of telavancin was determined against 20 enterococcal strains, including vancomycin-susceptible *E. faecalis* (n = 5), vancomycin-susceptible *E. faecium* (n = 5), VanA-type vancomycin-resistant *E. faecalis* (n = 3), VanA-type vancomycin-resistant *E. faecium* (n = 3), VanB-type vancomycin-resistant *E. faecalis* (n = 2), and VanB-type vancomycin-resistant *E. faecium* (n = 2). In a second study, 152 enterococcal isolates were evaluated for telavancin bactericidal activity. Data from both studies suggest that telavancin, like the tested comparators, displayed reduced bactericidal activity against enterococcal species, compared to activity against other genera of Gram positive pathogens (e.g. staphylococci and streptococci). Calculated MBC:MIC ratios were generally ≥ 8 (higher than the "bactericidal" cutoff defined by the applicant). Data from the smaller study is summarized in Table 2.

Table 2: MIC and MBC data for *E. faecalis* and *E. faecium*

| Organism | N | Antibiotic[a] | MIC (µg/mL) | | | MBC (µg/mL) | | |
|---|---|---|---|---|---|---|---|---|
| | | | Range | $MIC_{50}$ | $MIC_{90}$ | Range | $MBC_{50}$ | $MBC_{90}$ |
| *E. faecalis* | 10 | TLV | | 0.5 | 8 | | 16 | 32 |
| | | VAN | | 2 | 512 | | 64 | >512 |
| | | TEI | | 0.12 | 64 | | 8 | >128 |
| | | LZD | | 1 | 2 | | 32 | >32 |
| | | DAP | | 1 | 2 | | 1 | 2 |
| *E. faecium* | 10 | TLV | | 0.25 | 4 | | 4 | 32 |
| | | VAN | | 2 | 256 | | 64 | >512 |
| | | TEI | | 0.5 | 32 | | 8 | >128 |
| | | LZD | | 1 | 2 | | >32 | >32 |
| | | DAP | | 2 | 2 | | 4 | 8 |

[a]TLV, telavancin; VAN, vancomycin; TEI, teicoplanin; LZD, linezolid; DAP, daptomycin

Source: 5.3.5.4.1.5 Table 7, this submission

b(4)

*Minimum Bactericidal Concentration Studies ~ Conclusions:*
The applicant has provided data to support the claim of consistent bactericidal activity against the organisms included in the proposed indication, with the exception of vancomycin-susceptible *Enterococcus faecalis*. Bactericidal activity against enterococcal species did not meet the established criteria for bactericidal activity (MBC:MIC ratio of ≤ 4), but MBC values for these strains were superior to glycopeptide comparators and indicated some bactericidal activity.

**II. Time-kill Studies**

Vancomycin treatment failures have been associated with the relatively slow bactericidal action of the antimicrobial [Sakoulas 2004]. The applicant claims rapid bactericidal activity of telavancin against pathogens included in the proposed indications, with concomitant improved efficacy, compared to vancomycin and other glycopeptides. The applicant has submitted data and conclusions from multiple time-kill studies, designed to support the claim for a comparatively rapid rate of bacterial killing. Killing kinetics were studied using fixed concentrations of telavancin and comparators, concentrations representing multiples of the MIC, and concentrations approximating peak and trough concentrations. Bactericidal activity was defined as a 3 $\log_{10}$ reduction of viable cells within 24 hours.

In a time-kill study (Focus Bio-Inova 2006); using multiples of the MIC, telavancin was bactericidal against five of seven strains of *S. aureus* at ≤ 8X MIC (data from the Focus Bio-Inova study is summarized in Table 3). At 100 µg/ml (plasma peak concentration) telavancin was bactericidal against all tested strains at 24 hours, including vancomycin-susceptible and –resistant enterococcal species. At low multiples of the MIC (2X and 4X) bactericidal activity was inconsistent.

Data from a separate, similar study conducted by the applicant (Report 06-6424-MCB-09) were consistent with the above. Telavancin was bactericidal against all tested staphylococcal strains (n = 5) at 8X MIC, with the exception of MRSA 13405084 ($\log_{10}$ reduction at 8X MIC, 24 hours = -2.20). Telavancin was also bactericidal at 24 hours against tested strains of ß-hemolytic streptococci (0.03 to 0.5 µg/ml). Telavancin was not bactericidal at 8X MIC against tested strains of *E. faecium* or *E. faecalis*.

Data from seven additional time-kill studies using multiples of the MIC to determine telavancin bactericidal activity, and one study using multiples of the MBC, support the bactericidal activity of telavancin against *S. aureus*, including strains with relative tolerance to vancomycin, at 8X MIC.

Table 3: $Log_{10}$ reduction[a] in viable counts for each organism tested against telavancin at 2, 4 and 8 times the MIC and at 100 µg/ml

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 0.25 | 1345074 | *S. aureus* | MRSA/Dap-NS | | 0.5 µg/mL | 1 µg/mL | 2 µg/mL | 100 µg/mL |
| | | | | 2 | 0.5 | 0.3 | 0.5 | 0.6 |
| | | | | 4 | 1.4 | 0.7 | 1.4 | -4.1 |
| | | | | 8 | 0.1 | -4.1 | 2.4 | -4.1 |
| | | | | 24 | -1.3 | -4.1 | 0.7 | -4.1 |
| 0.5 | 1345076 | *S. aureus* | ATCC 29213 | | 1 µg/mL | 2 µg/mL | 4 µg/mL | 100 µg/mL |
| | | | | 2 | 0.6 | 0.6 | 0.2 | -4.2 |
| | | | | 4 | 1.3 | 1.6 | 1.9 | -4.2 |
| | | | | 8 | -4.2 | -4.2 | -4.2 | -4.2 |
| | | | | 24 | 1.7 | -4.2 | -4.2 | -4.2 |
| 4 | 1345078 | *S. aureus* | Van-R | | 8 µg/mL | 16 µg/mL | 32 µg/mL | 100 µg/mL |
| | | | | 2 | 0.1 | 0.3 | 2.2 | -3.7 |
| | | | | 4 | 0.7 | 0.8 | -3.7 | -3.7 |
| | | | | 8 | -3.7 | -3.7 | -3.7 | -3.7 |
| | | | | 24 | -3.7 | -3.7 | -3.7 | -3.7 |
| 1 | 1345079 | *S. aureus* | Van-R | | 2 µg/mL | 4 µg/mL | 8 µg/mL | 100 µg/mL |
| | | | | 2 | 1.2 | 1.0 | 0.9 | -3.9 |
| | | | | 4 | -3.9 | -3.9 | -3.9 | -3.9 |
| | | | | 8 | -3.9 | -3.9 | -3.9 | -3.9 |
| | | | | 24 | -3.9 | -3.9 | -3.9 | -3.9 |
| 0.5 | 1345080 | *S. aureus* | MR | | 1 µg/mL | 2 µg/mL | 4 µg/mL | 100 µg/mL |
| | | | | 2 | 0.3 | 0.1 | 0.2 | -4.3 |
| | | | | 4 | 1.3 | 1.1 | 1.0 | -4.3 |
| | | | | 8 | -4.3 | 2.9 | -4.3 | -4.3 |
| | | | | 24 | 0.1 | 2.0 | -4.3 | -4.3 |
| 0.5 | 1345081 | *S. aureus* | Van-I (Mu50) | | 1 µg/mL | 2 µg/mL | 4 µg/mL | 100 µg/mL |
| | | | | 2 | 0.4 | 0.4 | 0.4 | -4.1 |
| | | | | 4 | 0.4 | 0.6 | 0.4 | -4.1 |
| | | | | 8 | 0.9 | 0.9 | 0.9 | -4.1 |
| | | | | 24 | 0.1 | -0.4 | 2.5 | -4.1 |
| 0.12 | 1345084 | *S. aureus* | MR/Van-S | | 0.25 µg/mL | 0.5 µg/mL | 1 µg/mL | 100 µg/mL |
| | | | | 2 | 0.2 | 0.2 | 0.1 | -4.1 |
| | | | | 4 | 0.3 | 0.5 | 0.6 | -4.1 |
| | | | | 8 | 1.7 | 1.8 | 2.1 | -4.1 |
| | | | | 24 | 0.3 | 0.6 | 1.0 | 2.3 |
| 8 | 1345082 | *E. faecium* | *vanA* | | 16 µg/mL | 32 µg/mL | 64 µg/mL | 100 µg/mL |
| | | | | 2 | 0.2 | 1.3 | -3.7 | 1.2 |
| | | | | 4 | 0.6 | -3.7 | -3.7 | -3.7 |
| | | | | 8 | 0.3 | -3.7 | -3.7 | -3.7 |
| | | | | 24 | -3.7 | -3.7 | -3.7 | -3.7 |
| 0.12 | 1345083 | *E. faecium* | *vanB* | | 0.25 µg/mL | 0.5 µg/mL | 1 µg/mL | 100 µg/mL |
| | | | | 2 | 0.5 | 0.0 | 0.0 | -4.0 |
| | | | | 4 | 0.7 | 0.3 | 0.1 | -4.0 |
| | | | | 8 | -0.1 | 0.3 | 0.4 | -4.0 |
| | | | | 24 | -1.3 | -1.5 | -0.2 | -4.0 |
| 0.25 | 1345088 | *E. faecium* | Van-S | | 0.5 µg/mL | 1 µg/mL | 2 µg/mL | 100 µg/mL |
| | | | | 2 | -0.1 | -0.1 | 0.0 | -3.8 |
| | | | | 4 | 0.4 | 0.0 | 0.1 | -3.8 |
| | | | | 8 | 0.3 | 0.5 | 0.3 | -3.8 |
| | | | | 24 | -1.8 | -2.2 | -1.6 | -3.8 |
| 0.03 | 1345089 | *S. pneumoniae* | MDR | | 0.06 µg/mL | 0.12 µg/mL | 0.25 µg/mL | 100 µg/mL |
| | | | | 2 | 1.0 | 1.6 | 1.5 | -4.9 |
| | | | | 4 | 2.4 | 2.6 | 2.1 | -4.9 |
| | | | | 8 | 2.9 | -4.9 | -4.9 | -4.9 |
| | | | | 24 | -4.9 | -4.9 | -4.9 | -4.9 |

[a]Light gray shading indicates that there was ≥3 $log_{10}$ reduction compared with the initial inoculum.

Source: Table 2; Focus Bio-Inova Inc. Time Kill Kinetics of Telavancin and Comparators Tested at Multiples of the MIC, Staphylococci, Enterococci, and Streptococci. 2006 (this submission)

In a time-kill study employing fixed concentrations (4, 8, 16 and 32 µg/ml), telavancin was bactericidal against all strains tested, including *S. aureus* (MRSA, daptomycin-nonsusceptible *S. aureus*, and vancomycin-intermediate *S. aureus*), ß-hemolytic streptococci (*S. pyogenes* and *S. agalactiae*), and vancomycin-susceptible enterococcus (*E. faecium* and *E. faecalis*).
At 8 µg/ml (the mean trough concentration for healthy volunteers dosed at 10 mg/kg, reported in Phase 2 Study, 202b), telavancin was bactericidal against all strains except the enterococci. The data for the Focus Bio-Inova study is summarized in Table 4 (Focus Bio-Inova 2006).

In a similar study, conducted by the applicant (Report 06-6424-MCB-10), fixed concentrations were determined based on predicted human plasma peak and trough concentrations. Data from this investigation support rapid (≤ 24 hrs) bactericidal activity of telavancin against all strains of *S. aureus*, including strains non-susceptible to vancomycin. Against tested strains of ß-hemolytic streptococci, telavancin was bactericidal at 24 hours at $C_{max}$ values, but variable at $C_{min}$ values. Against *E. faecalis* ATCC 51575 (VanB), telavancin was bactericidal, but only at the $C_{max}$ concentration.

Table 4: $Log_{10}$ reduction[a] in viable counts for all isolates tested against telavancin at 4,8,16 and 32 times the MIC

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 0.25 | 1345074 | *S. aureus* | MRSA Dap-NS | 2 | 0.0 | 0.1 | 0.3 | 1.1 |
| | | | | 4 | 0.4 | 0.5 | 0.7 | 3.2 |
| | | | | 8 | 1.2 | 1.6 | 3.5 | 4.2 |
| | | | | 24 | 1.2 | 3.5 | 3.5 | 3.5 |
| 0.5 | 1345081 | *S. aureus* | VISA (Mu50) | 2 | 0.1 | 0.2 | 0.3 | 1.5 |
| | | | | 4 | 0.3 | 0.4 | 0.8 | 2.4 |
| | | | | 8 | 0.9 | 1.1 | 2.4 | 3.4 |
| | | | | 24 | 0.6 | 3.7 | 3.7 | 3.7 |
| 0.12 | 1345084 | *S. aureus* | MRSA/VSSA | 2 | 0.2 | 0.2 | 0.3 | 0.7 |
| | | | | 4 | 0.5 | 0.7 | 0.9 | 1.3 |
| | | | | 8 | 1.4 | 2.1 | 2.4 | 2.4 |
| | | | | 24 | 2.3 | 4.0 | 4.0 | 4.0 |
| 0.03 | 1443443 | *S. agalactiae* | Ery-R, Pen S | 2 | 0.5 | 0.7 | 1.2 | 2.3 |
| | | | | 4 | 0.7 | 1.0 | 2.0 | 3.6 |
| | | | | 8 | 1.0 | 3.6 | 3.6 | 3.6 |
| | | | | 24 | 3.6 | 3.6 | 3.6 | 3.6 |
| 0.03 | 1443442 | *S. pyogenes* | Ery-R, Pen S | 2 | 3.6 | 3.6 | 3.6 | 3.6 |
| | | | | 4 | 3.6 | 3.6 | 3.6 | 3.6 |
| | | | | 8 | 3.6 | 3.6 | 3.6 | 3.6 |
| | | | | 24 | 3.6 | 3.6 | 3.6 | 3.6 |
| 1 | 1443444 | *E. faecalis* | Van-S | 2 | -0.2 | 0.0 | 0.1 | 0.5 |
| | | | | 4 | 0.1 | 0.2 | 0.2 | 0.9 |
| | | | | 8 | 0.4 | 0.6 | 0.6 | 1.2 |
| | | | | 24 | 1.0 | 1.9 | 3.4 | 3.7 |
| 0.25 | 1345088 | *E. faecium* | Van-S | 2 | 0.0 | 0.0 | 0.0 | 0.7 |
| | | | | 4 | 0.0 | 0.0 | 0.0 | 1.0 |
| | | | | 8 | 0.1 | 0.1 | 0.2 | 1.5 |
| | | | | 24 | 0.2 | 0.3 | 0.3 | 3.7 |

[a]Light gray shading indicates that there was >=3 $log_{10}$ reduction compared with the initial inoculum.

Source: Table 2; Focus Bio-Inova Inc. Time Kill Kinetics of Telavancin at Fixed Concentrations against Staphylococci, Enterococci, and Streptococci. 2006 (this submission)

*Time-kill Studies ~ Conclusions:*

The applicant has submitted sufficient data from time-kill kinetic studies to support a claim of bactericidal activity of telavancin against a variety of strains of *S. aureus*, including strains susceptible and non-susceptible to methicillin, and strains 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 strains of ß-hemolytic streptococci (*S. pyogenes* and *S. agalactiae*) was also demonstrated, but at low fixed concentrations, activity was variable (i.e. concentrations representing $C_{min}$ for vancomycin in healthy adults dosed at 10 mg/kg).

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.

## HUMAN AND ANIMAL STUDIES

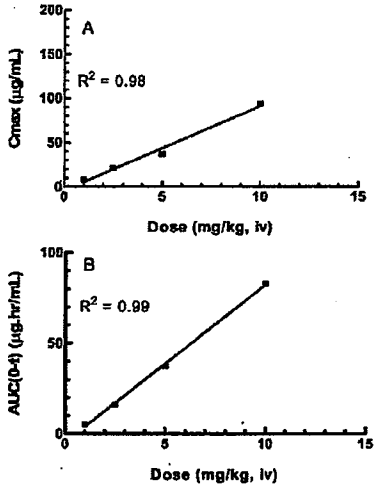
### ANIMAL DISEASE MODELS

The applicant has 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. For the purposes of this review, the murine subcutaneous infection model (one study), and neutropenic murine thigh models (three studies) will be of primary interest.

In a study of telavancin in vivo pharmacodynamics (Hegde 2004), the investigators determined MIC values of telavancin against a variety of strains of Gram positive bacteria (Table 1), using methods approved by the CLSI. Telavancin protein binding was determined by equilibrium dialysis. Experimental treatments, using both the MSI and MNT models (i.e. models with and without immune suppression), included single-dose studies (0.1 to 80 mg/kg, i.v.) and dose-fractionation studies (single dose, two divided doses [q 12 h], three divided doses [q 8 h], or four divided doses [q 6 h]). Vancomycin, linezolid, and nafcillin were included as comparators. The response producing 50% of the maximum response was defined as the $ED_{50}$. In this study, protein binding of telavancin was concentration-independent, ranging from 94 to 96%. MICs of telavancin against MRSA 33591 (0.4 µg/ml in MHB alone) increased by 5-fold in the presence of 95% mouse serum (to 2 µg/ml), and 10-fold in the presence of 95% mouse albumin (to 4 µg/ml).

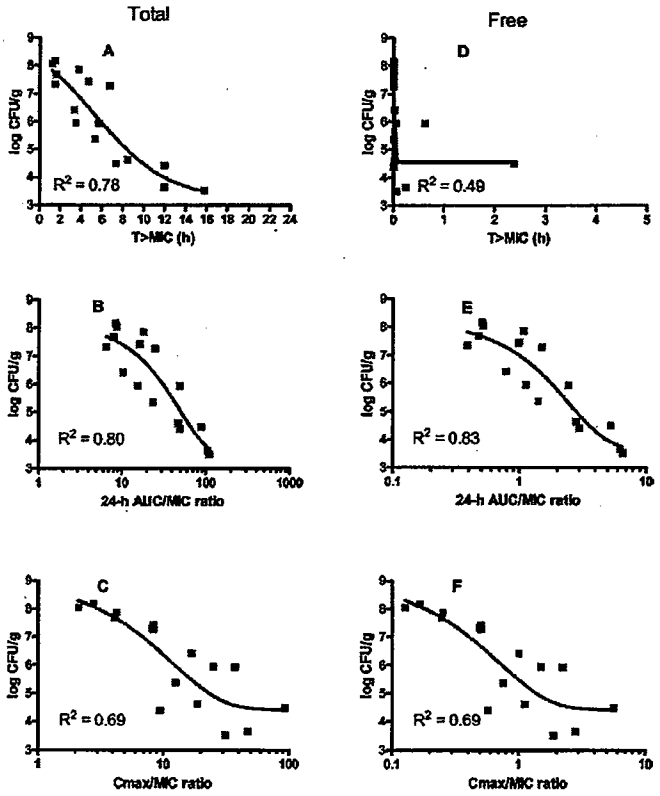
Results of the Hegde study indicate that while $AUC_{(0-24)}$/MIC and T>MIC are comparable predictors of efficacy, $AUC_{(0-24)}$/MIC was more predictive when free drug concentrations were considered (Figures 1 and 2). Results from single-dose administration indicated dose-dependent activity of telavancin against all tested strains, with activity of telavancin superior to comparators (Table 1 and Figure 3). Results from dose-fractionation studies indicated that the four dosing intervals were comparable. This finding, in combination with the identification of $AUC_{(0-24)}$/MIC as the best PD predictor of efficacy, supports a once-daily dosing regimen. The potency of all tested antimicrobials were greater in the subcutaneous infection model, compared to the neutropenic thigh model, with the difference in telavancin potency less notable than comparators (Table 2). The investigators suggest that one explanation for this observation may be that telavancin is less affected by the immune status of the animal, than specific comparators (notably, linezolid).

Figure 1: Relationship between telavancin dose and Cmax (A) and dose versus AUC (B) for various doses of telavancin. The values are means (n=3)




Source: Figure 3; Hegde 2004

Figure 2: Relationship between titer observed in thigh samples and the following pharmacodynamically linked variables: time above the MIC (A and D), 24-h AUC/MIC ratio (B and E), and Cmax/MIC ratio (C and F) using total (A,B, and C) and free-drug (D,E, and F) concentrations. The organism studied was MRSA 33591.




