

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022407Orig1s000**

**OTHER REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**PATIENT LABELING REVIEW**

Date: May 30, 2013

To: John Farley, MD, MPH  
Director  
**Division of Anti-Infective Products (DAIP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Melissa Hulett, MSBA, BSN, RN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Shawna Hutchins, MPH, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: DMPP Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): VIBATIV (telavancin)

Dosage Form and Route: For Intravenous Injection

Application Type/Number: NDA 22-407

Applicant: Theravance Inc.

## **1 INTRODUCTION**

On March 13, 2013, Theravance, Inc., re-submitted for the Agency's review a New Drug Application (NDA-22407) for VIBATIV (telavancin) for intravenous injection, indicated for the treatment of adults with complicated skin and skin structure infections. The purpose of the submission was to provide revised labeling to include a new indication for use of VIBATIV (telavancin) for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia. This NDA was originally submitted on January 23, 2009, received a Complete Response (CR) Letter on November 23, 2009, which cited safety and efficacy deficiencies, was re-submitted on July 12, 2012, and received a second CR letter on February 22, 2013, which cited clinical and statistical deficiencies. VIBATIV (telavancin) is also approved under NDA 22110.

On May 28, 2013, the Division of Anti-Infective Products (DAIP) requested that the Division of Medical Policy Programs (DMPP) provide a review of the Applicant's proposed Medication Guide (MG) for VIBATIV (telavancin) for intravenous injection. This review is written in response to the request by DAIP for DMPP to provide a review the Applicant's proposed MG for VIBATIV (telavancin) for intravenous injection.

The Risk Evaluation and Mitigation Strategies (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DAIP under separate cover.

## **2 MATERIAL REVIEWED**

- Draft VIBATIV (telavancin) MG submitted on March 13, 2013 and received by DMPP on May 28, 2013.
- Draft VIBATIV (telavancin) Prescribing Information (PI) received on March 13, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on May 28, 2013.
- VIBATIV (telavancin) DMPP MG review provided to DAIP on January 18, 2013.

## **3 REVIEW METHODS**

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

## **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

## 5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/  
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SHAWNA L HUTCHINS  
05/30/2013

MELISSA I HULETT  
05/30/2013

LASHAWN M GRIFFITHS  
05/30/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**PATIENT LABELING REVIEW**

Date: January 18, 2013

To: John Farley, MD, MPH  
Director  
**Division of Anti-Infective Products (DAIP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Melissa Hulett, MSBA, BSN, RN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Shawna Hutchins, MPH, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: DMPP Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): VIBATIV (telavancin)

Dosage Form and Route: For Intravenous Injection

Application Type/Number: NDA 22-110

Supplement Number: (b) (4)

Applicant: Theravance Inc.

## 1 INTRODUCTION

(b) (4)

VIBATIV (telavancin) for intravenous injection was originally approved on September 11, 2009.

(b) (4) the Division of Anti-Infective Products (DAIP) requested that the Division of Medical Policy Programs (DMPP) provide a review of the Applicant's proposed Medication Guide (MG) for VIBATIV (telavancin) for intravenous injection. This review is written in response to the request by DAIP for DMPP to provide a review the Applicant's proposed MG for VIBATIV (telavancin) for intravenous injection.

The Risk Evaluation and Mitigation Strategies (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DAIP under separate cover.

## 2 MATERIAL REVIEWED

- Draft VIBATIV (telavancin) MG (b) (4) received by DMPP (b) (4).
- Draft VIBATIV (telavancin) Prescribing Information (PI) (b) (4) revised by the Review Division throughout the review cycle, and received by DMPP (b) (4).

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our focused review of the MG, the target reading level is at an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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SHAWNA L HUTCHINS  
01/18/2013

MELISSA I HULETT  
01/18/2013

LASHAWN M GRIFFITHS  
01/18/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**PATIENT LABELING REVIEW**

Date: January 09, 2013

To: John Farley, MD, MPH  
Director  
**Division of Anti-Infective Products (DAIP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Melissa Hulett, MSBA, BSN, RN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Shawna Hutchins, MPH, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: DMPP Focused Review of Patient Labeling: Medication  
Guide (MG)

Drug Name (established name): VIBATIV (telavancin)

Dosage Form and Route: For Intravenous Injection

Application Type/Number: NDA 22-407

Applicant: Theravance Inc.