Source: Figure 3; Hegde 2004

Table 1: Point Dose Estimates of Telavancin Required to Attain Different Pharmacodynamic Endpoints against Gram-positive Bacterial Strains in the Neutropenic Murine Thigh Model

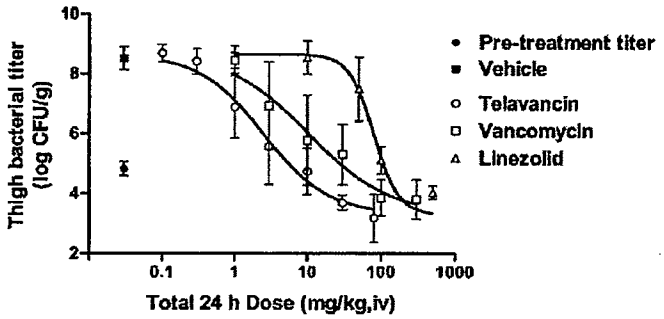
| Organism | | MIC (µg/mL) | 24hours growth (log CFU/g)[1] | Doses of Telavancin (mg/kg, IV) Required to Attain Different Pharmacodynamic Endpoints | | |
|---|---|---|---|---|---|---|
| | | | | $ED_{50}$ | $ED_{Stasis}$ | $ED_{1\ log\ kill}$ |
| *Staphylococcus. aureus* | MRSA 33591 | | 3.7 | 2.5 | 6.3 | 27.5 |
| | MRSA MCJ25 | | 3.3 | 3.1 | 4.4 | 8.9 |
| | MRSA SFVA06 | | 2.8 | 3.7 | 3.3 | 6.1 |
| | MRSA MGH 10 | | 4.0 | 4.4 | 8.5 | 29.5 |
| | MSSA 13709 | | 3.5 | 1.7 | 2.5 | 5.5 |
| | MSSA KPB01 | | 3.7 | 2.2 | 6.3 | 47.8 |
| | MSSA KPB04 | | 4.1 | 1.7 | 6.3 | 32.3 |
| | MSSA MED 415 | | 4.2 | 2.0 | 2.8 | 4.8 |
| *Staphylococcus. epidermidis* | MRSE SFVA01 | | 1.0 | 1.0 | 0.7 | 1.4 |
| | MSSE SU03 | | 2.0 | 1.2 | 0.9 | 2.9 |
| *Streptococcus pneumoniae* | PRSP SU2 | | 2.2 | 0.5 | 0.4 | 0.6 |
| | PRSP CHM11 | | 3.5 | 2.9 | 3.3 | 5.4 |
| | PSSP SU10 | | 3.3 | 1.8 | 1.7 | 2.6 |
| | PSSP SU07 | | 4.1 | 2.0 | 2.8 | 5.2 |
| *Enterococcus faecalis* | VRE VanA A256 | | 2.0 | 6.6 | 50 | NA |

b(4)

$ED_{50}$ was defined as the dose required to produce 50% of the maximum response. $Log_{10}$ Stasis Dose ($ED_{stasis}$) was defined as the dose producing no net change in thigh titer compared to pre-treatment titer. 1 $log_{10}$ kill dose ($ED_{1\text{-}log\ kill}$) was defined as the dose required to produce a decrease in titer of 1 log CFU/g from pre-treatment controls. [1] the magnitude of growth of the organism at 24 hrs after inoculation in untreated animals. NA = not achieved.

Source: 5.3.5.4.1.9 Table 1, this submission

Figure 3: Efficacies of telavancin, vancomycin, and linezolid against MRSA 33591 in the mouse neutropenic thigh model. The abscissa shows the total 24-h dosage, and the ordinate shows the titer observed in thighs. Vehicle (n=16) and telavancin (n = 5 to 16 per dose) were administered q 24 h, whereas vancomycin (n = 5 per dose) and linezolid (n = 6 per dose) were administered q 12 h. n = 16 for the control pretreatment group. Data are expressed as means ± 1 SD (error bars).




Source: Figure 6; Hegde 2004

Table 2: Comparison of the Dose Estimates of Telavancin, Vancomycin and Linezolid against Infection Caused by MRSA 33591 in the Neutropenic Murine Thigh and Murine Subcutaneous Infection Models

| Antibiotic | Neutropenic Thigh Model $ED_{1\text{-}logkill}$ | Subcutaneous Infection Model $ED_{1\text{-}logkill}$ | $ED_{1\text{-}logkill}$ ratio (MNT/MSI) |
|---|---|---|---|
| Telavancin | 27.5 | 2.1 | 13 |
| Vancomycin | 199.5 | 3.9 | 51 |
| Linezolid | > 500 | 2.6 | > 192 |

$ED_{1\text{-}logkill}$: dose (mg/kg, IV) required to produce 1-log kill reduction in titer from pre-treatment levels

Source: 5.3.5.4.1.9 Table 2, this submission

In additional studies of telavancin in vivo efficacy in mouse neutropenic thigh models, the applicant conducted investigations of telavancin compared to daptomycin (Report No 04-6424-PH-02) and telavancin compared to vancomycin (Report No 05-6424-PH-01). In both studies, dosing was designed to approximate human exposure (AUC), and efficacy was compared at two stringency levels by adjustments to post-dose inoculation times (high stringency treatment was initiated at 8-hours post inoculation, low stringency treatment was initiated at 3-hours post inoculation). The activity of telavancin (40 mg/kg IV, bid), vancomycin (110 mg/kg, IV, bid), and daptomycin (24 mg/kg, IV, bid) against MRSA 33591 were compared. At high pre-treatment titers (high stringency), telavancin efficacy was comparable to vancomycin but more efficacious than daptomycin. At low pre-treatment titers (low stringency) telavancin was more efficacious than vancomycin, but comparable to daptomycin.

*Animal Disease Models ~ Conclusions:*

The applicant has submitted data from animal in vivo studies that supports the use of $AUC_{(0\text{-}24)}$/MIC as the best PK/PD predictor of antimicrobial efficacy for unbound (free) telavancin. Comparison of data from the MNT and MSI models 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. Studies included the antibacterial activity of primary metabolites. The pharmacokinetic summary for the proposed package insert is presented below (Table 1).

Table 1: Non-compartmental Pharmacokinetic Parameters for Telavancin Following Single-dose or Multiple-dose Administration of 10 mg/kg Telavancin via a 60-Minute Intravenous Infusion

| | Single Dose | Multiple Dose |
|---|---|---|
| | (n=42) | (n=36) |
| $C_{max}$ (µg/mL) | 93.6 ± 14.2 | 108 ± 26 |
| $C_{min}$ (µg/mL) | – | 8.6 ± 2.8 |
| $AUC_{0-\infty}$ (µg·hr/mL) | 747 ± 129 | – |
| $AUC_{0-24h}$ (µg·hr/mL) | 666 ± 107 | 780 ± 125 |
| $t_{1/2}$ (hr) | 8.0 ± 1.5 | 8.1 ± 1.5 |
| CL (mL/hr/kg) | 13.9 ± 2.9 | 13.1 ± 2.0 |
| MRT (hr) | 10.8 ± 2.1 | 10.2 ± 1.9 |
| $V_{ss}$ (mL/kg) | 145 ± 23 | 133 ± 24 |
| $C_{max}$ = maximum plasma concentration; $C_{min}$ = steady-state plasma concentration at 24 hours; AUC = area under concentration-time course; $t_{1/2}$ = terminal elimination half-life; CL = clearance; MRT = mean residence time; $V_{ss}$ = apparent volume of distribution at steady state. | | |

Source: 5.3.5.4.1.8 Table 1, this submission

In one study of telavancin pharmacokinetics (Report I6424-108a), healthy males and females 18-50 years of age received 10mg/kg of the drug for three consecutive days. Results of this study indicated that following IV administration, the mean telavancin $C_{max}$ was 116 µg/ml, mean half-life was 7.4 hours, and mean plasma clearance was 13 ml/hr/kg. Mean trough concentrations were 8.11 ± 2.28 µg/ml.

Results of a single-dose study (Report I6424-101a), dosing at 10 mg/kg of telavancin in healthy males aged 18-50 resulted in $C_{max}$ values of 105 µg/ml and trough concentrations 8.92 µg/ml. Pharmacokinetics was approximately linear, with $C_{max}$ proportional to dose, but AUC values were higher than expected with doses ≥ 5 mg/kg. Renal excretion was found to be the primary route of elimination. In this study, serum bactericidal activity against methicillin-resistant *S. aureus* persisted at 24 hours, after a single 5 mg/kg dose (Table 1).

Table 1: Serum Bactericidal Activity and Plasma Concentrations Following Multiple Doses of Telavancin in Healthy Subjects (Study 101a)

| | Plasma Concentration on Day 7 | | Median Reciprocal Bactericidal Titers on Day 7 Against Indicated Isolate | | | |
|---|---|---|---|---|---|---|
| | (µg/mL) | | MRSA[a] | | PRSP[b] | |
| Dose (mg/kg/day) | Peak | Trough | Peak | Trough | Peak | Trough |
| 7.5 | 96.7 | 9.30 | 256 | 16 | ≥ 512 | 128 |
| 12.5 | 151 | 13.5 | ≥ 512 | 24 | ≥ 512 | 256 |
| 15 | 203 | 15.2 | ≥ 512 | 32 | ≥ 512 | ≥ 512 |

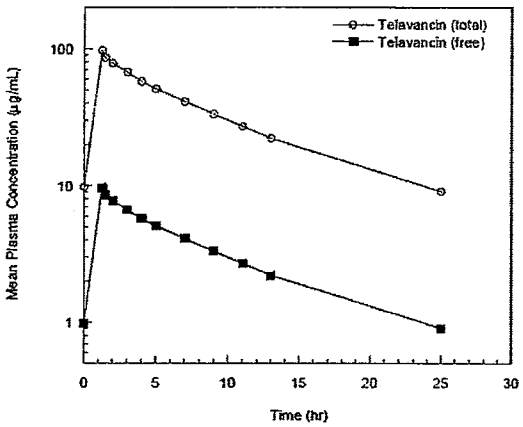
[a] *S. aureus* ATCC 33591 (telavancin MIC = 0.5 µg/mL)

[b] *S. pneumoniae* MED 1090 (telavancin MIC = 0.015 µg/mL)

Source: 5.3.5.4.1.8 Table 2, this submission

The estimated free fraction of plasma telavancin (assuming ~ 90% protein binding) was calculated in a study of daily 10 mg/kg dosing over seven consecutive days (Figure 1). In this study, the mean steady-state AUC values were 776 ± 143 µg·hr/ml.

Figure 1: Semi-log Plot of Mean Plasma Concentrations of Telavancin (total and free) versus Time Following Intravenous Administration to Healthy Subjects at a Dose of 10 mg/kg (Study 0032)



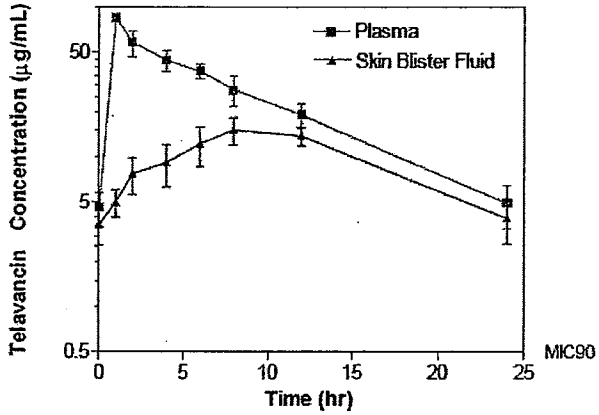

Source: 5.3.5.4.1.8 Figure 1, this submission

Single-dose pharmacokinetic studies in animals (mice, rats, rabbits, dogs and monkeys) demonstrated dose-proportional increases for $C_{max}$ (up to 25 mg/kg in rodents and from 10 to 50 mg/kg in rabbits). In rats and dogs, telavancin was excreted primarily in the urine, largely unchanged. Protein binding in binding in all tested animal species was similar to that determined in humans (~ 90%).

The primary metabolite, AMI-11352, in human urine samples was also the primary metabolite found in dog serum, and rat and dog urine. AMI-11352 was shown to possess antimicrobial activity (Report 05-6424-MB-04), with MIC values approximately 10-fold higher than telavancin and 4-fold higher than vancomycin against all strains tested (*S. aureus* ATCC 13709, *S. aureus* ATCC 33591, and *E. faecalis* ATCC 29212).

In a study of the steady-state pharmacokinetics of telavancin in plasma and skin blister fluid, telavancin levels in blister fluid were shown to reach $C_{max}$ (16 µg/ml) 6 to 12 hours after dosing and declined at a rate similar to the rate observed in plasma. When dosed at 7.5 mg/kg, telavancin levels in skin blister fluid of the 8 subjects tested remained at least 4-fold higher than the stated telavancin MIC of S. aureus (0.5 µg/ml), throughout the 24-hour dosing interval. Results of the skin blister fluid study are summarized in Figure 2 and Table 2.

Figure 2: Semi-log Plot of Mean ± SD Concentrations of Telavancin in Plasma and Skin Blister Fluids versus Time Following Intravenous Administration to Healthy Subjects at a Dose of 7.5 mg/kg (Study 107a)




Source: 5.3.5.4.1.8 Figure 2, this submission

Table 2: Mean (± SD) Non-Compartmental Pharmacokinetic Parameters on Day 3 for Telavancin in Plasma and Skin Blister Fluid Following Intravenous Administration to 8 Healthy Subjects at a Dose of 7.5 mg/kg via a 60-Minute Infusion Once Daily for 3 days

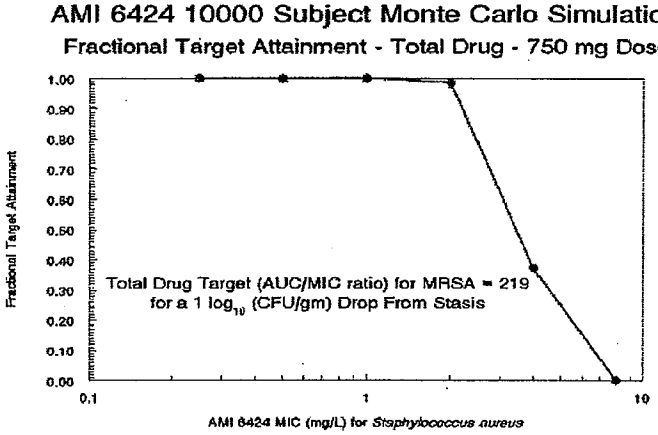
| Pharmacokinetic Parameters | Plasma (n=8) | Skin Blister Fluid (n=8) |
|---|---|---|
| $C_{max}$ (µg/mL) | 84.8 ± 5.3 | 16.0 ± 2.0 |
| $T_{max}$ (hr) | 1.0 ± 0.0 | 9.3 ± 2.4 |
| $AUC_{0-24}$ (µg.hr/mL) | 604 ± 83 | 241 ± 33 |
| $C_{24}$ on Day 3 (µg/mL) | 4.92 ± 1.58 | 3.90 ± 1.24 |
| $T_{1/2}$ (hr) | 6.26 ± 0.78 | 6.91 ± 0.53[1] |
| $CL_{ss}$ (mL/hr/kg) | 12.6 ± 2.1 | ND |
| $V_{ss}$ (mL/kg) | 105 ± 16 | ND |
| MRT (hr) | 8.37 ± 1.03 | ND |
| | SBF/Plasma Ratios | |
| $C_{max}$ | 0.189 ± 0.030 | |
| AUC | 0.403 ± 0.058 | |
| $C_{24}$ (Day 3) | 0.816 ± 0.182 | |

[1]n=5
ND: Not determined

Source: Theravance Inc. Clinical Pharmacokinetic Report 107a: Pharmacokinetic Evaluation of Intravenous Telavancin in Plasma and Blister Fluid. 2006.

The applicant simulated 10,000 $AUC_{(0-24)}$ values per dose, for at least three doses, using Monte Carlo simulation. Values were corrected for protein binding (~ 90%) and the $AUC_{(0-24)}$/MIC ratio was determined. One $log_{10}$ drop from stasis ($AUC_{(0-24)}$/MIC = 219 for MRSA with MIC = 1µg/ml) was chosen as a conservative target (and was used in Phase 2 and Phase 3 trials). Monte Carlo simulation, using a 750 mg dose (based on a 10mg/kg dose for an individual of average body weight) resulted in ≥ 99% target attainment rates for methicillin-resistant S. aureus with an MIC up to 2 µg/ml (Figure 3).

Figure 3: Fractional Target Attainment of the 1-$\log_{10}$ CFU Drop Based on the Total Drug Concentration of Telavancin (AMI-6424) in Plasma




Source: 5.3.5.4.1.8 Figure 3, this submission

*Pharmacokinetic / Pharmacodynamic Studies ~ Conclusions:*

The applicant has provided data from a variety of studies to support the proposed pharmacokinetic parameters. Levels of telavancin measured in skin blister studies, including trough levels, are higher than the proposed telavancin susceptible breakpoint for all indicated organisms (*S. aureus*, vancomycin-susceptible *E. faecalis*, and streptococcal spp. other than *S. pneumoniae*). 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).

## CLINICAL TRIALS

The applicant has provided data from four pivotal clinical trials (Studies 202a, 202b, 0017, and 0018). The acronym ATLAS is used to describe the two Phase 3 studies (0017 and 0018), and the acronym FAST to describe the two Phase 2 studies (FAST = 202a, FAST 2 = 202b). 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. For the purposes of microbiologic review (efficacy, susceptibility breakpoint determination, quality control parameters, etc.) only Post Amendment Study 202b and the two ATLAS studies will be considered. The study populations for the Post Amendment Clinical Studies are summarized in Table 1. The type and location of cSSSI observed in the Post Amendment Clinical Studies are summarized in Table 2.

Table 1: Data Sets Analyzed – Post Amendment Studies 0017, 0018 and 202b, Individually and Combined

| | 0017 Post-Amendment | | 0018 Post-Amendment | | 0017 + 0018 Post-Amendment | | 202b Post-Amendment | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Telavancin 10 mg/kg | VANC | Telavancin 10 mg/kg | VANC | Telavancin 10 mg/kg | VANC | Telavancin 10 mg/kg | VANC[1] | Telavancin 10 mg/kg | VANC[1] |
| AT | 426 (100) | 429 (100) | 502 (100) | 510 (100) | 928 (100) | 939 (100) | 100 (100) | 95 (100) | 1028 (100) | 1034 (100) |
| MAT | 307 (72) | 322 (75) | 373 (74) | 381 (75) | 680 (73) | 703 (75) | 80 (80) | 70 (74) | 760 (74) | 773 (75) |
| CE | 346 (81) | 349 (81) | 399 (79) | 395 (77) | 745 (80) | 744 (79) | 77 (77) | 77 (81) | 822 (80) | 821 (79) |
| ME | 237 (56) | 255 (59) | 290 (58) | 281 (55) | 527 (57) | 536 (57) | 61 (61) | 53 (56) | 588 (57) | 589 (57) |

Percentages are based on number of patients in the AT population.
[1] Includes 7 patients who received a semi-synthetic penicillin instead of vancomycin, none of whom had MRSA as a BL pathogen.
Analysis populations are defined in Table 13.
Source: ISE

AT: All-treated population; MAT: Modified all-treated population; CE: Clinically evaluable population; ME: Microbiologically evaluable population
Source: 5.3.5.4.1.10 Table 16, this submission

Table 2: Type and Location of cSSSI – Post Amendment Studies 0017, 0018 & 202b Individually and Combined – AT Population

| | 0017 Post Amendment | | 0018 Post Amendment | | 0017 + 0018 Post Amendment | | 202b Post Amendment | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Telavancin 10 mg/kg (N=426) | VANC (N=429) | Telavancin 10 mg/kg (N=502) | VANC (N=510) | Telavancin 10 mg/kg (N=928) | VANC (N=939) | Telavancin 10 mg/kg (N=100) | VANC[1] (N=95) | Telavancin 10 mg/kg (N=1028) | VANC[1] (N=1034) |
| | Number (%) of Patients | | | | | | | | | |
| **Description of Complicated Skin/Skin Structure Infection** | | | | | | | | | | |
| Major Abscess | 179 (42) | 193 (45) | 209 (42) | 209 (41) | 388 (42) | 402 (43) | 58 (58) | 55 (58) | 446 (43) | 457 (44) |
| Wound Infection | 72 (17) | 60 (14) | 72 (14) | 64 (13) | 144 (16) | 124 (13) | 11 (11) | 10 (11) | 155 (15) | 134 (13) |
| Deep/Extensive Cellulitis | 156 (37) | 161 (38) | 179 (36) | 195 (38) | 335 (36) | 356 (38) | 29 (29) | 27 (28) | 364 (35) | 383 (37) |
| Infected Ulcer | 16 (4) | 12 (3) | 29 (6) | 36 (7) | 45 (5) | 48 (5) | 2 (2) | 1 (1) | 47 (5) | 49 (5) |
| Infected Burn | 3 (<1) | 3 (<1) | 13 (3) | 6 (1) | 16 (2) | 9 (<1) | 0 (0) | 2 (2) | 16 (2) | 11 (1) |
| - Total - | 426 (100) | 429 (100) | 502 (100) | 510 (100) | 928 (100) | 939 (100) | 100 (100) | 95 (100) | 1028 (100) | 1034 (100) |
| **Location of Primary Infection Site** | | | | | | | | | | |
| Head/Neck | 29 (7) | 33 (8) | 36 (7) | 31 (6) | 65 (7) | 64 (7) | 10 (10) | 7 (7) | 75 (7) | 71 (7) |
| Front Torso | 61 (14) | 60 (14) | 75 (15) | 64 (13) | 136 (15) | 124 (13) | 13 (13) | 12 (13) | 149 (14) | 136 (13) |
| Back Torso | 43 (10) | 53 (12) | 56 (11) | 55 (11) | 99 (11) | 108 (12) | 13 (13) | 8 (8) | 112 (11) | 116 (11) |
| Upper Extremities | 84 (20) | 99 (23) | 70 (14) | 71 (14) | 154 (17) | 170 (18) | 19 (19) | 21 (22) | 173 (17) | 191 (18) |
| Lower Extremities | 209 (49) | 184 (43) | 265 (53) | 289 (57) | 474 (51) | 473 (50) | 45 (45) | 47 (49) | 519 (50) | 520 (50) |
| - Total - | 426 (100) | 429 (100) | 502 (100) | 510 (100) | 928 (100) | 939 (100) | 100 (100) | 95 (100) | 1028 (100) | 1034 (100) |

[1] Includes 7 patients who received a semi-synthetic penicillin instead of vancomycin, none of whom had MRSA as a BL pathogen.
Source: Dataset(s): ADSL Program: \\vol\sasunix\td-6424_nda_csssi_ise\hardlock\programs\t_btcssi.sas Run Date: 25AUG06/18:28 by JYuan on NET_ASRV SASv9.1

Source: 5.3.5.4.1.10 Table 16, this submission

*Reviewer's Note:*
The applicant submitted a statement of clarification (Document Code: N-000-BI), dated 9 March 2007 (received 12 March 2007), related to discrepancies reported in MIC test methods for isolates obtained during Phase 2 clinical studies (Studies 202a and 202b). Original documentation for those studies detailed broth dilution methods that were performed (using frozen panels provided by TREK Diagnostic Systems) without the addition of a wetting agent (polysorbate 80). Previous investigations (describe elsewhere in this review) had determined no requirement for P80, with regard to the in vitro testing of telavancin MICs, and the applicant chose to use a method without P80 for all testing of isolates from clinical trials.
In early 2007, the applicant learned that the central testing facility (ICON Labs), responsible for in vitro analysis of Phase 2 isolates, had performed MIC testing using 0.02% P80 in the inoculating fluid used in conjunction with the testing panels. All isolates were reevaluated in tests without the addition of P80, and were reported in the communication described above. Only this amended data will be considered, for the purposes of this review.

**SYNOPSIS OF FAST STUDY 202b**

Phase 2 trials were conducted in the United States and South Africa. Enrollment for Study 202b was from 20 February 2004 to 9 September 2004).

The Modified all-treated population (MAT) in Study 202b included all subjects with a "baseline pathogen" recovered from pre-treatment cultures. The Clinically Evaluable (CE) population included subjects with an evaluable analysis value (clinical "cure" or "failure") and had a baseline Gram-positive pathogen recovered from the infection site. Microbiologically evaluable (ME) populations included subjects with a baseline pathogen recovered from the cSSSI site of infection. Efficacy outcomes included Clinical Response, By Patient Microbiologic Response, and By Pathogen Microbiologic Response.

Acceptable specimens in Phase 2 studies included needle aspirates, biopsy, surgically obtained material, and pus or drainage fluid collected using aseptic procedures. Two sets of blood cultures

were drawn, in conjunction with each would culture. Initial Gram stain, culture, and identification of isolates were performed by the local testing facility. Pathogens were sent to the central testing laboratory (ICON Laboratories, Farmingdale, NY) for confirmatory identification and MIC testing. Isolates were stored (-20°C) at the local laboratory. MIC testing by disk diffusion was not performed in Phase 2 studies.

**SYNOPSIS OF ATLAS STUDIES (0017 & 0018)**

Phase 3 trials were conducted in 24 countries, worldwide. Analysis populations and prescribed protocols were identical for the two ATLAS studies (0017 and 0018).

The Modified all-treated population (MAT) in Phase 3 studies included all subjects with a pathogen recovered from pre-treatment cultures of the infected site and/or from blood cultures. The Clinically Evaluable (CE) population included subjects with no baseline Gram-positive pathogens resistant to vancomycin, and patients with a diagnosis of confirmed or suspected MRSA infection (from major abscesses, infected burns, deep cellulitis, infected ulcers, and/or wound infections). Microbiologically evaluable (ME) populations included subjects with a Gram-positive pathogen recovered from pre-treatment cultures of the primary infection and/or blood cultures. Efficacy outcomes included Clinical Response, By Patient Microbiologic Response, and By Pathogen Microbiologic Response.

Acceptable specimens in Phase 3 studies included needle aspirates, biopsy, surgically obtained material, and pus or drainage fluid collected using aseptic procedures. Two sets of blood cultures were drawn, in conjunction with each would culture. Initial Gram stain, culture, and identification

of isolates were performed by the local testing facility. Pathogens were sent to the central testing laboratory (Covance Central Laboratory Services) for confirmatory identification and MIC testing. Isolates were stored (-70°C or 4°C, with monthly subculture) at the local laboratory.

**QUALITY CONTROL PROCEDURES DURING CLINICAL STUDIES**

Development of quality control parameters for MIC testing of telavancin are discussed elsewhere in this review. CLSI approved telavancin quality control ranges are summarized in Table 1. Covance Laboratories (the Phase 3 central laboratory) used these ranges in their routine quality control. MIC values were not reported if QC strains were not within the specified range. QC strains were tested each day that clinical strains were tested.

Table 1: CLSI Approved Telavancin MIC Quality Control Ranges

| [a]QC Strain | CLSI Approved Range (µg/mL) | % of MIC Values Included |
|---|---|---|
| *S. aureus* ATCC 29213 | 0.12-1 | 100 |
| *E. faecalis* ATCC 29212 | 0.12-0.5 | 99.6 |
| *S. pneumoniae* ATCC 49619 | 0.004-0.03 | 100 |

[a]CLSI (64)

Source: 5.3.5.4.1.10 Table 2, this submission

Isolates tested by the MIC method were subcultured 18-24 hours prior to testing, in demineralized water or cation adjusted Mueller-Hinton broth. Microtiter panels were inoculated with approximately 5 x $10^4$ CFU, and incubated at 35°C in ambient air. Staphylococcal and enterococcal cultures were read at 16-20 hours. Streptococcal cultures were read at 20-24 hours.

Isolates tested by the disk diffusion method were plated to Mueller-Hinton agar (streptococcal isolates were plated to Mueller-Hinton with 5% sheep blood), and incubated at 35°C for 16-18 hours in ambient air (streptococcal cultures were incubated in 5-7% $CO_2$). Disk diffusion methods were only used in Phase 3 (ATLAS) studies, since telavancin disks were unavailable for earlier investigations.

No frozen panel, Mueller-Hinton media, or antibiotic disk lot-to-lot variation was noted in quality control data. Comparator (vancomycin) MIC values were all within established CLSI quality control ranges.

Summaries of MIC quality control data, obtained during testing of Phase 3 trial isolates, are provided in Tables 2 through 4. For *S. aureus* ATCC 29213, 99.0% of values were within the established QC range. For *E. faecalis* ATCC 29212, 96.9% were in the established range. For *S. pneumoniae* ATCC 49619 (tested daily, when streptococcal isolates were tested), 100% were within the established QC range.

Table 2: *S. aureus* ATCC 29213 – Number of Results at Each MIC from Phase 3 Clinical Studies

| Telavancin | | | | Vancomycin | | | |
|---|---|---|---|---|---|---|---|
| µg/mL | Geneva | Indianapolis | Both Sites | µg/mL | Geneva | Indianapolis | Both Sites |
| 0.12 | | 1 | 1 | <=0.5 | 30 | 59 | 89 |
| 0.25 | 43 | 69 | 112 | 0.5 | 41 | 66 | 107 |
| 0.5 | 65 | 110 | 175 | 1 | 42 | 62 | 104 |
| 1 | 4 | 6 | 10 | 2 | | 1 | 1 |
| 2 | 1 | 1 | 2 | | | | |
| 4 | | 1 | 1 | | | | |
| Totals | 113 | 188 | 301 | | 113 | 188 | 301 |

Shaded area indicates CLSI approved ranges

Source: 5.3.5.4.1.10 Table 3, this submission

Table 3: *E. faecalis* ATCC 29212 – Number of Results at Each MIC from Phase 3 Clinical Studies

| Telavancin | | | | Vancomycin | | | |
|---|---|---|---|---|---|---|---|
| µg/mL | Geneva | Indianapolis | Both Sites | µg/mL | Geneva | Indianapolis | Both Sites |
| 0.12 | 1 | 8 | 9 | 1 | | 3 | 3 |
| 0.25 | 85 | 101 | 186 | 2 | 105 | 182 | 287 |
| 0.5 | 23 | 72 | 95 | 4 | | | |
| 1 | 4 | 4 | 8 | | | | |
| 2 | | 1 | 1 | | | | |
| Totals | 113 | 186 | 299 | | 105 | 185 | 290 |

Shaded area indicates CLSI approved ranges

Source: 5.3.5.4.1.10 Table 4, this submission

Table 4: *S. pneumoniae* ATCC 49619 – Number of Results at Each MIC from Phase 3 Clinical Studies

| Telavancin | | | | Vancomycin | | | |
|---|---|---|---|---|---|---|---|
| µg/mL | Geneva | Indianapolis | Both Sites | µg/mL | Geneva | Indianapolis | Both Sites |
| 0.004 | | | | 0.12 | 26 | 5 | 31 |
| 0.008 | 1 | | 1 | 0.25 | 16 | 47 | 63 |
| 0.015 | 42 | 47 | 89 | 0.5 | 1 | | 1 |
| 0.03 | | 5 | 5 | | | | |
| Totals | 43 | 52 | 95 | | 43 | 52 | 95 |

Shaded area indicates CLSI approved ranges

Source: 5.3.5.4.1.10 Table 5, this submission

The CLSI approved QC range for disk diffusion testing of telavancin in summarized in Table 5. Data from quality control strains, tested during Phase 3 clinical studies is summarized in Table 6. Results for *S. pneumoniae* ATCC 49619 were all within the established QC range. For *S. aureus* ATCC 25923, 99.6% were within the established QC range.

Table 5: CLSI Approved Telavancin Disk Diffusion Zone Ranges

| QC Strain | [a]CLSI Approved Range (mm) | % of Results Included |
|---|---|---|
| *S. aureus* ATCC 25923 | 16-20 | 98.8 |
| *S. pneumoniae* ATCC 49619 | 17-24 | 100 |

[a](44)

Source: 5.3.5.4.1.10 Table 8, this submission

Table 6: Telavancin 30 µg Disk Results for *S. aureus* ATCC 25923 and *S. pneumoniae* ATCC 49619: Number of Results at Each Zone from Phase 3 Clinical Studies

| *S. aureus* ATCC 25923 | | | | *S. pneumoniae* ATCC 49619 | | | |
|---|---|---|---|---|---|---|---|
| mm | Geneva | Indianapolis | Both Sites | mm | Geneva | Indianapolis | Both Sites |
| 13 | | 1 | 1 | | | | |
| 16 | 8 | 7 | 15 | 16 | | | |
| 17 | 35 | 67 | 102 | 17 | | | |
| 18 | 29 | 44 | 73 | 18 | 2 | 6 | 8 |
| 19 | 59 | 7 | 66 | 19 | 10 | 13 | 23 |
| 20 | 1 | | 1 | 20 | 19 | 20 | 39 |
| 21 | | | | 21 | 14 | 9 | 23 |
| 22 | | | | 22 | 10 | 1 | 11 |
| 23 | | | | 23 | 2 | 1 | 3 |
| 24 | | | | 24 | 1 | 1 | 2 |
| Totals | 132 | 126 | 258 | | 58 | 51 | 109 |

Shaded area indicates CLSI approved ranges

Source: 5.3.5.4.1.10 Table 9, this submission

**SUMMARY OF CLINICAL STUDIES**

For the purposes of this review, only data from post-amendment studies (Studies 202b, 0017, and 0018) will be considered as relevant to the determination of telavancin breakpoints and quality control parameters. Significant dissimilarities between data from the original protocol and the post-amendment studies will be noted.

Gram positive pathogens were the dominant isolates from all post-amendment studies, and were well-balanced between treatment groups. For organisms sought in the proposed indication for telavancin, the total numbers of isolates (and percentages) isolated at baseline (MAT population), during post-amendment studies, are presented in Table 1. Isolates were primarily recovered from major abscesses, wound infections, and deep/extensive cellulitis (see Table 2). The lower extremities were the principle sites of recovery (50% in telavancin and comparator arms).

Table 1: Pathogens Isolated from the Primary Infection Site at Baseline – Post Amendment Studies 0017, 0018, and 202b, Individually and Combined – MAT Population (pathogens sought in the proposed indications for Telavancin)

| | 0017 Post Amendment | | 0018 Post Amendment | | 0017 + 0018 Post Amendment | | 202b Post Amendment | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Telavancin 10 mg/kg (N=307) | VANC (N=322) | Telavancin 10 mg/kg (N=373) | VANC (N=381) | Telavancin 10 mg/kg (N=680) | VANC (N=703) | Telavancin 10 mg/kg (N=80) | VANC[1] (N=70) | Telavancin 10 mg/kg (N=760) | VANC[1] (N=773) |
| | Number (%) of Patients | | | | | | | | | |
| Gram-Positive Pathogens | 279 (91) | 306 (95) | 360 (97) | 360 (94) | 639 (94) | 666 (95) | 71 (89) | 62 (89) | 710 (93) | 728 (94) |
| *S. aureus* (All) | 242 (79) | 270 (84) | 311 (83) | 320 (84) | 553 (81) | 590 84) | 59 (74) | 49 (70) | 612 (81) | 639 (83) |
| MRSA | 144 (47) | 167 (52) | 204 (55) | 202 (53) | 348 (51) | 369 (52) | 29 (36) | 24 (34) | 377 (50) | 393 (51) |
| MSSA | 102 (33) | 105 (33) | 107 (29) | 119 (31) | 209 (31) | 224 (32) | 30 (38) | 25 (36) | 239 (31) | 249 (32) |
| *Enterococcus faecalis* | 15 (5) | 18 (6) | 17 (5) | 25 (7) | 32 (5) | 43 (6) | 0 | 0 | 32 (4) | 43 (6) |
| *Streptococcus pyogenes* | 13 (4) | 14 (4) | 15 (4) | 19 (5) | 28 (4) | 33 (5) | 9 (11) | 10 (14) | 37 (5) | 43 (6) |
| *Streptococcus agalactiae* | 11 (4) | 7 (2) | 11 (3) | 15 (4) | 22 (3) | 22 (3) | 2 (3) | 0 | 24 (3) | 22 (3) |
| *Streptococcus anginosus* | 7 (2) | 3 (<1) | 7 (2) | 5 (1) | 14 (2) | 8 (1) | 0 | 0 | 14 (2) | 8 (1) |
| *Streptococcus constellatus* | 2 (<1) | 3 (<1) | 5 (1) | 5 (1) | 7 (1) | 8 (1) | 0 | 0 | 7 (<1) | 8 (1) |
| *Streptococcus intermedius* | 2 (<1) | 1 (<1) | 1 (<1) | 2 (<1) | 3 (<1) | 3 (<1) | 0 | 0 | 3 (<1) | 3 (<1) |

Source: 5.3.5.4.1.10 Table 23, this submission

The occurrence, during clinical trials, of the organisms included in the proposed "second list" is summarized in Table 2 (no isolates of *B. anthracis* or *S. haemolyticus* were recovered during clinical trials). b(4)

Table 2: Pathogens Isolated from the Primary Infection Site at Baseline – Post Amendment Studies 0017, 0018, and 202b, Individually and Combined – MAT Population (pathogens sought in the proposed second list)

| | 0017 Post Amendment | | 0018 Post Amendment | | 0017 + 0018 Post Amendment | | 202b Post Amendment | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Telavancin 10 mg/kg (N=307) | VANC (N=322) | Telavancin 10 mg/kg (N=373) | VANC (N=381) | Telavancin 10 mg/kg (N=680) | VANC (N=703) | Telavancin 10 mg/kg (N=80) | VANC[1] (N=70) | Telavancin 10 mg/kg (N=760) | VANC[1] (N=773) |
| | Number (%) of Patients | | | | | | | | | |
| *Enterococcus faecium* | 3 (<1) | 3 (<1) | 0 | 1 (<1) | 3 (<1) | 4 (<1) | 0 | 0 | 3 (<1) | 4 (<1) |
| *Streptococcus dysgalactiae* | 1 (<1) | 4 (1) | 6 (2) | 6 (2) | 7 (1) | 10 (1) | 0 | 1 (1) | 7 (<1) | 11 (1) |
| *Staphylococcus epidermidis* | 1 (<1) | 1 (<1) | 2 (<1) | 2 (<1) | 3 (<1) | 3 (<1) | 0 | 0 | 3 (<1) | 3 (<1) |
| *Streptococcus mitis* | 4 (1) | 1 (<1) | 4 (1) | 3 (<1) | 8 (1) | 4 (<1) | 0 | 0 | 8 (1) | 4 (<1) |
| *Streptococcus oralis* | 1 (<1) | 1 (<1) | 0 | 1 (<1) | 1 (<1) | 2 (<1) | 0 | 0 | 1 (<1) | 2 (<1) |
| *Streptococcus* spp. Group G | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1) | 0 | 1 (<1) |

Source: 5.3.5.4.1.10 Table 23, this submission

MIC population distributions for organisms listed in the proposed indications for telavancin are summarized in Table 3. No significant differences between population values for MRSA and MSSA are noted. $MIC_{range}$, $MIC_{50}$, and $MIC_{90}$ values for the two groups are identical. Ranges and summary MIC values for all listed pathogens are similar to the data seen in the large surveillance studies and to data obtained in original protocol clinical studies (data not shown).

Table 3: Telavancin MIC Population Distribution for Key Species Isolated from Patients in Post-Amendment Studies 202b, 0017, 0018 – MAT Population

| Organism (Phenotype[1]) | Study[2] | N | No. of Isolates Inhibited at Telavancin Concentration (µg/mL) | | | | | | | | | | | | | MIC[3] (µg/mL) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 0.008 | 0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | ≥ 32 | Range[4] | 50%[5] | 90%[6] |
| *Staphylococcus aureus* (All)[7] | Amended, US | 883 | | | | 23 | 24 | 415 | 378 | 43 | | | | | | 0.06 - 1 | 0.25 | 0.5 |
| | Amended, non-US | 321 | | | | 3 | 18 | 146 | 129 | 25 | | | | | | 0.06 - 1 | 0.25 | 0.5 |
| | Amended, global | 1204 | | | | 26 | 42 | 561 | 507 | 68 | | | | | | 0.06 - 1 | 0.25 | 0.5 |
| *Staphylococcus aureus* (MSSA) | Amended, US | 230 | | | | 3 | 16 | 108 | 92 | 13 | | | | | | 0.06 - 1 | 0.25 | 0.5 |
| | Amended, non-US | 239 | | | | 3 | 17 | 118 | 89 | 12 | | | | | | 0.06 - 1 | 0.25 | 0.5 |
| | Amended, global | 469 | | | | 6 | 33 | 224 | 181 | 25 | | | | | | 0.06 - 1 | 0.25 | 0.5 |
| *Staphylococcus aureus* (MRSA)[7] | Amended, US | 653 | | | | 20 | 8 | 309 | 286 | 30 | | | | | | 0.06 - 1 | 0.25 | 0.5 |
| | Amended, non-US | 82 | | | | | 1 | 28 | 40 | 13 | | | | | | 0.12 - 1 | 0.5 | 1 |
| | Amended, global | 735 | | | | 20 | 9 | 337 | 326 | 43 | | | | | | 0.06 - 1 | 0.5 | 0.5 |
| *Streptococcus pyogenes* (All) | Amended, US | 38 | 2 | | 22 | 11 | 2 | 1 | | | | | | | | 0.008 - 0.25 | 0.03 | 0.06 |
| | Amended, non-US | 37 | 1 | 6 | 13 | 9 | 8 | | | | | | | | | 0.008 - 0.12 | 0.03 | 0.12 |
| | Amended, global | 75 | 3 | 6 | 35 | 20 | 10 | 1 | | | | | | | | 0.008 - 0.25 | 0.03 | 0.12 |
| *Streptococcus agalactiae* (All) | Amended, US | 33 | | | | 30 | 2 | | 1 | | | | | | | 0.06 - 0.5 | 0.06 | 0.06 |
| | Amended, non-US | 12 | | | | 10 | 2 | | | | | | | | | 0.06 - 0.12 | 0.06 | 0.12 |
| | Amended, global | 45 | | | | 40 | 4 | | 1 | | | | | | | 0.06 - 0.5 | 0.06 | 0.12 |
| *Streptococcus anginosus* (All) | Amended, US | 16 | | 1 | 7 | 8 | | | | | | | | | | 0.015 - 0.06 | 0.03 | 0.06 |
| | Amended, non-US | 5 | | | 3 | 2 | | | | | | | | | | 0.03 - 0.12 | ND[7] | ND |
| | Amended, global | 21 | | 1 | 10 | 10 | | | | | | | | | | 0.015 - 0.06 | 0.03 | 0.06 |
| *Streptococcus constellatus* (All) | Amended, US | 11 | | | 6 | 5 | | | | | | | | | | 0.03 - 0.06 | 0.03 | 0.06 |
| | Amended, non-US | 4 | | 1 | 2 | 1 | | | | | | | | | | 0.015 - 0.06 | ND | ND |
| | Amended, global | 15 | | 1 | 8 | 6 | | | | | | | | | | 0.015 - 0.06 | 0.03 | 0.06 |
| *Streptococcus intermedius* (All) | Amended, US | 6 | | | 2 | 4 | | | | | | | | | | 0.03 - 0.06 | ND | ND |
| | Amended, non-US | 0 | | | | | | | | | | | | | | | | |
| | Amended, global | 6 | | | 2 | 4 | | | | | | | | | | 0.03 - 0.06 | ND | ND |
| *Enterococcus faecalis* (VSE) | Amended, US | 33 | | | | | | 5 | 21 | 7 | | | | | | 0.25 - 1 | 0.5 | 1 |
| | Amended, non-US | 41 | | | | | | 4 | 19 | 18 | | | | | | 0.25 - 1 | 0.5 | 1 |
| | Amended, global | 74 | | | | | | 9 | 40 | 25 | | | | | | 0.25 - 1 | 0.5 | 1 |

Source: 5.3.5.4.1.10 Table 24, this submission

In vitro susceptibility testing data for *S. aureus* infections, related to combined clinical outcome data for post-amendment studies, are summarized in Tables 4 and 5. Microbiologically evaluable (ME) populations from all regional studies are included in the summary (344 patients from US studies, 141 from non-US studies). In this population, telavancin achieved eradication of MRSA in 260 out of 289 (90%) patients, and eradication of MSSA in 173 out of 195 patients

(89%). Vancomycin achieved eradication of MRSA in 262 out of 308 patients (85%), and eradication of MSSA in 165 out of 187 patients (88%). The $MIC_{range}$ for telavancin, in this population, was [redacted] µg/ml. Approximately 95% of isolates analyzed from this population had MIC values ≤ 0.5 µg/ml. Zone size diameters for *S. aureus* isolates from this population ranged from 15 – 21 mm. Greater than 99% of values were ≥ 16 mm. $MIC_{50}$ and $MIC_{90}$ results from US and non-US studies were similar. $MIC_{50}$ and $MIC_{90}$ values from survey studies and clinical studies were also identical. Because vancomycin-resistant isolates were analyzed in pre-clinical studies and excluded from clinical trials, the reported MIC range in the clinical studies was narrower than that reported in the survey studies.

b(4)

Clinical outcome vs. telavancin MIC data (baseline isolate, ME population, global studies) are summarized in Table 6. As described above, the majority of *S. aureus* isolates had telavancin MICs of 0.5 µg/ml or less. For those isolates, telavancin demonstrated cure rates approximating or exceeding 90%. No isolates were identified with MICs greater than 1 µg/ml. *S. aureus* isolates with MICs of 1 µg/ml demonstrated decreased clinical cure rates (approximately 81-83%).