## 1 INTRODUCTION

On July 12, 2012, Theravance, Inc., re-submitted for the Agency's review a New Drug Application (NDA 22407) for VIBATIV (telavancin) for intravenous injection, indicated for the treatment of adults with complicated skin and skin structure infections, and hospital-acquired and ventilator-associated bacterial pneumonia. NDA 22407 was originally submitted on January 23, 2009, but received a Complete Response (CR) Letter issued by the Agency on December 21, 2010, citing clinical, statistical, and safety issues. VIBATIV (telavancin) for intravenous injection was originally approved on September 09, 2009, under a separate NDA (NDA 22110).

On January 08, 2013, the Division of Anti-Infective Products (DAIP) requested that the Division of Medical Policy Programs (DMPP) provide a focused review of the Applicant's proposed Medication Guide (MG) for VIBATIV (telavancin) for intravenous injection. This review is written in response to the request by DAIP for DMPP to provide a focused review of the Applicant's proposed MG for VIBATIV (telavancin) for intravenous injection.

The Risk Evaluation and Mitigation Strategies (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DAIP under separate cover.

## 2 MATERIAL REVIEWED

- Draft VIBATIV (telavancin) MG received on January 04, 2013 and received by DMPP on January 08, 2013.
- Draft VIBATIV (telavancin) Prescribing Information (PI) received on July 12, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on January 08, 2013.
- Approved VIBATIV (telavancin) comparator labeling dated September 09, 2009.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our focused review of the MG, the target reading level is at an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our focused review of the MG we have:

- simplified wording and clarified concepts where possible

- ensured that the MG is consistent with the Prescribing Information (PI)
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our focused review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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SHAWNA L HUTCHINS  
01/09/2013

MELISSA I HULETT  
01/09/2013

LASHAWN M GRIFFITHS  
01/09/2013

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
Division of Consumer Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

**Memorandum**

**Date:** January 9, 2013  
**To:** J. Christopher Davi, MS, Regulatory Project Manager  
Division of Anti-Infective Products  
**From:** Adora Ndu, Pharm.D., Regulatory Review Officer,  
Division of Consumer Drug Promotion (DCDP)  
**Subject:** NDA 022407  
DCDP comments for Vibativ (telavancin) for Injection  
Medication Guide

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On January 4, 2013, DCDP received a consult request from DAIP to review the proposed Medication Guide for Vibativ (telavancin) for Injection.

DCDP has reviewed the proposed labeling using the following versions of the proposed labels received from DAIP on January 4, and January 7, 2013 respectively:

- medguide.doc
- VibativHAPLabel04Jan13trkd.doc

After review of the proposed labeling, DCDP offers the following comments.

If you have any questions regarding the patient labeling, please contact Adora Ndu at 301-796-5114 or [adora.ndu@fda.hhs.gov](mailto:adora.ndu@fda.hhs.gov).

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ADORA NDU  
01/09/2013

Memo to the Division File

NDA 22-407, Vibativ (televancin)

January 3, 2013

From: Wendelyn Schmidt, Ph.D.; Pharmacology/Toxicology Supervisor, DAIP

Background:

The sponsor has submitted new labeling for the nosocomial pneumonia application. No new pharmacology/toxicology data was provided. Similarly, no new pharmacology/toxicology information was included in the package insert label.

Recommendation: Pharmacology/toxicology has no changes to the label, objections to approval of the NDA, or issues to discuss with the sponsor.

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/s/  
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WENDELYN J SCHMIDT  
01/03/2013

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
Division of Professional Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** December 28, 2012

**To:** J. Christopher Davi, MS, Regulatory Project Manager  
Division of Anti-Infective Products

Eileen Navarro-Almario, MD, Lead Medical Officer  
Division of Anti-Infective Products

**From:** Christine Corser, Pharm.D., Regulatory Review Officer  
Division of Professional Drug Promotion

**Subject:** NDA #22407  
Vibativ (telavancin) for injection, for intravenous use

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As requested in your consult dated November 30, 2012, OPDP has reviewed the draft labeling for Vibativ® (telavancin) for injection, for intravenous use.

The Division of Professional Drug Promotion (DPDP) has reviewed the proposed PI. Our comments are based on the substantially complete version of the labeling titled, "VibativHAPLabel26Dec12clean.doc" which was sent via email from Chris Davi on December 26, 2012.

DPDP's comments are provided in the attached, clean version of the labeling.

If you have any questions about our comments, please contact Christine Corser at 6-2653 or at [Christine.Corser@fda.hhs.gov](mailto:Christine.Corser@fda.hhs.gov).

Thank you for the opportunity to provide comments on this PI.

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/s/  
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CHRISTINE G CORSER  
12/28/2012

**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY**

DATE: 08-24-2009

TO: J. Christopher Davi, Regulatory Project Manager  
Alfred Sorbello, M.D., Medical Officer  
Division of Anti-Infective and Ophthalmology Products

FROM: Jean Mulinde, M.D.  
Good Clinical Practice Branch 2  
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch 2  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-407

APPLICANT: Theravance, Inc.