Table 4: Global Results for *S. aureus* (Post-Amendment Combined Studies, ME population, MIC versus Microbiological Eradication)

| MIC (µg/mL) | No. Eradicated/Total (%) | | |
|---|---|---|---|
| | *S. aureus* | MRSA | MSSA |
| ≤ 0.015 | | | |
| 0.03 | | | |
| 0.06 | 11/11 (100) | 7/7 (100) | 4/4 (100) |
| 0.12 | 19/20 (95) | 4/5 (80) | 15/15 (100) |
| 0.25 | 207/228 (91) | 130/140 (93) | 77/88 (88) |
| 0.5 | 173/197 (88) | 106/121 (88) | 67/76 (88) |
| 1 | 23/28 (82) | 13/16 (81) | 10/12 (83) |
| 2 | | | |
| Total | 433/484 (90) | 260/289 (90) | 173/195 (89) |

Source: 5.3.5.4.1.10 Table 26, this submission

Table 5: Global Results for *S. aureus* (Post-Amendment Combined Studies, ME population, Zone Diameter versus Microbiological Eradication)

| Zone (mm) | No. Eradicated/Total (%) | | |
|---|---|---|---|
| | *S. aureus* | MRSA | MSSA |
| 20 | | | |
| 21 | 3/3 (100) | 1/1 (100) | 2/2 (100) |
| 20 | 7/8 (88) | | 7/8 (89) |
| 19 | 31/34 (91) | 15/17 (88) | 16/17 (94) |
| 18 | 122/135 (90) | 74/80 (93) | 48/55 (87) |
| 17 | 172/197 (87) | 106/121 (88) | 66/76 (87) |
| 16 | 50/55 (91) | 39/43 (91) | 11/12 (92) |
| 15 | 2/2 (100) | 1/1 (100) | 1/1 (100) |
| 14 | | | |
| Total | 387/434 (89) | 236/263 (90) | 151/171 (88) |

Source: 5.3.5.4.1.10 Table 27, this submission

Table 6: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin MIC Value

Studies 202b, 0017, and 0018 (all Post-Amendment) Combined
Telavancin 10 mg/kg
Microbiologically Evaluable (ME)
Global
Baseline Pathogens/Susceptibility: *S. aureus*/Oxacillin (OX)

| Baseline Pathogen [1] | Baseline Susceptibility [2] | Baseline Telavancin MIC (µg/mL) | Clinical Outcome at Test-of-Cure Visit | | | | Microbiological Outcome at Test-of-Cure Visit | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cured N (%) [3] | Not Cured N (%) [3] | No. Indeterminate | No. Missing | Eradication [4] N (%) [5] | Non-Eradication [6] N (%) [5] | No. Indeterminate | No. Missing |
| *S. aureus* | Missing | | 1(100) | | | | 1(100) | | | |
| | OX:R | 0.06 | 7(100) | | | | 7(100) | | | |
| | | 0.12 | 4(80) | 1(20) | | | 4(80) | 1(20) | | |
| | | 0.25 | 131(93.6) | 9(6.4) | | | 130(92.9) | 10(7.1) | | |
| | | 0.5 | 108(89.3) | 13(10.7) | | | 106(87.6) | 15(12.4) | | |
| | | 1 | 13(81.3) | 3(18.8) | | | 13(81.2) | 3(18.8) | | |
| | OX:S | 0.06 | 4(100) | | | | 4(100) | | | |
| | | 0.12 | 15(100) | | | | 15(100) | | | |
| | | 0.25 | 78(88.6) | 10(11.4) | | | 77(87.5) | 11(12.5) | | |
| | | 0.5 | 67(88.2) | 9(11.8) | | | 67(88.2) | 9(11.8) | | |
| | | 1 | 10(83.3) | 2(16.7) | | | 10(83.3) | 2(16.7) | | |
| | Total | 485 | 438 | 47 | | | 434 | 51 | | |

[1] Identification of baseline pathogen.
[2] S = Susceptible, I = Intermediate, R = Resistant.
[3] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.
[4] Documented Eradication, Presumed Eradication.
[5] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.
[6] Documented Persistence, Presumed Persistence.

Source: 5.3.5.4.1.10 Supplemental Table 101, this submission

MIC versus Outcome data for *S. pyogenes* infections is summarized in Tables 7 and 8. In the global ME population (13 US patients and 17 non-US patients), *S. pyogenes* was eradicated in 93% of the cases (28/30). $MIC_{50}$ and $MIC_{90}$ values for isolates from US studies and non-US studies were similar. Vancomycin eradication, in the same population, was 94% (30/32). The $MIC_{range}$ for telavancin, in this population, was ( ) , µg/ml. Approximately 97% of MIC values were ≤ 0.12 µg/ml. $MIC_{50}$ and $MIC_{90}$ values obtained from clinical and pre-clinical studies were identical. Disk diffusion zone sizes ranged from 15 – 19 mm, with approximately 90% of values ≥ 16 mm. b(4)

Clinical outcome vs. telavancin MIC data (baseline isolate, ME population, global studies) are summarized in Table 9. The total number of *S. pyogenes* isolates was small, and the few clinical failures did not correlate with high MIC values.

Table 7: Global Results for *S. pyogenes* (Post-Amendment Combined Studies, ME population, MIC versus Microbiological Eradication)

| MIC (µg/mL) | No. Eradicated/Total (%) |
|---|---|
| | *S. pyogenes* |
| ≤ 0.015 | 6/6 (100) |
| 0.03 | 11/12 (92) |
| 0.06 | 4/5 (80) |
| 0.12 | 6/6 (100) |
| 0.25 | 1/1 (100) |
| 0.5 | |
| 1 | |
| 2 | |
| **Total** | **28/30 (93)** |

Source: 5.3.5.4.1.10 Table 28, this submission

Table 8: Global Results for *S. pyogenes* (Post-Amendment Combined Studies, ME population, Zone Diameter versus Microbiological Eradication)

| Zone (mm) | No. Eradicated/Total (%) |
|---|---|
| | *S. pyogenes* |
| 20 | |
| 19 | 2/2 (100) |
| 18 | 6/6 (100) |
| 17 | 5/6 (83) |
| 16 | 4/5 (80.0) |
| 15 | 2/2 (100) |
| 14 | |
| **Total** | **19/21 (90)** |

Source: 5.3.5.4.1.10 Table 29, this submission

Table 9: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin MIC Value

Studies 202b, 0017, and 0018 (all Post-Amendment) Combined
Telavancin 10 mg/kg
Microbiologically Evaluable (ME)
Global
Baseline Pathogens: *S. pyogenes*

| Baseline Pathogen [1] | Baseline Telavancin MIC (µg/mL) | Clinical Outcome at Test-of-Cure Visit | | | | Microbiological Outcome at Test-of-Cure Visit | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Cured N (%) [3] | Not Cured N (%) [3] | No. Indeterminate | No. Missing | Eradication [4] N (%) [5] | Non-Eradication [6] N (%) [5] | No. Indeterminate | No. Missing |
| *S. pyogenes* | <=0.015 | 1(100) | | | | 1(100) | | | |
| | 0.015 | 5(100) | | | | 5(100) | | | |
| | 0.03 | 11(91.7) | 1(8.3) | | | 11(91.7) | 1(8.3) | | |
| | 0.06 | 4(80) | 1(20) | | | 4(80) | 1(20) | | |
| | 0.12 | 6(100) | | | | 6(100) | | | |
| | 0.25 | 1(100) | | | | 1(100) | | | |
| Total | | 30 | 28 | 2 | | 28 | 2 | | |

[1] Identification of baseline pathogen.
[2] S = Susceptible, I = Intermediate, R = Resistant.
[3] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.
[4] Documented Eradication, Presumed Eradication.
[5] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.
[6] Documented Persistence, Presumed Persistence.

Source: 5.3.5.4.1.10 Supplemental Table 209, this submission

MIC versus Outcome data for *Streptococcus agalactiae* is summarized in Tables 10 and 11. In the global ME population (13 US patients, 6 non-US patients), telavancin achieved microbial eradication in 89% (17/19) cases, compared to 94% (17/18) of cases treated with vancomycin. No significant differences were noted between US patients and non-US patients. $MIC_{50}$ and $MIC_{90}$ values were identical in clinical and pre-clinical studies. Disk diffusion zone sizes ranged from 15-18 mm.

Clinical outcome vs. telavancin MIC data (baseline isolate, ME population, global studies) are summarized in Table 12. The total number of recovered isolates of *S. agalactiae* was small, and no correlation was noted between the rate of clinical success and MIC values.

Table 10: Global Results for *S. agalactiae* (Post-Amendment Combined Studies, ME Population, MIC versus Microbiological Eradication)

| MIC (µg/mL) | No. Eradicated/Total (%) *S. agalactiae* |
|---|---|
| ≤ 0.015 | |
| 0.03 | |
| 0.06 | 14/16 (88) |
| 0.12 | 3/3 (100) |
| 0.25 | |
| 0.5 | |
| 1 | |
| 2 | |
| Total | 17/19 (89) |

Source: 5.3.5.4.1.10 Table 30, this submission

Table 11: Global Results for *S. agalactiae* (Post-Amendment Combined Studies, ME Population, Zone Diameter versus Microbiological Eradication)

| Zone (mm) | No. Eradicated/Total (%) *S. agalactiae* |
|---|---|
| 19 | |
| 18 | 1/1 (100) |
| 17 | 4/5 (80.0) |
| 16 | 8/9 (89.0) |
| 15 | 3/3 (100) |
| 14 | |
| Total | 16/18 (89) |

Source: 5.3.5.4.1.10 Table 31, this submission

Table 12: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin MIC Value

Studies 202b, 0017, and 0018 (all Post-Amendment) Combined
Telavancin 10 mg/kg
Microbiologically Evaluable (ME)
Global
Baseline Pathogens: *S. agalactiae*

| Baseline Pathogen [1] | Baseline Susceptibility [2] | Baseline Telavancin MIC (µg/mL) | Clinical Outcome at Test-of-Cure Visit | | | | Microbiological Outcome at Test-of-Cure Visit | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cured N (%) [3] | Not Cured N (%) [3] | No. Indeterminate | No. Missing | Eradication [4] N (%) [5] | Non-Eradication [6] N (%) [5] | No. Indeterminate | No. Missing |
| *S. agalactiae* | Missing | | | | | | | | | |
| | | 0.06 | 13(81) | 3(19) | | | 14(88) | 2(12) | | |
| | | 0.12 | 1(50) | 1(50) | | 1 | 3(100) | | | |
| | Total | 19 | 14(78) | 4(22) | | 1 | 17(89) | 2(11) | | |

[1] Identification of baseline pathogen.
[2] S = Susceptible, I = Intermediate, R = Resistant.
[3] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.
[4] Documented Eradication, Presumed Eradication.
[5] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.
[6] Documented Persistence, Presumed Persistence.

Source: 5.3.5.4.1.10 Supplemental Table 317, this submission

MIC versus Outcome data for species included in the *S. anginosus* group is summarized in Tables 10 – 11. Numbers for each species sought in the proposed indication were small (global enrollment, telavancin-treated ME population: 10 *S. anginosus*, 7 *S. constellatus*, and 3 *S. intermedius*). The number of vancomycin-treated species included in the *S. anginosus* group was slightly less than the telavancin-treated group (8 *S. anginosus*, 6 *S. constellatus*, and 1 *S. intermedius*). In the global ME population, telavancin treatment resulted in eradication of

*S. anginosus* group in 90% of patients (18/20). Vancomycin treatment resulted in 93% eradication (14/15). No significant difference in telavancin activity was noted between US isolates and non-US isolates. The $MIC_{range}$ of *S. anginosus* group isolates in the ME population was 0.015 – 0.06 µg/ml (zone diameter: 14 – 29 mm). $MIC_{50}$ and $MIC_{90}$ values in isolates obtained from clinical trials were identical to survey studies.

Clinical outcome vs. telavancin MIC data (baseline isolate, ME population, global studies) are summarized in Tables 15, 16, and 17.

Table 13: Global Results for *S. anginosus* grp (Post-Amendment Combined Studies, ME Population, MIC versus Microbiological Eradication)

| MIC (µg/mL) | No. Eradicated/Total (%) | | | |
|---|---|---|---|---|
| | *S. anginosus* | *S. constellatus* | *S. intermedius* | *S. anginosus* grp |
| ≤ 0.015 | 1/1 (100) | 1/1 (100) | | 2/2 (100) |
| 0.03 | 5/5 (100) | 2/3 (67) | 0/1 (0) | 7/9 (78) |
| 0.06 | 4/4 (100) | 2/2 (100) | 2/2 (100) | 8/8 (100) |
| 0.12 | | | | |
| **Total** | **10/10 (100)** | **5/6 (83)** | **2/3 (67)** | **17/19 (89)** |
| Source | Supplemental Table 425 | Supplemental Table 533 | Supplemental Table 641 | – |

Source: 5.3.5.4.1.10 Table 32, this submission

Table 14: Global Results for *S. anginosus* grp (Post-Amendment Combined Studies, ME Population, Zone Diameter versus Microbiological Eradication)

| Zone (mm) | No. Eradicated/Total (%) | | | |
|---|---|---|---|---|
| | *S. anginosus* | *S. constellatus* | *S. intermedius* | *S. anginosus* grp |
| 29 | 1/1 (100) | | | 1/1 (100) |
| 28 | | | | |
| 27 | | | 0/1 (0) | 0/1 (0) |
| 26 | | | | |
| 25 | 1/1 (100) | 2/3 (67) | 1/1 (100) | 4/5 (80) |
| 24 | 1/1 (100) | 1/1 (100) | 1/1 (100) | 3/3 (100) |
| 23 | 1/1 (100) | | | 1/1 (100) |
| 22 | 2/2 (100) | | | 2/2 (100) |
| 21 | 3/3 (100) | 1/1 (100) | | 4/4 (100) |
| 20 | 1/1 (100) | 1/1 (100) | | 2/2 (100) |
| 19 | | | | |
| 18 | | | | |
| 17 | | | | |
| 16 | | | | |
| 15 | | | | |
| 14 | | 1/1 (100) | | 1/1 (100) |
| | | | | |
| **Total** | **10/10 (100)** | **6/7 (86)** | **2/3 (67)** | **17/19 (89)** |
| Source | Supplemental Table 432 | Supplemental Table 540 | Supplemental Table 648 | – |

Source: 5.3.5.4.1.10 Table 33, this submission

## Table 15: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin MIC Value

Studies 202b, 0017, and 0018 (all Post-Amendment) Combined
Telavancin 10 mg/kg
Microbiologically Evaluable (ME)
Global
Baseline Pathogens: *S. anginosus*

| Baseline Pathogen [1] | Baseline Susceptibility [2] | Baseline Telavancin MIC (µg/mL) | Clinical Outcome at Test-of-Cure Visit | | | | Microbiological Outcome at Test-of-Cure Visit | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cured N (%) [3] | Not Cured N (%) [3] | No. Indeterminate | No. Missing | Eradication [4] N (%) [5] | Non-Eradication [6] N (%) [5] | No. Indeterminate | No. Missing |
| *S. anginosus* | Missing | | | | | | | | | |
| | | 0.015 | 1(100) | | | | 1(100) | | | |
| | | 0.03 | 5(100) | | | | 5(100) | | | |
| | | 0.06 | 4(100) | | | | 4(100) | | | |
| | | | | | | | | | | |
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| | | | | | | | | | | |
| | | | | | | | | | | |
| | Total | 10 | 10(100) | | | | 10(100) | | | |

[1] Identification of baseline pathogen.
[2] S = Susceptible, I = Intermediate, R = Resistant.
[3] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.
[4] Documented Eradication, Presumed Eradication.
[5] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.
[6] Documented Persistence, Presumed Persistence.

Source: 5.3.5.4.1.10 Supplemental Table 425, this submission

## Table 16: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin MIC Value

Studies 202b, 0017, and 0018 (all Post-Amendment) Combined
Telavancin 10 mg/kg
Microbiologically Evaluable (ME)
Global
Baseline Pathogens: *S. constellatus*

| Baseline Pathogen [1] | Baseline Telavancin MIC (µg/mL) | Clinical Outcome at Test-of-Cure Visit | | | | Microbiological Outcome at Test-of-Cure Visit | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Cured N (%) [3] | Not Cured N (%) [3] | No. Indeterminate | No. Missing | Eradication [4] N (%) [5] | Non-Eradication [6] N (%) [5] | No. Indeterminate | No. Missing |
| *S. constellatus* | 0.015 | 1(100) | | | | 1(100) | | | |
| | 0.03 | 2(66.7) | 1(33.3) | | | 2(66.7) | 1(33.3) | | |
| | 0.06 | 1(50) | 1(50) | | | 2(100) | | | |
| | (blank) | 1(100) | | | | 1(100) | | | |
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| | | | | | | | | | |
| | | | | | | | | | |
| Total | 7 | 5 | 2 | | | 6 | 1 | | |

[1] Identification of baseline pathogen.
[2] S = Susceptible, I = Intermediate, R = Resistant.
[3] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.
[4] Documented Eradication, Presumed Eradication.
[5] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.
[6] Documented Persistence, Presumed Persistence.

Source: 5.3.5.4.1.10 Supplemental Table 533, this submission

Table 17: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin MIC Value

Studies 202b, 0017, and 0018 (all Post-Amendment) Combined
Telavancin 10 mg/kg
Microbiologically Evaluable (ME)
Global
Baseline Pathogens: *S. intermedius*

| Baseline Pathogen [1] | Baseline Telavancin MIC (µg/mL) | Clinical Outcome at Test-of-Cure Visit | | | | Microbiological Outcome at Test-of-Cure Visit | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Cured N (%) [3] | Not Cured N (%) [3] | No. Indeterminate | No. Missing | Eradication [4] N (%) [5] | Non-Eradication [6] N (%) [5] | No. Indeterminate | No. Missing |
| *S. intermedius* | 0.03 | | 1(100) | | | | 1(100) | | 0.03 |
| | 0.06 | 2(100) | | | | 2(100) | | | 0.06 |
| Total | 3 | 2 | 1 | | | 2 | 1 | | 3 |

[1] Identification of baseline pathogen.
[2] S = Susceptible, I = Intermediate, R = Resistant.
[3] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.
[4] Documented Eradication, Presumed Eradication.
[5] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.
[6] Documented Persistence, Presumed Persistence.

Source: 5.3.5.4.1.10 Supplemental Table 641, this submission

MIC versus Outcome data for vancomycin-susceptible *E. faecalis* is summarized in Tables 12 and 13. Global isolates (ME population) included 12 from US patients and 15 from non-US patients. No significant difference was noted in telavancin activity between US isolates and non-US isolates. Telavancin treatment resulted in 93% eradication (25/27), while vancomycin treatment resulted in 92% eradication (31/34). $MIC_{50}$ and $MIC_{90}$ values for survey and clinical isolates were identical. The $MIC_{range}$ was [redacted] µg/ml. The telavancin zone size range was 16 – 20 mm. b(4)

Clinical outcome vs. telavancin MIC data (baseline isolate, ME population, global studies) are summarized in Table 20. While the number if vancomycin-susceptible isolates recovered in clinical studies was relatively small, the data suggests a possible correlation between isolates with MIC values ≥ 1 µg/ml and clinical failure (18.1% of isolate within this MIC range were listed as "not cured").

Table 18: Global Results for *E. faecalis*, vancomycin-susceptible strains only (Post-Amendment Combined Studies, ME Population, MIC versus Microbiological Eradication)

| MIC (µg/mL) | No. Eradicated/Total (%) *E. faecalis* (VSE) |
|---|---|
| 0.12 | |
| 0.25 | 3/3 (100) |
| 0.5 | 13/13 (100) |
| 1 | 9/11 (82) |
| 2 | |
| Total | 25/27 (93) |

Source: 5.3.5.4.1.10 Table 34, this submission

Table 19: Global Results for *E. faecalis*, vancomycin-susceptible strains only (Post-Amendment Combined Studies, ME Population, Zone Diameter versus Microbiological Eradication)

| Zone (mm) | No. Eradicated/Total (%) |
|---|---|
| | *E. faecalis* (VSE) |
| 21 | |
| 20 | 3/3 (100) |
| 19 | 5/5 (100) |
| 18 | 4/5 (80.0) |
| 17 | 8/8 (100) |
| 16 | 5/6 (83.3) |
| 15 | |
| **Total** | **25/27 (93)** |

Source: 5.3.5.4.1.10 Table 35, this submission

Table 20: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin MIC Value

Studies 202b, 0017, and 0018 (all Post-Amendment) Combined
Telavancin 10 mg/kg
Microbiologically Evaluable (ME)
Global
Baseline Pathogens: *E. faecalis, VSE*

| Baseline Pathogen [1] | Baseline Telavancin MIC (µg/mL) | Clinical Outcome at Test-of-Cure Visit | | | | Microbiological Outcome at Test-of-Cure Visit | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Cured N (%) [3] | Not Cured N (%) [3] | No. Indeterminate | No. Missing | Eradication [4] N (%) [5] | Non-Eradication [6] N (%) [5] | No. Indeterminate | No. Missing |
| *E. faecalis, VSE* | 0.25 | 3(100) | | | | 3(100) | | | |
| | 0.5 | 13(100) | | | | 13(100) | | | |
| | 1 | 9(81.9) | 2(18.1) | | | 9(81.9) | 2(18.1) | | |
| Total | 27 | 25 | 2 | | | 25 | 2 | | |

[1] Identification of baseline pathogen.
[2] S = Susceptible, I = Intermediate, R = Resistant.
[3] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.
[4] Documented Eradication, Presumed Eradication.
[5] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.
[6] Documented Persistence, Presumed Persistence.

Source: 5.3.5.4.1.10 Supplemental Table 749, this submission

The number of isolates of proposed "second list" pathogens, from clinical studies, was small (fewer than 10 telavancin-treated isolates, with regard to each listed species). Efficacy data on these isolates was not presented.

The rates of superinfection (defined as isolation of a pathogen different than the baseline pathogen, recovered from patients in the "not cured" population) and colonization (defined as the isolation of a pathogen different than the baseline pathogen, recovered from patients in the "cured" population) were low in the Phase 3 studies (0017 and 0018). Results of superinfection and colonization analysis for the ME populations are summarized in Tables 14 and 15. Numbers of colonized patients, from both studies, were slightly higher in the telavancin-treated population, but were too low to provide a meaningful comparison. The number of superinfections was similar in both studies, with Gram negative pathogens predominating in Study 0018.

Table 14: Superinfection and Colonization in Study 0017 (ME Population)

| Study 0017 | Telavancin 10 mg/kg (N=237) | VAN (N=255) |
|---|---|---|
| Number (%) of Patients | | |
| | | |
| Clinical Response | | |
| Cure at TOC | 210 (89%) | 220 (86%) |
| | | |
| Colonization [1] | 2 (<1%) | 1 (<1%) |
| STAPHYLOCOCCUS AUREUS, MRSA | 1 (<1%) | 0 |
| STAPHYLOCOCCUS AUREUS, MSSA | 1 (<1%) | 0 |
| STREPTOCOCCUS PARASANGUIS | 0 | 1 (<1%) |
| Clinical Response | | |
| Not Cured at TOC | 27 (11%) | 35 (14%) |
| | | |
| Superinfection [2] | 1 (<1%) | 0 |
| STAPHYLOCOCCUS AUREUS, MRSA | 1 (<1%) | 0 |

[1] Colonization = Clinical Response of Cure at TOC, but new pathogen not present at Baseline was isolated from post-treatment culture.
[2] Superinfection = Clinical Response of Not Cured at TOC and new pathogen that was not present at Baseline was isolated from post-treatment culture.
Source: 5.3.5.4.1.10 Table 44, this submission

Table 15: Superinfection and Colonization in Study 0018 (ME Population)

| Study 0018 | Telavancin 10 mg/kg (N=290) | VAN (N=281) |
|---|---|---|
| Number (%) of Patients | | |
| | | |
| Clinical Response | | |
| Cure at TOC | 260 (90%) | 250 (89%) |
| | | |
| Colonization [1] | 5 (2%) | 3 (1%) |
| ACINETOBACTER BAUMANNII | 0 | 1 (<1%) |
| ACINETOBACTER CALCOACETICUS | 1 (<1%) | 0 |
| ENTEROBACTER CLOACAE | 2 (<1%) | 0 |
| KLEBSIELLA PNEUMONIAE | 0 | 2 (<1%) |
| MORGANELLA MORGANII | 1 (<1%) | 0 |
| STAPHYLOCOCCUS AUREUS, MSSA | 1 (<1%) | 0 |
| Clinical Response | | |
| Not Cured at TOC | 30 (10%) | 31 (11%) |
| | | |
| Superinfection [2] | 8 (3%) | 8 (3%) |
| ACHROMOBACTER XYLOSOXIDANS | 0 | 1 (<1%) |
| ACINETOBACTER CALCOACETICUS | 1 (<1%) | 0 |
| ENTEROBACTER CLOACAE | 1 (<1%) | 0 |
| ENTEROCOCCUS FAECALIS | 1 (<1%) | 0 |
| ENTEROCOCCUS SPP | 0 | 1 (<1%) |
| ESCHERICHIA COLI | 1 (<1%) | 0 |
| KLEBSIELLA PNEUMONIAE | 0 | 1 (<1%) |
| PSEUDOMONAS AERUGINOSA | 1 (<1%) | 2 (<1%) |
| STAPHYLOCOCCUS AUREUS, MRSA | 3 (1%) | 1 (<1%) |
| STENOTROPHOMONAS MALTOPHILIA | 0 | 2 (<1%) |

[1] Colonization = Clinical Response of Cure at TOC, but new pathogen not present at Baseline was isolated from post-treatment culture.
[2] Superinfection = Clinical Response of Not Cured at TOC and new pathogen that was not present at Baseline was isolated from post-treatment culture.
Source: 5.3.5.4.1.10 Table 46, this submission

No development of resistance was noted in isolates obtained during the clinical studies. No isolate obtained at EOT or TOC had an MIC greater than 2-fold higher than baseline (within the acceptable standard of error for MIC procedures).

*Clinical Trials ~ Conclusions:*

Data from post-amendment clinical trials indicate that telavancin is efficacious in infections involving pathogens in the proposed indication. 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 clinical trials, was low.

## SUSCEPTIBILITY TEST METHODS

### VALIDATION STUDIES

In studies comparing broth dilution methods of MIC testing with agar dilution methods, all staphylococcal isolates (153 *S. aureus* isolates and 51 coagulase-negative staphylococcal isolates) had telavancin agar dilution MICs within one doubling dilution of broth dilution MICs (Table 1). Enterococcal species were also largely equivalent when tested by the two methods, with 98.1% of *E. faecalis* and 94.5% of *E. faecium* with one doubling dilution. Agar dilution methods yielded notably higher values, compared to broth dilution, when streptococcal isolates were tested. In a comparison of CLSI methods (requiring Mueller-Hinton agar for staphylococci and enterococci, and Mueller-Hinton supplemented with 5% sheep blood for streptococci) with British Society for Antimicrobial Chemotherapy (BSAC) methods (requiring Iso-Sensitest agar in place of Mueller-Hinton agar used in CLSI methods), results were similar.

Table 1: Number of Doubling Dilution Difference in Broth Microdilution MIC versus Agar Dilution MIC

| Agent | Organism | Total N | Isolates within one doubling dilution | | Number of doubling dilution difference between broth MIC and agar MIC ($log_2$ broth MIC minus $log_2$ agar MIC)[a,b] | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | N | (%) | -3 | -2 | -1 | 0 | 1 | 2 | 3 |
| Telavancin | *S. aureus* | 153 | 153 | 100.0 | | | 24 | 119 | 10 | | |
| | CoNS | 51 | 51 | 100.0 | | | 1 | 30 | 20 | | |
| | *E. faecalis* | 105 | 103 | 98.1 | | | 20 | 79 | 4 | 2 | |
| | *E. faecium* | 55 | 52 | 94.5 | | 1 | 8 | 12 | 32 | 2 | |
| | *S. pneumoniae*[c] | 100 | 38 | 38.0 | 2 | 60 | 36 | 2 | | | |
| | *Streptococcus* spp. | 64 | 46 | 71.9 | 3 | 15 | 43 | 3 | | | |
| Vancomycin | *S. aureus* | 153 | 135 | 88.2 | | 16 | 37 | 52 | 46 | 1 | 1 |
| | CoNS | 51 | 40 | 78.4 | 5 | 6 | 6 | 32 | 2 | | |
| | *E. faecalis* | 105 | 102 | 97.1 | 1 | 2 | 2 | 67 | 33 | | |
| | *E. faecium* | 55 | 51 | 92.7 | | 4 | 12 | 35 | 4 | | |
| | *S. pneumoniae* | 100 | 100 | 100.0 | | | 3 | 81 | 16 | | |
| | *Streptococcus* spp. | 64 | 64 | 100.0 | | | 3 | 49 | 12 | | |

Source Data (69)
[a]Negative number indicates that the broth microdilution MIC was lower than the agar dilution MIC, a positive number indicates that the broth microdilution MIC was higher than the agar dilution MIC, and a zero indicates that the broth microdilution MIC and the agar dilution MIC were equivalent.
[b]MIC values that were off-scale high (>) were calculated with an MIC value one-doubling dilution higher than the last dilution tested; MIC values that were off-scale low (≤) were calculated with the lowest dilution tested.
[c]Agar dilution testing is contra-indicated for *S. pneumoniae* according to the CLSI.

Source: 5.3.5.4.1.6 Table 15, this submission

In an investigation of the effects of different testing parameters on in vitro telavancin activity ( ), testing parameters, including inoculum concentration, incubation conditions, media pH, cation supplementation, and incubation time, were varied one at a time and compared to the MICs for the isolate when tested by standard CLSI-approved methods. Tested organisms included six *S. aureus* strains (including resistant phenotypes), one strain of *E. faecalis*, two strains of *E. faecium* (*vanA* and *vanB*), and two strains of *S. pneumoniae*. Vancomycin was tested as a comparator. Specific variations and test results are summarized in Table 2. Most single parameter alterations resulted in MIC changes within one doubling dilution. *Streptococcus pneumoniae* isolates were dramatically affected by changes to the pH of the growth medium (no growth of *S. pneumoniae* 1094443 on media of pH 6.4 or 8.4) and by changes to the inoculum concentration. *Streptococcus pneumoniae* is not included in the proposed indications for this application.

b(4)

Table 2: In Vitro Susceptibility Results for Telavancin with Systematic Variation of In Vitro Parameters

| Species | Strain | Phenotype[a] | MIC Under Standard Conditions[b] | Telavancin MIC (µg/mL) (Strains were tested in duplicate) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 48 hour incubation | $Ca^{2+}$ = 50 µg/mL | pH = 6.4 | pH = 8.4 | Inoculum = $10^3$ CFU/mL | Inoculum = $10^7$ CFU/mL | Incubation = 5% $CO_2$ |
| *S. aureus* | ATCC 29213 | MSSA | 0.25 / 0.25 | 0.25 / 0.25 | 0.5 / 0.5 | 0.25 / 0.5 | 0.5 / 0.5 | 0.25 / 0.25 | 0.5 / 0.5 | 0.25 / 0.25 |
| | 1085571 | MRSA | 0.25 / 0.25 | 0.25 / 0.25 | 0.25 / 0.25 | 0.25 / 0.25 | 1 / 1 | 0.25 / 0.25 | 1 / 1 | 0.25 / 0.25 |
| | 898492 | MRSA | 0.5 / 0.25 | 0.5 / 0.25 | 0.5 / 0.5 | 0.25 / 0.25 | 1 / 1 | 0.25 / 0.25 | 1 / 1 | 0.5 / 0.25 |
| | Mu50 | VISA | 2 / 2 | 2 / 2 | 2 / 2 | 1 / 1 | 2 / 2 | 1 / 1 | 2 / 4 | 1 / 1 |
| | VRSA-MI | VRSA | 8 / 8 | 8 / 8 | 8 / 8 | 8 / 8 | 16 / 16 | 4 / 8 | 8 / 8 | 16 / 8 |
| | VRSA-PA | VRSA | 4 / 4 | 4 / 4 | 4 / 4 | 2 / 2 | 16 / 16 | 2 / 4 | 4 / 4 | 4 / 4 |
| *E. faecalis* | ATCC 29212 | VSE | 0.25 / 0.25 | 0.25 / 0.25 | 1 / 0.5 | 0.25 / 0.25 | 2 / 2 | 0.25 / 0.25 | 2 / 2 | 0.5 / 0.5 |
| *E. faecium* | NS[c] | VRE (VanA) | 16 / 16 | 16 / 16 | 16 / 16 | 8 / 8 | 16 / 16 | 8 / 8 | >32 / >32 | 8 / 16 |
| | NS | VRE (VanB) | 0.5 / 0.25 | 1 / 0.5 | 0.5 / 0.5 | 0.12 / 0.12 | 2 / 2 | 0.5 / 0.25 | 8 / 4 | 0.25 / 0.25 |
| *S. pneumoniae* | ATCC 49619 | PSSP | 0.015 / 0.015 | 0.015 / 0.015 | 0.03 / 0.03 | 0.004 / 0.004 | 0.03 / 0.03 | 0.015 / 0.015 | 0.12 / 0.12 | 0.015 / 0.015 |
| | 1094443 | PRSP | 0.03 / 0.03 | 0.03 / 0.03 | 0.03 / 0.03 | NG[d] | NG | 0.015 / 0.015 | >1 / >1 | 0.03 / 0.03 |

Source data (79)
[a]MSSA, methicillin-sensitive *S. aureus*; MRSA, methicillin-resistant *S. aureus*; VISA, vancomycin-intermediate *S. aureus*; VRSA, vancomycin-resistant *S. aureus*; VSE, vancomycin-sensitive Enterococcus; VRE, vancomycin-resistant Enterococcus
[b]Standard NCCLS broth microdilution conditions as defined in M7-A6 (2003) are as follows: inoculum, 5 x $10^5$ CFU/mL; incubation conditions, ambient air; pH, 7.2-7.4; cation supplementation, 25 µg/mL $Ca^{2+}$; incubation time, 16-20 hours for staphylococci and enterococci, 20-24 hours for streptococci (144).
[c]NS, Not specified by study authors
[d]NG, No growth

Source: 5.3.5.4.1.6 Table 17, this submission

In a second study of the effects of growth parameters on in vitro activity of telavancin (Kaniga 2004), the investigators tested alterations in pH (6.4 to 8.4), inoculum size ($10^5$ to $10^8$ CFU/ml) against strains of *E. faecalis*, *S. aureus*, and *S. pneumoniae*. The effect of inoculum size and growth media (cation adjusted Mueller Hinton broth and brain heart infusion broth) was tested against *S. aureus* strain MRSA 33591. The researchers reported little impact of high inoculum of telavancin against *S. aureus* strains, and little effect of pH variation against *S. aureus* and enterococci. Growth in cation adjusted MHB or BHI produced no notable difference in bactericidal activity.

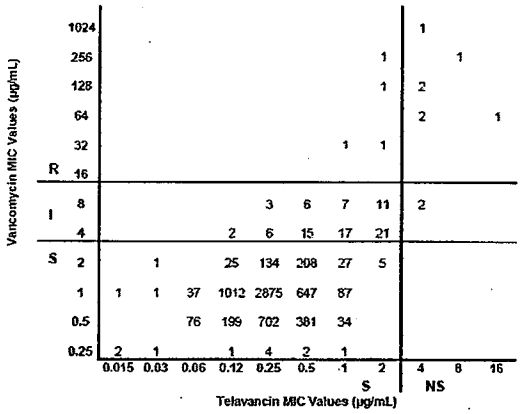
In a study of the variations of telavancin MICs and zone diameters, caused by the usage of multiple lots of commercial Mueller Hinton broth or agar (Protocol 04-THE-01, this application), researchers found significant differences in telavancin zone diameters for coagulase-negative staphylococci, *E. faecium*, and *S. pneumoniae*, dependent on media lots (using two lots of media from each of five manufacturers, and disks supplied by two separate manufacturers). Vancomycin zone sizes were less affected. Broth dilution testing resulted in acceptable correlation (all values within one doubling dilution, regardless of lot or manufacturer).

Surfactants are occasionally used to optimize testing conditions for MIC determinations using broth microdilution techniques. The effect of a standard wetting agent, Tween-80, on MIC testing of telavancin, was investigated in two studies. In the first (Protocol 04-THE-01, this submission), investigators found no significant changes in telavancin MIC values (tested against strains of *S. aureus*, *E. faecalis*, *E. faecium*, coagulase-negative staphylococcus, and *S. pneumoniae*) with the addition of Tween-80 to the inoculating blanks. Values were lowered by a fraction of a $\log_2$ dilution step, and quality control values remained in an acceptable range. In the second study, Tween 80 was added to inoculating water at a final concentration of 0.002% to inoculating water for frozen MIC panels. Results indicated MIC values approximately one doubling dilution lower than those obtained from tests without Tween 80, against staphylococcal and enterococcal isolates. The effect of Tween 80 on MIC testing was also studied by HPLC analysis of telavancin solutions in polystyrene 96-well microtiter plate (Report 04-6424-AC-002). Investigators demonstrated that in the presence of Tween 80, absorption of telavancin to the wells of polystyrene plates, effectively decreasing the concentration in the media.

The applicant investigated the applicability of vancomycin susceptibility testing as a meaningful surrogate for telavancin in vitro activity. Baseline MIC values from all telavancin surveillance studies, and post-amendment clinical trials, including FAST Study 202b, and ATLAS Studies 0017 and 0018, were presented as scatter plots. Telavancin interpretive values were based on the breakpoints proposed by the applicant (susceptible ≤ µg/ml, non-susceptible ≥ µg/ml). Vancomycin interpretive values were based on the current, CLSI-approved range (susceptible ≤ 2 µg/ml, intermediate 4-8 µg/ml, resistant ≥ 16 µg/ml). For both staphylococci and enterococci (Figures 1 and 2), vancomycin was a good predictor of telavancin susceptibility. For vancomycin-resistant organisms, however (VISA, VRSA, and VRE) vancomycin lacked correlation (correlation coefficient for VRE = 0.30, correlation coefficient for combined *S. aureus* population = 0.30).

b(4)

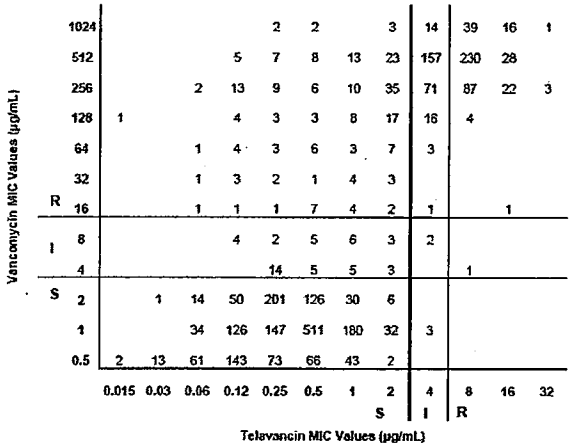
Figure 1: Telavancin and Vancomycin MIC Values of *S. aureus* (n=6,564) from Clinical and Surveillance Studies




Baseline MIC values from telavancin, vancomycin and standard arms of studies 202b, 0017 and 0018, ME population and MIC values from all surveillance studies

Source: 5.3.5.4.1.6 Figure 8, this submission

Figure 2: Telavancin and Vancomycin MIC Values of Enterococcal spp. (n=2,835) from Clinical and Surveillance Studies




Baseline MIC values from telavancin, vancomycin and standard arms of studies 2026, 0017 and 0018, ME population and MIC values from all surveillance studies.

Source: 5.3.5.4.1.6 Figure 9, this submission

*Validation Studies ~ Conclusions:*

Broth microdilution methods were used for the determination of telavancin in vitro activity in all pivotal clinical studies, and surveillance studies. This data was the primary source of information in the development of provisional interpretive criteria and proposed quality control ranges. Correlation of microbroth dilution methods and disk diffusion methods are discussed elsewhere in this review. Investigations by the applicant suggest the correlation of microbroth dilution methods do not correlate reliably with agar dilution methods.

Alterations in standard testing parameters, employed in CLSI-approved microbroth dilution MIC testing, produced minimal changes in telavancin MIC for pathogens claimed in the proposed indication (*S. aureus*, *S. pyogenes*, *S. agalactiae*, *S. intermedius* group, and vancomycin-susceptible *E. faecalis*). Studied parameters included incubation time, $Ca^{2+}$ concentration, pH, inoculum size, and incubation in the presence of 5% $CO_2$. Investigations of multiple lots of Mueller-Hinton broth media suggested no significant performance differences. Similar investigations of Mueller-Hinton agar media suggested notable differences (particularly with regard to coagulase-negative staphylococcal species, *E. faecium*, and *S. pneumoniae*). No significant differences were noted in the comparison of telavancin disk lots, prepared by two separate manufacturers (BBL and Hardy). The use of solid media to test telavancin activity (e.g. disk diffusion method, agar dilution method) appears problematic and will require additional investigation.