DRUG: Vibativ™ (telavancin) for injection

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Treatment of Hospital Acquired Pneumonia

CONSULTATION REQUEST DATE: 04/09/2009

DIVISION ACTION GOAL DATE: 11/26/2009

PDUFA DATE: 11/26/2009

**I. BACKGROUND:**

Vibativ™ (telavancin) is a lipoglycopeptide antibiotic for intravenous administration. The mechanism of action of telavancin is via inhibition of bacterial cell wall synthesis and increased bacterial cell membrane permeability. Based on in vitro testing telavancin is predicted to be efficacious for treatment of infections due to gram positive organisms, including common respiratory pathogens that may cause hospital acquired pneumonia (methicillin susceptible and resistant *Staphylococcus aureus*, and *Streptococcus pneumoniae*).

To support approval, the Applicant has provided data from two pivotal clinical trials (Protocol 0015 and Protocol 0019), which they believe provide sufficient evidence for the safety and efficacy of once daily dosing of telavancin 10 mg/kg administered over 60 minutes for 7 to (b)  
(4) days for the treatment of hospital acquired pneumonia (HAP).

The protocols inspected include:

1. PROTOCOL NUMBER: 0015 “A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, MULTINATIONAL TRIAL OF INTRAVENOUS TELAVANCIN VERSUS VANCOMYCIN FOR TREATMENT OF HOSPITAL-ACQUIRED PNEUMONIA WITH A FOCUS ON PATIENTS WITH INFECTIONS DUE TO METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS”

This study was a multicenter, double-blind, parallel-group, randomized trial comparing telavancin to vancomycin in patients with Gram-positive HAP that was conducted at 201 centers in 25 countries [United States, Canada, South America, Europe (east and west), Asia, Australia, and South Africa]. Patients were enrolled in the study from February 8, 2005 through July 11, 2007 (Date of final study report: December 23, 2008). Subjects were randomly assigned in a 1:1 ratio to receive either telavancin 10 mg/kg once a day IV for 7-21 days or vancomycin 1 g q 12 hr IV for 7-21 days (the investigator was to determine the total duration of study therapy, as clinically indicated). Dummy infusions of Dextrose 5% were used to maintain the blind between the two study groups. At enrollment, subjects were evaluated for etiologic pathogens (via serology, respiratory and blood cultures, and antigen identification); signs and symptoms of HAP; severity of disease; oxygenation; and acute pulmonary infiltrates via chest x-ray or chest CT.

The primary efficacy endpoint for this study was the clinical response at the Test-of-Cure evaluation (assessments of “failure” at End-of-Therapy were to be carried forward to Test-of-Cure).

**Of note, subsequent to an extensive review of the literature by the review division and discussion of the matter at a recent advisory committee, the review division has determined that it is not possible to support a determination of an appropriate non-inferiority margin for this clinical endpoint (clinical response). Instead the review division has stated that they will use all cause mortality as the primary efficacy endpoint in assessing both this study and Study 0019.**

Secondary/tertiary efficacy endpoints of particular significance included: all-cause

mortality; mortality attributable to primary infection; clinical response at end of therapy; Clinical Pulmonary Infection Score; by-pathogen microbiologic response at the Follow-up visit, determined from cultures of respiratory specimens (for each Gram-positive baseline pathogen, response was categorized as “eradicated” or “persisted.” If culture results were not available, then eradication or persistence was to be presumed according to a clinical response of cure or failure, respectively); by-patient microbiologic response at the Follow-up visit, categorized as “success” (all Gram-positive baseline pathogens eradicated, no superinfection, and no new infection; colonization may be present) or “failure” (at least one Gram-positive baseline pathogen persisted, or superinfection, or new infection)

Safety endpoints included adverse events, ECGs (in particular QT and QTc assessments), and laboratory results.

PROTOCOL NUMBER: 0019 “A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, MULTINATIONAL TRIAL OF INTRAVENOUS TELAVANCIN VERSUS VANCOMYCIN FOR TREATMENT OF HOSPITAL-ACQUIRED PNEUMONIA WITH A FOCUS ON PATIENTS WITH INFECTIONS DUE TO METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS”

This study was a multicenter, double-blind, parallel-group, randomized trial comparing telavancin to vancomycin in patients with Gram-positive HAP that was conducted at 250 centers in 33 countries [United States, Canada, Mexico, South America, Europe (east and west), Russia, Asia, Australia, Philippines, and South Africa]. Patients were enrolled in the study from January 23, 2005 through May 2, 2007 (Date of final study report: December 23, 2008). The design of Study 0019 (including protocol amendments), as well as monitoring and data management plans, were identical to those outlined above for Study 0015.