Studies of the effect of Tween-80 in susceptibility testing methods suggest that the inclusion of the surfactant in microbroth techniques (e.g. methods using polystyrene plates) may reduce telavancin MIC values. Surfactants were not used in the investigations that support the provisional interpretive criteria and quality control ranges.

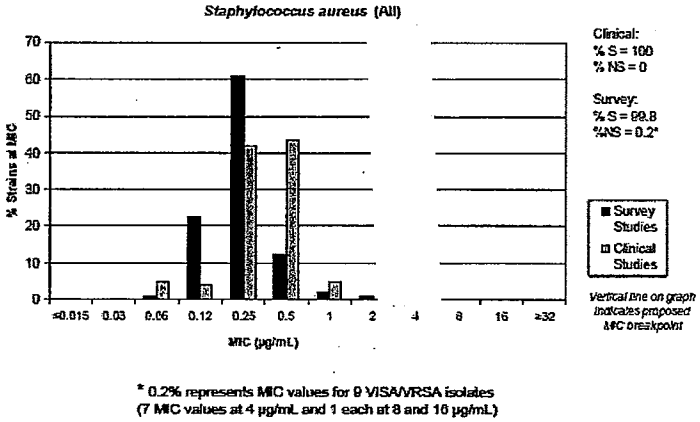
Data submitted by the applicant does not support the testing of vancomycin as a class-representative surrogate for telavancin.

**BROTH DILUTION METHODS**

The $MIC_{range}$ for *S. aureus* isolates recovered in clinical trials (n = 1,408) was ~ µg/ml. The range for isolates tested in surveillance studies (n = 5,148) was ~ µg/ml. Surveillance studies included vancomycin-intermediate isolates (n = 90) and vancomycin-resistant isolates (n = 11), both of which were excluded from the clinical trials, by design. The distribution for pooled data (clinical studies and surveillance studies) is unimodal. MRSA and methicillin-susceptible distributions were similar. Distributions for all *S. aureus* and MRSA are summarized in Figures 1 and 2. One hundred percent of clinical isolates and 98% of survey isolates had MICs of ≤ 1 µg/ml.

b(4)

Figure 1: Frequency Distribution of Telavancin MIC Values against *S. aureus* from Clinical Studies (n = 1,408 all baseline isolates) and Survey Studies (n = 5,148)

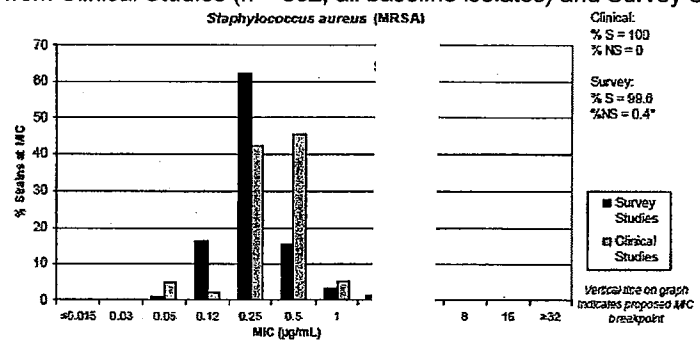



b(4)

* 0.2% represents MIC values for 9 VISA/VRSA isolates (7 MIC values at 4 µg/mL and 1 each at 8 and 16 µg/mL)

Source: 5.3.5.4.1.11 Figure 1, this submission

Figure 2: Frequency Distribution of Telavancin MIC Values against Methicillin-resistant *S. aureus* from Clinical Studies (n = 852, all baseline isolates) and Survey Studies (n = 2,228)




b(4)

* 0.4% represents MIC values for 9 VISA/VRSA isolates (7 MIC values at 4 µg/mL and 1 each at 8 and 16 µg/mL)

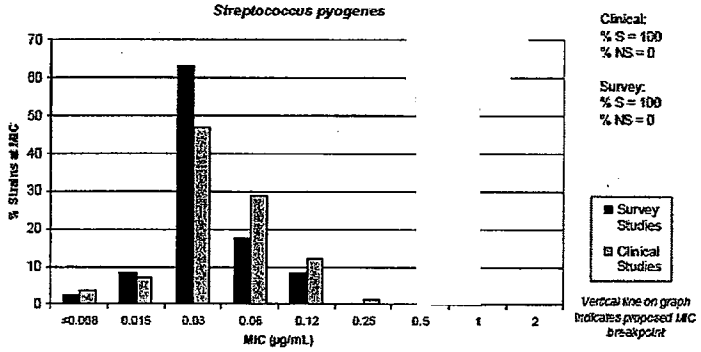
Source: 5.3.5.4.1.11 Figure 2, this submission

Data for isolates of *S. pyogenes*, tested during clinical trials and surveillance studies, is summarized in Figure 3. The MIC~ for isolates recovered during clinical studies (n = 83) was ~ µg/ml, and ~ µg/ml for isolates tested during the surveillance studies (n = 412). No tested isolates had MICs at or above the proposed breakpoint of ~ µg/ml.

b(4)

Distribution of MIC values in the clinical and surveillance isolates was similar, and was unimodal.

Figure 3: Frequency Distribution of Telavancin MIC Values against *S. pyogenes* from Clinical Studies (n=83, all baseline isolates) and Survey Studies (n=412)



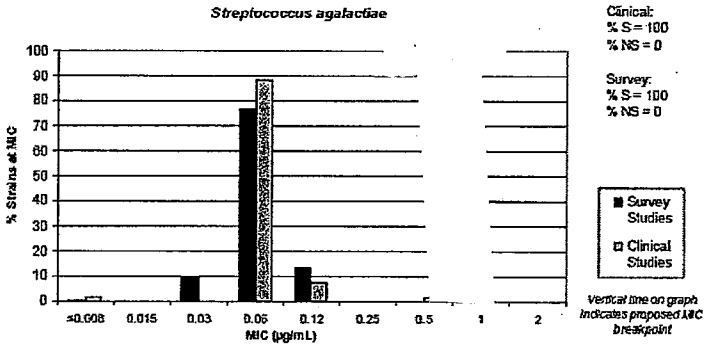

b(4)

Source: 5.3.5.4.1.11 Figure 3, this submission

Summary data for telavancin MIC values against *S. agalactiae* is presented in Figure 4. The distribution for pooled data from clinical trials (n = 51) and surveillance studies (n = 339) is unimodal. The $MIC_{range}$ for baseline isolates from clinical studies was ( µg/ml, with the MIC of > 98% of isolates at < 0.12 µg/ml. The $MIC_{range}$ for the ME population in the combined global clinical trial data (n = 19) was ( µg/ml. The distribution of MIC values in the clinical trials was similar to the distribution in the surveillance studies.

b(4)

Figure 4: Frequency Distribution of Telavancin MIC Values against *S. agalactiae* from Clinical Studies (n = 51, all baseline isolates) and Survey Studies (n = 339)



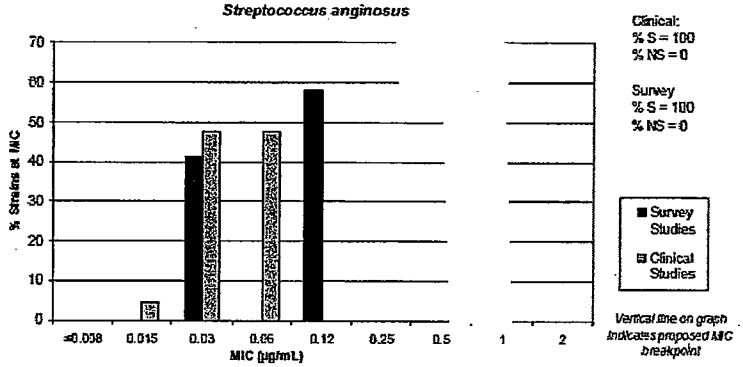

b(4)

Source: 5.3.5.4.1.11 Figure 4, this submission

Comparative distributions for pathogens included in the *S. anginosus* group are presented in Figures 5 (*S. anginosus*), 6 (*S. constellatus*) and 7 (*S. intermedius*). Numbers of tested isolates, both in clinical trials and survey studies, were low (i.e. ≈ 30 isolates per species, 101 total isolates tested in *S. anginosus* group). Distributions of MIC values for each species, isolated during clinical trials, were similar to those derived from survey study data. For *S. anginosus*, the $MIC_{range}$ for isolates from clinical trials (n = 21) was ( µg/ml ($MIC_{50/90}$ = 0.03/0.06 µg/ml). For *S. constellatus*, the $MIC_{range}$ for isolates from clinical studies (n = 16) was ( µg/ml ($MIC_{50/90}$ = 0.03/0.06 µg/ml), and ( µg/ml ($MIC_{50/90}$ = 0.12/0.12) for isolates from survey studies (n = 15). For *S. intermedius*, the $MIC_{range}$ for isolates from clinical trials (n = 7) was ( µg/ml, and ( µg/ml for isolates from the survey studies (n = 30). No isolate of the S. anginosus group, from the clinical trials, had an MIC greater than 0.06 µg/ml.

b(4)

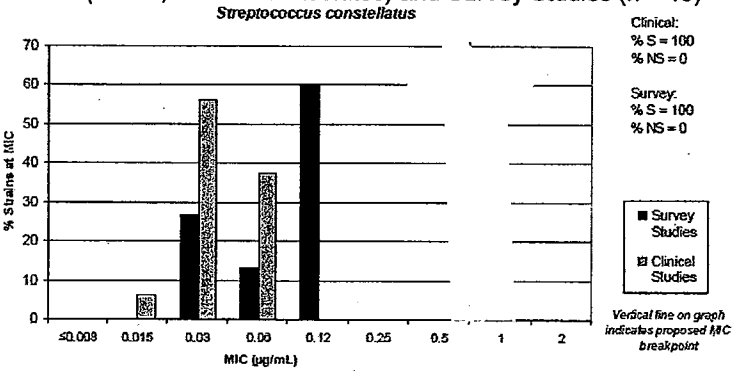
Figure 5: Frequency Distribution of Telavancin MIC Values against *S. anginosus* from Clinical Studies (n = 21, all baseline isolates) and Survey Studies (n =12)




b(4)

Source: 5.3.5.4.1.11 Figure 5, this submission

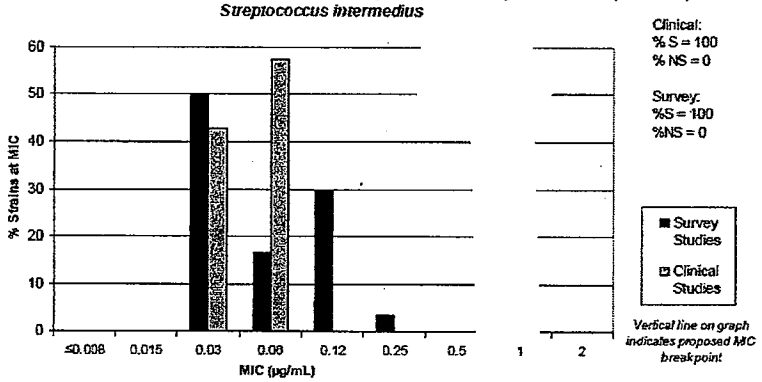
Figure 6: Frequency Distribution of Telavancin MIC Values against *S. constellatus* from Clinical Studies (n = 16, all baseline isolates) and Survey Studies (n = 15)




b(4)

Source: 5.3.5.4.1.11 Figure 6, this submission

Figure 7: Frequency Distribution of Telavancin MIC Values against *S. intermedius* from Clinical Studies (n = 7, all baseline isolates) and Survey Studies (n = 30)



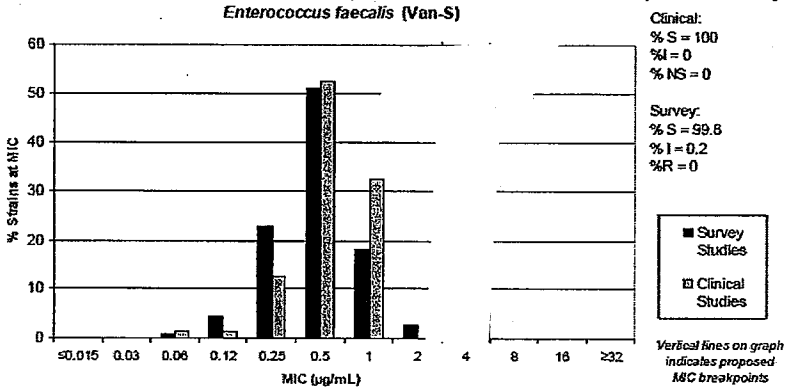

b(4)

Source: 5.3.5.4.1.11 Figure 7, this submission

Comparative distributions of telavancin MIC values from clinical trials and survey studies are presented in Figure 8. Distributions are similar for both sets of data, and both are unimodal. The $MIC_{range}$ for vancomycin-susceptible *E. faecalis*. recovered during clinical trials (n = 80), was ( ) µg/ml ($MIC_{50/90}$ = 0.5/1 µg/ml), and( ) µg/ml ($MIC_{50/90}$ = 0.5/1 µg/ml) for isolates tested in survey studies. No vancomycin-resistant *E. faecalis* isolates were obtained in the clinical studies, by design (patients with vancomycin-resistant pathogens were excluded from the clinical trials). MIC distributions for add *E. faecalis* isolates tested in both clinical trials and survey studies are presented in Figure 9. The distribution is bimodal, indicating a resistant population distinguishable from wild-type strains. The peak of the resistant population is 8 µg/ml.

b(4)

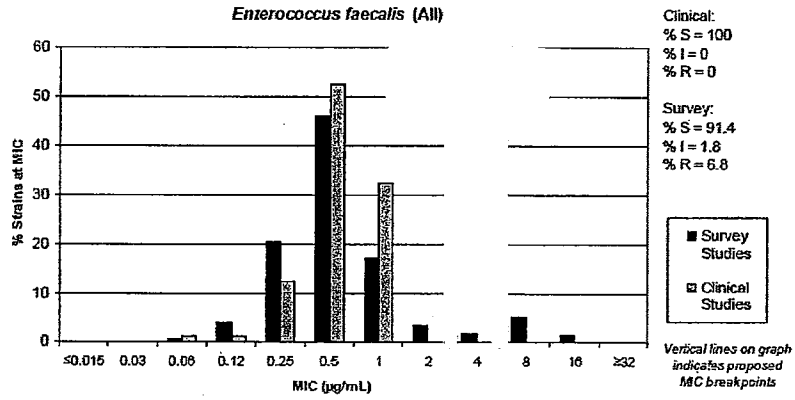
Figure 8: Frequency Distribution of Telavancin MIC Values against Vancomycin-susceptible *E. faecalis* from Clinical Studies (n = 80, all baseline isolates) and Survey Studies (n = 1,230)




b(4)

Source: 5.3.5.4.1.11 Figure 8, this submission

Figure 9: Frequency Distribution of Telavancin MIC Values against E. faecalis, Vancomycin-susceptible from Clinical Studies (n = 80) and Vancomycin-susceptible and –resistant from Survey Studies (n = 1,412)




b(4)

Source: 5.3.5.4.1.11 Figure 9, this submission

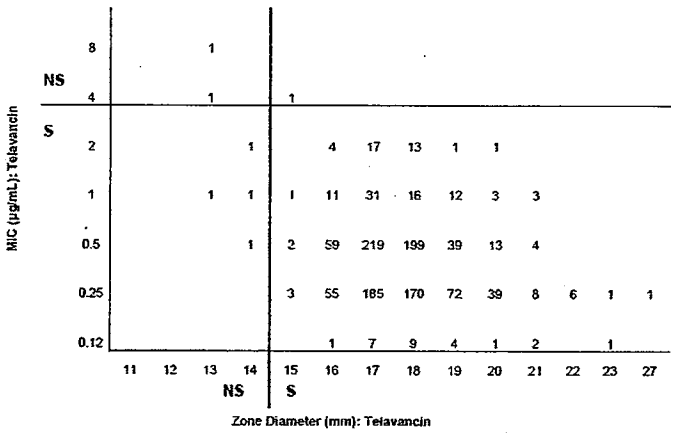
*Broth Dilution Methods ~ Conclusions:*
Telavancin MIC distributions from clinical trials and survey studies are unimodal for *S. aureus* (both methicillin-susceptible and methicillin-resistant strains), the ß-hemolytic streptococci (*S. pyogenes* and *S. agalactiae*), and the *Streptococcus anginosus* group. Distributions derived from clinical studies, for these pathogens, are similar to those derived from survey studies. The upper range of MICs, from pathogens isolated during clinical studies, are 1-2 doubling dilutions less than the proposed susceptible breakpoints for *S. aureus*, S. pyogenes, *S. agalactiae*, and the *S. anginosus* group. $MIC_{range}$ values for isolates of these pathogens, tested in survey studies, also support susceptibility breakpoints 1-2 dilutions lower than proposed.

**DISK DIFFUSION METHODS**

Scatter plots, comparing MIC and disk diffusion results from isolates tested in clinical trials (ME population from post-amendment studies) and survey studies (where disk diffusion was performed), are presented in Figures 1 through 14.

The scatter plot for *S. aureus* (combined clinical and survey studies) is presented In Figure 1, along with charted categorical errors. The combined data include numerous isolates from survey studies that were included to characterize telavancin activity against glycopeptide-resistant phenotypes. Data from clinical studies only is presented in Figures 2 and 4.

Figure 1: Telavancin Broth Microdilution MIC vs. Disk Diffusion Zone Diameter against *S. aureus* from Combined Clinical (ME Population) and Survey Studies (n = 1,220)

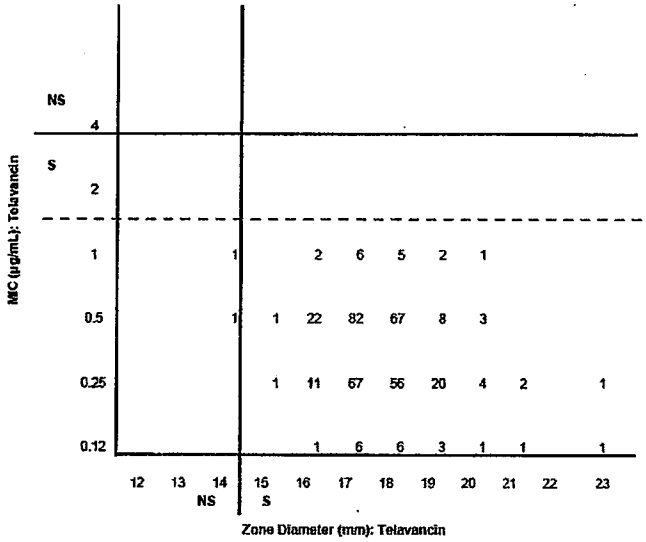



| Summary of Categorical Errors: | | | | | |
|---|---|---|---|---|---|
| MIC Range | Total N | Very Major | | Major | |
| | | N | % | N | % |
| ≥R+1 | 1 | 0 | 0.0 | N/A | N/A |
| R+S | 39 | 1 | 2.6 | 1 | 2.6 |
| ≤S-1 | 1,180 | N/A | N/A | 3 | 0.3 |
| Total | 1,220 | 1 | 0.1 | 4 | 0.3 |

Source: 5.3.5.4.1.11 Figure 11, this submission

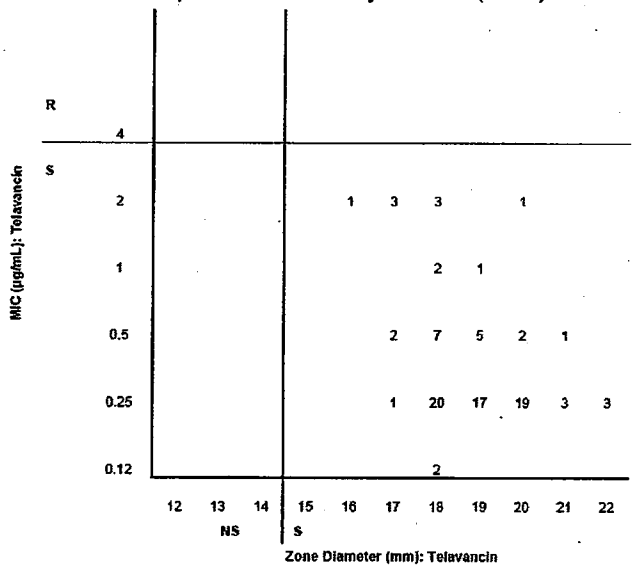
Using only data from clinical studies, and the Agency-proposed susceptible breakpoint of 1 µg/ml (susceptible zone size = 15mm), the very major error rate for *S. aureus* (methicillin-resistant and –susceptible) is 0%. The major discrepancy rate for methicillin-resistant isolates is 0% and for methicillin-susceptible isolates the major discrepancy rate is 0.5%. Clinical outcome data, comparing cure rates during clinical trials to baseline telavancin susceptibility (disk diffusion method) is presented in Table 1.

Figure 2: Telavancin Broth Microdilution MIC vs. Disk Diffusion Zone Diameter against *S. aureus*, Methicillin-susceptible from Clinical Studies (ME Population) (n=382); dotted line indicates susceptible breakpoint proposed by the Agency



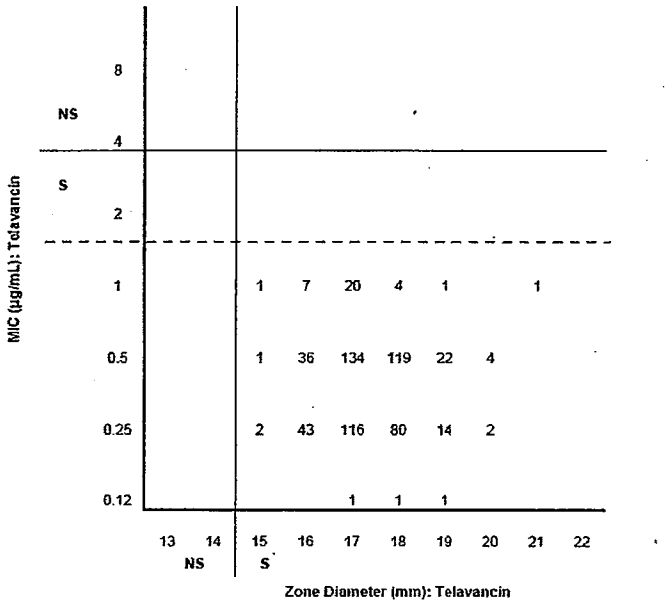

Source: 5.3.5.4.11.Appendix 1: Supplemental Figure 1, this submission

Figure 3: Telavancin Broth Microdilution MIC vs. Disk Diffusion Zone Diameter against *S. aureus*, Methicillin-susceptible from Survey Studies (n=93)



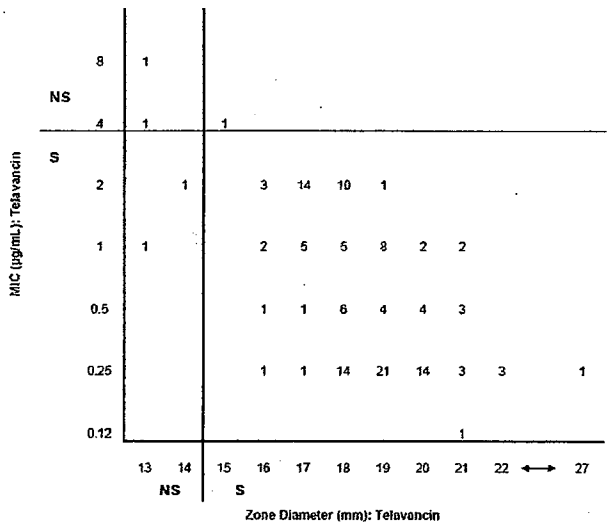

Source: 5.3.5.4.11.Appendix 1: Supplemental Figure 4, this submission

Figure 4: Telavancin Broth Microdilution MIC vs. Disk Diffusion Zone Diameter against *S. aureus*, Methicillin-resistant from Clinical Studies (ME Population) (n = 610); dotted line indicates susceptible breakpoint proposed by the Agency




Source: 5.3.5.4.11.Appendix 1: Supplemental Figure 2, this submission

Figure 5: Telavancin Broth Microdilution MIC vs. Disk Diffusion Zone Diameter against *S. aureus*, Methicillin-resistant from Survey Studies (n = 135)




Source: 5.3.5.4.11.Appendix 1: Supplemental Figure 5, this submission

Table 1: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin Zone Diameter Value

Studies 202b, 0017, and 0018 (all Post-Amendment) Combined
Telavancin 10 mg/kg
Microbiologically Evaluable (ME)
Global
Baseline Pathogens/Susceptibility: *S. aureus*/Oxacillin (OX)

| Baseline Pathogen [1] | Baseline Susceptibility [2] | Baseline Telavancin Zone Diameter (mm) | Clinical Outcome at Test-of-Cure Visit | | | | Microbiological Outcome at Test-of-Cure Visit | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cured N (%) [3] | Not Cured N (%) [3] | No. Indeterminate | No. Missing | Eradication [4] N (%) [5] | Non-Eradication [6] N (%) [5] | No. Indeterminate | No. Missing |
| *S. aureus* | Missing | | 49(96.1) | 2(3.9) | | | 47(92.2) | 4(7.8) | | |
| | OX:R | 15 | 1(100) | | | | 1(100) | | | |
| | | 16 | 39(90.7) | 4(9.3) | | | 39(90.7) | 4(9.3) | | |
| | | 17 | 108(89.3) | 13(10.7) | | | 106(87.6) | 15(12.4) | | |
| | | 18 | 74(92.5) | 6(7.5) | | | 74(92.5) | 6(7.5) | | |
| | | 19 | 15(88.2) | 2(11.8) | | | 15(88.2) | 2(11.8) | | |
| | | 21 | 1(100) | | | | 1(100) | | | |
| | | | | | | | | | | |
| | OX:S | 15 | 1(100) | | | | 1(100) | | | |
| | | 16 | 11(91.7) | 1(8.3) | | | 11(91.7) | 1(8.3) | | |
| | | 17 | 85(85.5) | 11(14.5) | | | 86(86.8) | 10(13.2) | | |
| | | 18 | 49(89.1) | 6(10.9) | | | 48(87.3) | 7(12.7) | | |
| | | 19 | 16(94.1) | 1(5.9) | | | 16(94.1) | 1(5.9) | | |
| | | 20 | 7(87.5) | 1(12.5) | | | 7(87.5) | 1(12.5) | | |
| | | 21 | 2(100) | | | | 2(100) | | | |
| | | | | | | | | | | |
| | Total | 485 | 438 | 47 | | | 434 | 51 | | |

[1] Identification of baseline pathogen.
[2] S = Susceptible, I = Intermediate, R = Resistant.
[3] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.
[4] Documented Eradication, Presumed Eradication.
[5] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.
[6] Documented Persistence, Presumed Persistence.

Source: 5.3.5.4.10, Supplemental Table 108

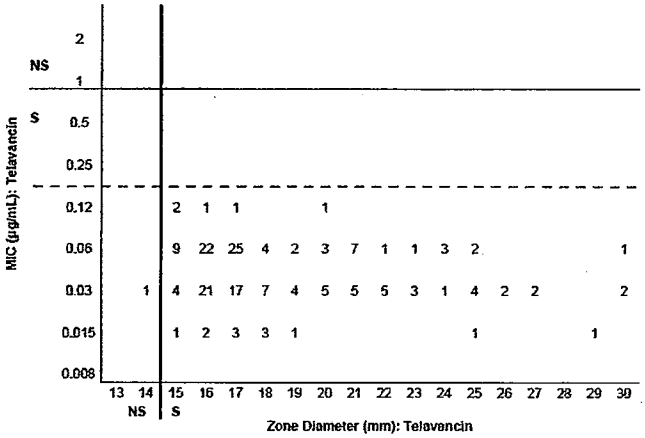
The scatter plot for all streptococcal species sought in the indication (combined clinical and survey studies) is presented In Figure 6, along with charted categorical errors. Data from clinical studies only (separated by species) is presented in Figures 6 through 12.

Data for *S. pyogenes* only is summarized in Figure 7 (data from clinical trials) and Figure 8 (data from survey studies). Using data from clinical studies only, and the susceptible breakpoint proposed by the Agency (≤ 0.012 µg/ml), very major and major discrepancy rates remain within the accepted ranges of the error rate-bounded method, using CLSI criteria. Clinical outcome data, comparing cure rates during clinical trials to baseline telavancin susceptibility (disk diffusion method) is presented in Table 2.

Data for *S. agalactiae* only is summarized in Figure 9 (data from clinical trials) and Figure 10 (data from survey studies). Although a correlation between cure rates and decreasing zone sizes (Table 3) is suggested, the number of *S. agalactiae* isolates analyzed in clinical trials was small. Using data from clinical studies only, and the susceptibility breakpoint proposed by the Agency (≤ 0.012 µg/ml), the very major and major discrepancy rates are both 0%.

Data for the *S. anginosus* group is summarized in Figures 11 and 12. Clinical outcome data, summarized by baseline telavancin zone size, is presented (by individual species) in Tables 4, 5 and 6. As with *S. agalactiae*, the number of *S. anginosus* group isolates recovered in clinical trials was low (10 isolates of *S. anginosus*, 7 isolates of *S. constellatus*, and 3 isolates of *S. intermedius*). No useful correlation is noted between zone sizes and clinical outcome. Using only data from clinical studies, and the susceptible breakpoint proposed by the Agency (≤ 0.012 µg/ml), the very major discrepancy rate is 9% and the major discrepancy rate is 2.8%.

Figure 6: Telavancin Broth Microdilution MIC vs. Disk Diffusion Zone Diameter against Streptococci (*S. agalactiae*, *S. anginosus* group, *S. pyogenes*) from Combined Clinical (ME Population) and Survey Studies (n = 180); dotted line indicates susceptible breakpoint proposed by the Agency

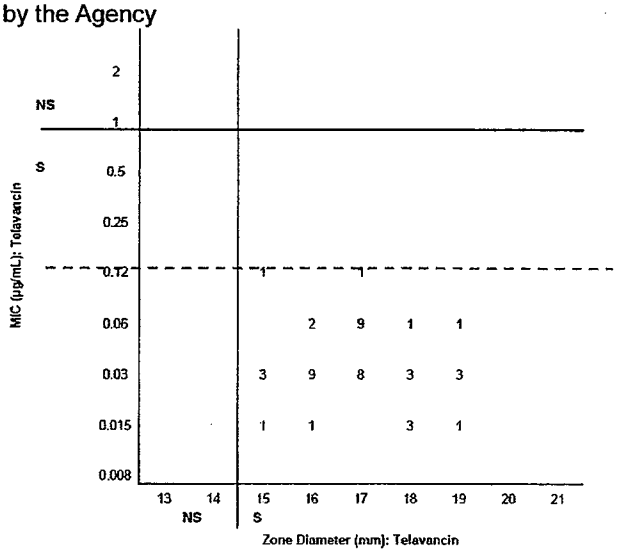



Summary of Categorical Errors:

| MIC Range | Total N | Very Major | | Major | |
|---|---|---|---|---|---|
| | | N | % | N | % |
| ≥R+1 | 0 | 0 | 0.0 | N/A | N/A |
| R+S | 0 | 0 | 0.0 | 0 | 0.0 |
| ≤S-1 | 180 | N/A | N/A | 1 | 0.6 |
| Total | 180 | 0 | 0.0 | 1 | 0.6 |

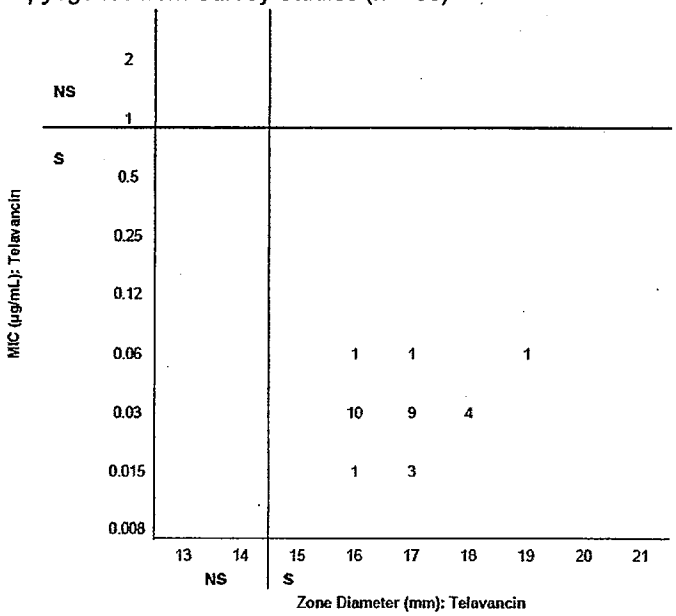
Source: 5.3.5.4.1.11 Figure 15, this submission

Figure 7: Telavancin Broth Microdilution MIC vs. Disk Diffusion Zone Diameter against *S. pyogenes* from Clinical Studies (n = 47); dotted line indicates susceptible breakpoint proposed by the Agency




Source: 5.3.5.4.1.Appendix 1: Supplemental Figure 10, this submission

Figure 8: Telavancin Broth Microdilution MIC vs. Disk Diffusion Zone Diameter against *S. pyogenes* from Survey Studies (n = 30)




Source: 5.3.5.4.1.Appendix 1: Supplemental Figure 11, this submission

Table 2: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin Zone Diameter Value

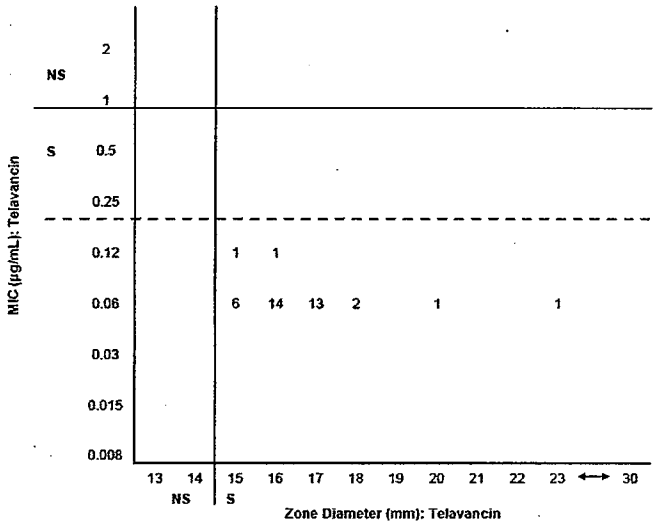
Studies 202b, 0017, and 0018 (all Post-Amendment) Combined
Telavancin 10 mg/kg
Microbiologically Evaluable (ME)
US Studies
Baseline Pathogens: *S. pyogenes*

| Baseline Pathogen [1] | Baseline Telavancin Zone Diameter (mm) | Clinical Outcome at Test-of-Cure Visit | | | | Microbiological Outcome at Test-of-Cure Visit | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Cured N (%) [3] | Not Cured N (%) [3] | No. Indeterminate | No. Missing | Eradication [4] N (%) [5] | Non-Eradication [6] N (%) [5] | No. Indeterminate | No. Missing |
| *S. pyogenes* | Missing | 3(100) | | | | 3(100) | | | |
| | 16 | 3(75) | 1(25) | | | 3(75) | 1(25) | | |
| | 17 | 3(75) | 1(25) | | | 3(75) | 1(25) | | |
| | 18 | 1(100) | | | | 1(100) | | | |
| | 19 | 1(100) | | | | 1(100) | | | |
| Total | | 13 | 11 | 2 | | 11 | 2 | | |

[1] Identification of baseline pathogen.
[2] S = Susceptible, I = Intermediate, R = Resistant.
[3] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.
[4] Documented Eradication, Presumed Eradication.
[5] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.
[6] Documented Persistence, Presumed Persistence.

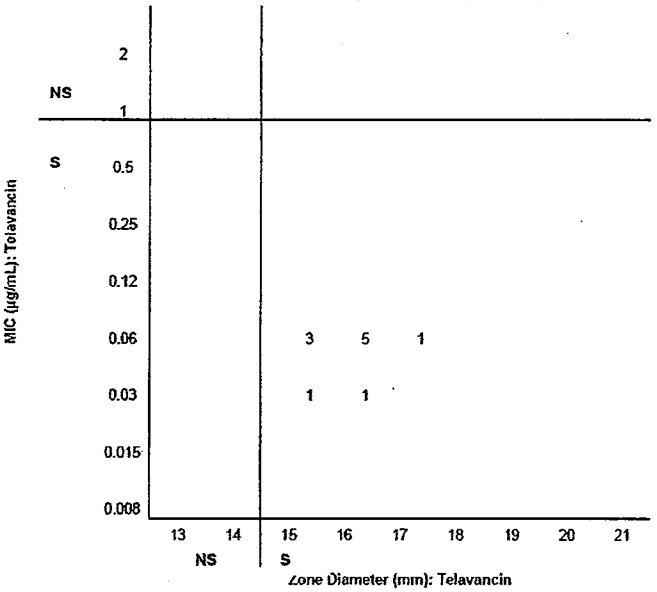
Source: 5.3.5.4.10, Supplemental Table 180

Figure 9: Telavancin Broth Microdilution MIC vs. Disk Diffusion Zone Diameter against *S. agalactiae* from Clinical Studies (ME Population) (n = 39); dotted line indicates susceptible breakpoint proposed by the Agency




Source: 5.3.5.4.1.Appendix 1: Supplemental Figure 6, this submission

Figure 10: Telavancin Broth Microdilution MIC vs. Disk Diffusion Zone Diameter Against *S. agalactiae* from Survey Studies (n = 11)




Source: 5.3.5.4.1.Appendix 1: Supplemental Figure 7, this submission

Table 3: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin Zone Diameter Value

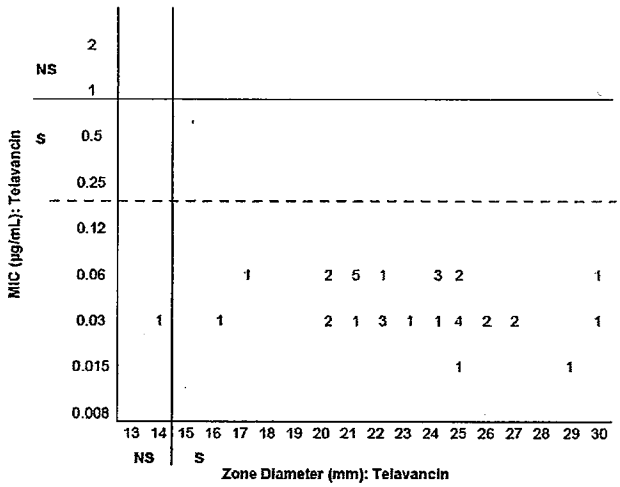
Studies 202b, 0017, and 0018 (all Post-Amendment) Combined
Telavancin 10 mg/kg
Microbiologically Evaluable (ME)
Global
Baseline Pathogens: *S. agalactiae*

| Baseline Pathogen [1] | Baseline Susceptibility [2] | Baseline Telavancin Zone Diameter (mm) | Clinical Outcome at Test-of-Cure Visit | | | | Microbiological Outcome at Test-of-Cure Visit | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cured N (%) [3] | Not Cured N (%) [3] | No. Indeterminate | No. Missing | Eradication [4] N (%) [5] | Non-Eradication [6] N (%) [5] | No. Indeterminate | No. Missing |
| *S. agalactiae* | Missing | | 1(100) | | | | 1(100) | | | |
| | | 15 | 2(67) | 1(33) | | | 3(100) | | | |
| | | 16 | 7(78) | 2(22) | | | 8(89) | 1(11) | | |
| | | 17 | 4(80) | 1(20) | | | 4(80) | 1(20) | | |
| | | 18 | 1(100) | | | | 1(100) | | | |
| | Total | 19 | 15 | 4 | | | 17(89) | 2(11) | | |

[1] Identification of baseline pathogen.
[2] S = Susceptible, I = Intermediate, R = Resistant.
[3] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.
[4] Documented Eradication, Presumed Eradication.
[5] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.
[6] Documented Persistence, Presumed Persistence.

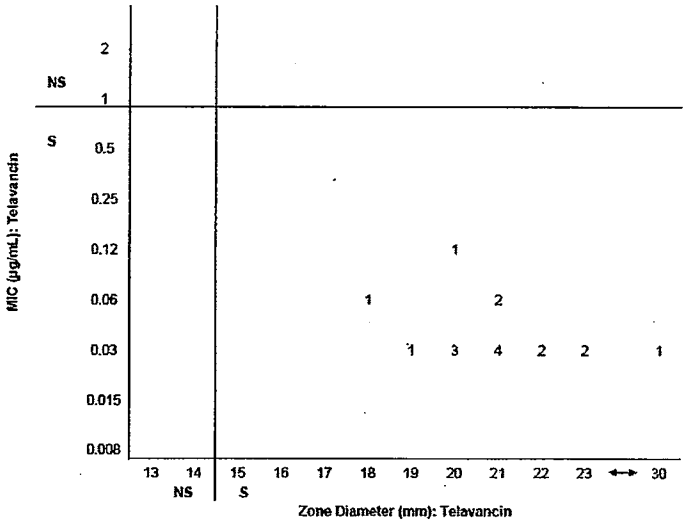
Source: 5.3.5.4.10, Supplemental Table 324

Figure 11: Telavancin Broth Microdilution MIC vs. Disk Diffusion Zone Diameter against S. anginosus group from Clinical Studies (ME Population) (n = 36); dotted line indicates susceptible breakpoint proposed by the Agency




Source: 5.3.5.4.1.Appendix 1: Supplemental Figure 8, this submission

Figure 12: Telavancin Broth Microdilution MIC vs. Disk Diffusion Zone Diameter against *S. anginosus* group from Survey Studies (n = 17)




Source: 5.3.5.4.1.Appendix 1: Supplemental Figure 9, this submission

Table 4: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin Zone Diameter Value

Studies 202b, 0017, and 0018 (all Post-Amendment) Combined
Telavancin 10 mg/kg
Microbiologically Evaluable (ME)
Global
Baseline Pathogens: *S. anginosus*

| Baseline Pathogen [1] | Baseline Susceptibility [2] | Baseline Telavancin Zone Diameter (mm) | Clinical Outcome at Test-of-Cure Visit | | | | Microbiological Outcome at Test-of-Cure Visit | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cured N (%) [3] | Not Cured N (%) [3] | No. Indeterminate | No. Missing | Eradication [4] N (%) [5] | Non-Eradication [6] N (%) [5] | No. Indeterminate | No. Missing |
| *S. anginosus* | Missing | | | | | | | | | |
| | | 20 | 1(100) | | | | 1(100) | | | |
| | | 21 | 3(100) | | | | 3(100) | | | |
| | | 22 | 2(100) | | | | 2(100) | | | |
| | | 23 | 1(100) | | | | 1(100) | | | |
| | | 24 | 1(100) | | | | 1(100) | | | |
| | | 25 | 1(100) | | | | 1(100) | | | |
| | | 29 | 1(100) | | | | 1(100) | | | |
| | Total | 10 | 10(100) | | | | 10(100) | | | |

[1] Identification of baseline pathogen.
[2] S = Susceptible, I = Intermediate, R = Resistant.
[3] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.
[4] Documented Eradication, Presumed Eradication.
[5] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.
[6] Documented Persistence, Presumed Persistence.

Source: 5.3.5.4.10, Supplemental Table 432

Table 5: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin MIC Value

Studies 202b, 0017, and 0018 (all Post-Amendment) Combined
Telavancin 10 mg/kg
Microbiologically Evaluable (ME)
Global
Baseline Pathogens: *S. constellatus*

| Baseline Pathogen [1] | Baseline Telavancin Zone Diameter (mm) | Clinical Outcome at Test-of-Cure Visit | | | | Microbiological Outcome at Test-of-Cure Visit | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Cured N (%) [3] | Not Cured N (%) [3] | No. Indeterminate | No. Missing | Eradication [4] N (%) [5] | Non-Eradication [6] N (%) [5] | No. Indeterminate | No. Missing |
| *S. constellatus* | 14 | 1(100) | | | | 1(100) | | | |
| | 20 | 1(100) | | | | 1(100) | | | |
| | 21 | | 1(100) | | | 1(100) | | | |
| | 24 | 1(100) | | | | 1(100) | | | |
| | 25 | 2(66.7) | 1(33.3) | | | 2(66.7) | 1(33.3) | | |
| Total | 7 | 5 | 2 | | | 6 | 1 | | |

[1] Identification of baseline pathogen.
[2] S = Susceptible, I = Intermediate, R = Resistant.
[3] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.
[4] Documented Eradication, Presumed Eradication.
[5] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.
[6] Documented Persistence, Presumed Persistence.

Source: 5.3.5.4.10, Supplemental Table 540

Table 6: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin Zone Diameter Value

Studies 202b, 0017, and 0018 (all Post-Amendment) Combined
Telavancin 10 mg/kg
Microbiologically Evaluable (ME)
Global
Baseline Pathogens: *S. intermedius*

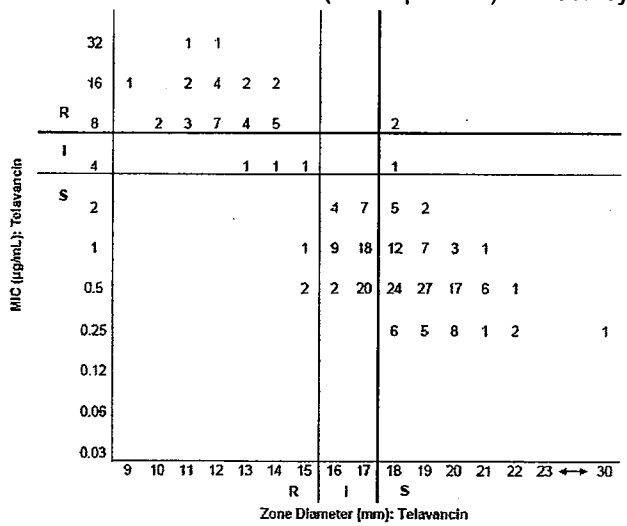
| Baseline Pathogen [1] | Baseline Telavancin Zone Diameter (mm) | Clinical Outcome at Test-of-Cure Visit | | | | Microbiological Outcome at Test-of-Cure Visit | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Cured N (%) [3] | Not Cured N (%) [3] | No. Indeterminate | No. Missing | Eradication [4] N (%) [5] | Non-Eradication [6] N (%) [5] | No. Indeterminate | No. Missing |
| *S. intermedius* | 24 | 1(100) | | | | 1(100) | | | |
| | 25 | 1(100) | | | | 1(100) | | | |
| | 27 | | 1(100) | | | | 1(100) | | |
| Total | 3 | 2 | 1 | | | 2 | 1 | | |

[1] Identification of baseline pathogen.
[2] S = Susceptible, I = Intermediate, R = Resistant.
[3] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.
[4] Documented Eradication, Presumed Eradication.
[5] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.
[6] Documented Persistence, Presumed Persistence.

Source: 5.3.5.4.10, Supplemental Table 648

Data for enterococcal species (including vancomycin-susceptible *E. faecalis*) is summarized in Figures 13 and 14, and Table 7.

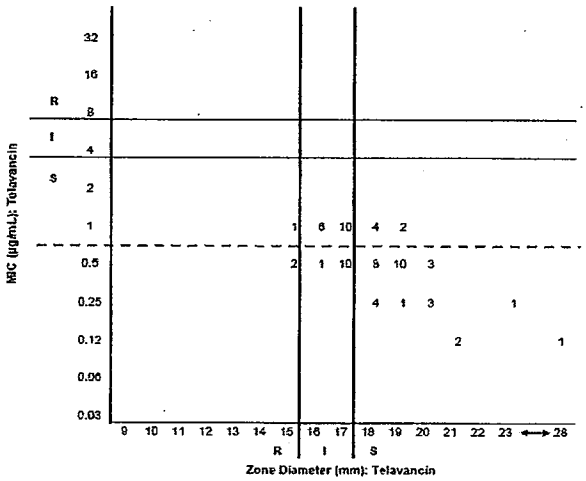
Figure 13: Telavancin Broth Microdilution MIC vs. Disk Diffusion Zone Diameter against *E. faecalis* from Combined Clinical (ME Population) and Survey Studies (n = 231)




| Summary of Categorical Errors: | | | | | | | |
|---|---|---|---|---|---|---|---|
| MIC Range | Total N | Very Major | | Major | | Minor | |
| | | N | % | N | % | N | % |
| ≥I+2 | 13 | 0 | 0.0 | N/A | N/A | 0 | 0.0 |
| I+1 to I-1 | 45 | 2 | 4.4 | 0 | 0.0 | 15 | 33.3 |
| ≤I-2 | 173 | N/A | N/A | 3 | 1.7 | 49 | 28.3 |
| Total | 231 | 2 | 0.9 | 3 | 1.3 | 64 | 27.7 |

Source: 5.3.5.4.1.11 Figure 18, this submission

Figure 14: Telavancin Broth Microdilution MIC vs. Disk Diffusion Zone Diameter against Enterococci from Clinical Studies (ME Population) (n=69); dotted line indicates susceptible breakpoint proposed by the Agency




Source: 5.3.5.4.1.11 Figure 19, this submission

Table 7: Frequency Table for Sponsor's Clinical Outcome and Microbiological Outcome by Baseline Telavancin Zone Diameter Value

Studies 202b, 0017, and 0018 (all Post-Amendment) Combined
Telavancin 10 mg/kg
Microbiologically Evaluable (ME)
Global
Baseline Pathogens: *E. faecalis, VSE*

| Baseline Pathogen [1] | Baseline Telavancin Zone Diameter (mm) | Clinical Outcome at Test-of-Cure Visit | | | | Microbiological Outcome at Test-of-Cure Visit | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Cured N (%) [3] | Not Cured N (%) [3] | No. Indeterminate | No. Missing | Eradication [4] N (%) [5] | Non-Eradication [6] N (%) [5] | No. Indeterminate | No. Missing |
| *E. faecalis, VSE* | 16 | 5(83.3) | 1(16.7) | | | 5(83.3) | 1(16.7) | | |
| | 17 | 8(100) | | | | 8(100) | | | |
| | 18 | 4(80) | 1(20) | | | 4(80) | 1(20) | | |
| | 19 | 5(100) | | | | 5(100) | | | |
| | 20 | 3(100) | | | | 3(100) | | | |
| Total | 27 | 25 | 2 | | | 25 | 2 | | |

[1] Identification of baseline pathogen.
[2] S = Susceptible, I = Intermediate, R = Resistant.
[3] Percentages are based upon Cured + Not Cured. N = number of patients with given baseline pathogen.
[4] Documented Eradication, Presumed Eradication.
[5] Percentages are based upon Eradication + Non-Eradication. N = number of patients with given baseline pathogen.
[6] Documented Persistence, Presumed Persistence.

Source: 5.3.5.4.10, Supplemental Table 756

*Disk Diffusion Methods ~ Conclusions:*

Correlation studies comparing the disk diffusion method of susceptibility testing with the minimum inhibitory concentration method support the zone size recommendations of the Applicant. Changes to the MIC susceptible breakpoint, proposed by the Agency, have negligible or no effect on the percentages of very major or major discrepancies, predicted by the error rate-bounded method.

Data from reference laboratory reports 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. Laboratories performing telavancin disk diffusion testing will be advised to closely monitor performance of the assay. Susceptibility testing by the agar diffusion method is not recommended.

**QUALITY CONTROL STUDIES**

The Applicant developed quality control parameters, using CLSI (formerly NCCLS) methods, detailed in their M23 publication (NCCLS 2001). Assessment of telavancin performance, using the disk diffusion method, was performed by eight laboratories, all testing Mueller-Hinton agar provided by three separate manufacturers and telavancin disks provided by two separate manufacturers. Vancomycin susceptibility testing was performed concurrently, as a control. Broth microdilution assays, used in quality control studies, clinical studies, and the primary surveillance studies, were performed using frozen MIC panels provided by TREK Diagnostics (Cleveland, OH).

Telavancin powder was prepared in either water of 50% water/50% dimethyl sulfoxide (DMSO). Stability studies by Covance indicated that 50% aqueous DMSO solutions of telavancin are stable for 7 days at 5°C ± 3°C, and for 26 weeks at -20°C ± 5°C.
Results of the 8-laboratory study, discussed above, are summarized in Table 2. Based on these results, the Applicant developed the MIC quality control ranges presented in Table 3. During clinical studies, 99.0% of *S. aureus* ATCC 29213 (n = 301) were within the acceptable QC range, and 97.0% of *E. faecalis* ATCC 29212 were within range.

Table 2: Number of Telavancin Results at Each MIC from M23-based QC Study

| [a]MIC (µg/mL) | Lot 1 | Lot 2 | Lot 3 | All Lots |
|---|---|---|---|---|
| *S. aureus* ATCC 29213 (CLSI Range: 0.12-1 µg/mL) | | | | |
| 0.12 | | | 1 | 1 |
| 0.25 | 45 | 49 | 57 | 151 |
| 0.5 | 26 | 27 | 18 | 71 |
| 1 | 9 | 4 | 4 | 17 |
| *E. faecalis* ATCC 29212 (CLSI Range: 0.12-0.5 µg/mL) | | | | |
| 0.12 | 1 | 1 | | 2 |
| 0.25 | 69 | 70 | 64 | 203 |
| 0.5 | 10 | 9 | 15 | 34 |
| 1 | | | 1 | 1 |
| *S. pneumoniae* ATCC 49619 (CLSI Range: 0.004-0.03 µg/mL) | | | | |
| 0.004 | 31 | 29 | 41 | 101 |
| 0.008 | 60 | 60 | 61 | 181 |
| 0.015 | 69 | 70 | 58 | 197 |
| 0.03 | | 1 | | 1 |

[a] Clinical Microbiology Institute (181)
Source: 5.3.5.4.1.10 Table 1, this submission

Table 3: CLSI Approved Telavancin MIC Quality Control Ranges

| [a]QC Strain | CLSI Approved Range (µg/mL) | % of MIC Values Included |
|---|---|---|
| *S. aureus* ATCC 29213 | 0.12-1 | 100 |
| *E. faecalis* ATCC 29212 | 0.12-0.5 | 99.6 |
| *S. pneumoniae* ATCC 49619 | 0.004-0.03 | 100 |

[a] CLSI (44)
Source: 5.3.5.4.1.10 Table 2, this submission

*Quality Control Studies ~ Conclusions:*
The proposed quality control ranges, based on CLSI M23 studies, are acceptable. As discussed elsewhere in this review, the inclusion of a wetting agent is not recommended for MIC susceptibility testing or quality control procedures.

**PROVISIONAL SUSCEPTIBILITY INTERPRETIVE CRITERIA**

Based on pre-clinical studies (including Monte Carlo simulations, animal efficacy models, and results of in vitro susceptibility testing from surveillance isolates), and prior to Phase 3 clinical studies, the Applicant proposed the following interpretive criteria for telavancin:

| Pathogen | Susceptible (µg/ml) |
|---|---|
| Staphylococcus species | |
| Streptococcus species | |
| Enterococcus species | |

b(4)

No provisional resistance criteria were proposed.

**APPLICANT PROPOSED SUSCEPTIBILITY TESTING INTERPRETIVE CRITERIA**

Based on data submitted with this NDA (reviewed above), the Applicant has proposed the following susceptibility breakpoints (Table 4):

Table 4: Susceptibility Breakpoints proposed by the Applicant

b(4)

Source: 5.3.5.4.1.11 Table 1, this submission

From the clinical microbiology perspective, the data provided by the Applicant do not provide sufficient clinical experience to support the Applicant's proposed susceptibility breakpoints. Based on telavancin in vitro susceptibility data, pharmacokinetic/pharmacodynamic characterization (including Monte Carlo simulation), and clinical success rates, the Agency proposes the following interpretive criteria:

Table 5: Susceptibility Breakpoints proposed by the Agency

| **Pathogen** | **Susceptible** [a] |
|---|---|
| *Staphylococcus aureus* (including methicillin-resistant isolates) | ≤ 1 µg/ml |
| *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus*, *Streptococcus constellatus* *Streptococcus intermedius* | ≤ 0.012 µg/ml |
| vancomycin-susceptible *Enterococcus faecalis* | 1µg/ml |

[a] The current absence of data on resistant isolates precludes defining any category other than "susceptible." If an isolate yields an MIC result other than susceptible, it should be retested, being sure that the test is performed correctly. If the results are other than susceptible on re-test, the isolate should be submitted to a reference laboratory for testing.

# 8 Page(s) Withheld

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__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Microbiology-* 2

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Kerry Snow, MS
Microbiologist, HFD-520
CDER-OND-DAIOP
15 August 2007

Fred Marsik, Ph.D.
HFD-520/MicroTL
16 Aug 07 FIN FJM

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/s/

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Kerry Snow
9/21/2007 03:43:20 PM
MICROBIOLOGIST

Frederic Marsik
9/26/2007 09:12:56 AM
MICROBIOLOGIST

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** 19 August 2009

**TO:** Chris Davi
Senior Regulatory Health Project Manager
OND/OAP/DAIOP

**FROM:** John W. Metcalfe, Ph.D.
Review Microbiologist
CDER/OPS/New Drug Microbiology Staff

**THROUGH:** James McVey
Team Leader
CDER/OPS/New Drug Microbiology Staff

**cc:** DARRTS

**SUBJECT:** NDA: 22-110/N-000 LO
Applicant: Theravance, Inc.
Drug Product: Televancin for Injection
Submission Date: 28 July 2009

Reference is made to this reviewer's 14 January 2009 Microbiology Review of NDA 22-110/N-000 BL (review conclusion: "approvable"). The subject of the 14 January 2009 review was the evaluation of data provided by the applicant in support of the label's post constitution holding conditions and times. The summary comment of the review included the following:

> Based on data presented in the subject submission, this reviewer recommends post constitution holding times of 4 hours at room temperature and 72 hours at refrigerated temperature.

The applicant modified the Dosage and Administration section of the label to be consistent with the comment summarized above (22-110/N-000 LO; 28 July 2009 submission).

**Satisfactory**

**Reviewer's Conclusion**
NDA 22-110/N-000 is recommended for approval on the basis of product quality microbiology.

**END**

| Linked Applications | Submission Type/Number | Sponsor Name | Drug Name / Subject |
|---|---|---|---|
| NDA 22110 | ORIG 1 | | TELAVANCIN |

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/s/

JOHN W METCALFE
08/19/2009

JAMES L MCVEY
08/19/2009
I concur.

# Product Quality Microbiology Review

**18 June 2007**

**NDA:** 22-110

**Drug Product Name**
**Proprietary:** ₹ ↄ (Proposed Name) b(4)
**Non-proprietary:** Telavancin
**Drug Product Priority Classification:** S

**Review Number:** 1.

**Dates of Submission(s) Covered by this Review**

| Letter | Stamp | Consult Sent | Assigned to Reviewer |
|---|---|---|---|
| 06 December 2006 | 07 December 2006 | 08 December 2006 | 08 December 2006 |
| 27 February 2007 | 28 February 2007 | N/A | N/A |
| 11 June 2007 | 13 June 2007 | N/A | N/A |

**Applicant/Sponsor**
**Name:** Theravance, Inc.
**Address:** 901 Gateway Boulevard
South San Francisco, CA 94080
**Representative:** Rebecca Coleman
**Telephone:** 650-808-6076

**Name of Reviewer:** John W. Metcalfe, Ph.D.

**Conclusion:** Recommended for Approval.

# Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** Original NDA

2. **SUBMISSION PROVIDES FOR:** A new drug.

3. **MANUFACTURING SITES:**

- Drug Product Manufacturing, release testing, packaging & labeling:
  Boehringer Ingelheim
  Ben Venue Laboratories, Inc. (BVL)
  300 North Field Rd. P.O. Box 46568
  Bedford, OH 44146

- 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:** Aseptic Processing.

6. **PHARMACOLOGICAL CATEGORY:** Antibiotic.

B. **SUPPORTING/RELATED DOCUMENTS:** Microbiology review (dated 20 April 2007) of Ben Venue Type V DMF ~~ b(4)

C. **REMARKS:**
The subject submission is electronic and is provided in the Common Technical Document format.

An initial quality assessment was performed by the pharmaceutical assessment lead (PAL). The assessment did not identify any areas of concern regarding the microbiological quality of the drug product.

A request for information regarding sterility assurance information was forwarded to the applicant on 11 February 2007. The applicant provided a response to this request on 27 February 2007. The applicant response to this request is copied below. Note that questions directed from this reviewer to the applicant are in *italic print*.

Response to Request for Information Regarding DMF b(4)
27 February 2007

The following information is provided regarding the aseptic process manufacture of telavancin for injection at the contract manufacturer, Ben Venue Laboratories (BVL). The page numbers refer to the BVL DMF of April 2006. b(4)

*1. Provide the page numbers in DMF that contain the sterilization validation of the subject drug product with the In lieu of this information, provide the validation report.*

validation is ongoing. compatibility studies are complete and a report is in preparation, and microbial retention studies are in progress. The final reports can be provided as soon as they are available. b(4)

*2. Provide the filling suite number to be used in the aseptic manufacture of the subject drug product and the page numbers in DMF that contain the environmental monitoring data for this suite.* b(4)

The filling suite numbers used in the manufacture of telavancin for injection are Suite 4147 or 4165. Pages 45 to 54 contain the description of environmental monitoring operations, responses to viable monitoring results, and response levels and actions. The executed batch records provided as an attachment to NDA 22-110 contain environmental monitoring data.

*3. Provide the filling line number to be used in the manufacture of the subject drug product and the page numbers in DMF that contain media fill data for this filling line.* b(4)

The filling line number used in the manufacture of telavancin for injection are lines 7 and 8 (Suite 4147 or 4165). A written explanation of the media fill philosophy is provided on pages 40 to 45 of the narrative section. The actual media fill summaries for Suite 4147 and 4165 (lines 7 and 8) are on pages 699 to 724.

*4. Provide the lyophilizer number to be used in the manufacture of the subject drug product and the page numbers in DMF that contain sterilization validation data for this lyophilizer.* b(4)

The lyophilizer numbers used in the manufacture of telavancin for injection are 401, 402, 403, 404, 405, and 406. A written summary of the sterilization of units (401, 402, 403, 404, 405, and 406) is on pages 463 to 466. The initial validation summaries are on pages 482 to 487 and the routine performance qualification data is on page 594 to 632. b(4)

An additional request for information regarding product quality microbiology questions was provided to the applicant on 25 April 2007. The following questions were submitted with this information request:

- Has the sterile i/ 0 validation study been completed? If so, provide the report demonstrating the ability of the sterilizing ~ to retain a microbial challenge from the subject drug solution.
- What is the action level for the ~ ~test?

b(4)

An amendment to the subject submission containing a response to these questions was provided by the applicant on 11 June 2007. The applicant responses are summarized in appropriate sections of this review.

**File Name:** N022110R1.doc

# Executive Summary

I. **Recommendations**

A. **Recommendation on Approvability** – NDA 22-110 is recommended for approval on the basis of issues pertaining to product quality microbiology.

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** - The bulk drug solution is

b(4)

B. **Brief Description of Microbiology Deficiencies** – There are no microbiology deficiencies identified.

C. **Assessment of Risk Due to Microbiology Deficiencies** - Not applicable.

III. **Administrative**

A. **Reviewer's Signature** _____

B. **Endorsement Block**
Stephen Langille, Ph.D.

C. **CC Block**
N/A

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/s/
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John Metcalfe
6/22/2007 01:52:19 PM
MICROBIOLOGIST

Stephen Langille
6/22/2007 02:18:09 PM
MICROBIOLOGIST