Six clinical investigators, each of whom contributed large numbers of subjects to the study that they participated in, were chosen for FDA PDUFA inspections. One domestic site was selected for inspection, Dr Patrick Lee. Dr. Lee’s site was the largest domestic enroller in Study #0015 and unusually low subject evaluability rates were also observed at this site. Inspections of foreign investigators are considered essential as data from pivotal studies was largely generated by international sites. The international sites requested for inspection are among those centers with the largest number of enrolled patients in the pivotal studies. In addition, these sites were selected for the following reasons:

- Visnja Skerk (Croatia) – This site had unusually high subject evaluability and response rates for a HAP study and an unusually low number of protocol deviations reported in comparison with other sites enrolling in the study.
- Galia Rahav (Israel) – fewer than 50% of enrolled subjects were considered evaluable, but these were all considered treatment successes.
- Alejandro Ortiz and Martin Magana (Mexico) – With the exception of eligibility protocol deviations, no protocol deviations were reported for any subject, enrolled at any site in Mexico. This pattern is distinct and differs from findings reported in all other geographic regions and raises concerns with the adequacy of monitoring of sites

in Mexico and validity of data from these sites.

- Marcelo Rocha (Brazil) – This site had unusually low subject evaluability (30%).

In addition, a complaint was made to the FDA alleging that the sponsor manipulated data submitted in the NDA; therefore, inspections of the sponsor/applicant and the contract research organization (CRO) responsible for data management for these studies, were conducted to evaluate allegations made in the complaint. This was a re-inspection of a sponsor who was previously investigated on May 31, 2007 and received a final classification of NAI.

## II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol # Site # # of Subjects	Inspection Date	Final Classification
Patrick Lee, MD Baystate Medical Center 759 Chestnut St Springfield, MA 01199	Study 0015 Site #38024 45 subjects	05/27/2009- 06/12/2009	VAI
Visnja Skerk, MD, PhD University Clinic for Infectious Diseases "Dr. Fan Mihaljevic" Mirogojska 810000 Zagreb, Croatia	Study 0015 Site #09004 36 subjects	06/29/2009- 07/03/2009	Pending (Preliminary classification NAI)
Galia Rahav, MD Sheba Medical Center Infectious Disease Unit Tel-Hashomer, 52621 Isreal	Study 0019 Site #18004 54 subjects	07/05/2009- 07/09/2009	Pending (Preliminary classification NAI)
Martin Magana, MD Hospital Ignacio Morones Prieto Avenida Venustiano Carranza No. 2395 Zona Universitaria, 78240, San Luis Potosi San Luis Potosi, Mexico	Study 0019 Site #40000 18 subjects	07/13/2009- 07/17/2009	Pending (Preliminary classification NAI)
Alejandro Ortiz, MD Hospital Civil "Fray Antonio Alcalde" Calle Hospital No. 278 S.G. 44100, Guadalajara Jalisco, Mexico	Study 0019 Site #40001 24 subjects	07/06/2009- 07/10/2009	Pending (Preliminary classification VAI)
Marcelo Rocha Rua Prof. Annes Dias 285 Pavilhã Pereira Filho – UTI 2nd Andar Irmandade da Santa Casa de Misericórdia de Porto Alegre Porto Alegre RS – 90020-090 Brazil	Study 0019 Site #05003 24 subjects	07/13/2009- 07/17/2009	Pending (Preliminary classification VAI)
(b) (4)	NDA 22-407 Protocol 0015 Protocol 0019	(b) (4)	NAI
Theravance, Inc. 901 Gateway Boulevard South San Francisco, CA 94080	NDA 22-407 Protocol 0015 Protocol 0019	06/10/2009- 06/25/2009	Pending (Preliminary classification NAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary, letter has not yet issued to the CI.

**1. Patrick Lee, MD**

Baystate Medical Center  
759 Chestnut St  
Springfield, MA 01199  
Protocol #0015, Site #38024

**a. What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.811 between 05/27/2009-06/12/2009. A total of 111 subjects were screened, 45 subjects were enrolled and 34 completed the study. Records for all 45 enrolled subjects were reviewed to verify subject consent prior to study enrollment, eligibility criteria, adverse event reporting, and verification of reporting of primary efficacy endpoint reporting. Records for 18 subjects were also reviewed to verify adherence with dosing schedules, concomitant medication use, study visits, randomization, chest x-rays, gram stain and culture results, and ECG findings. In addition, protocol deviation logs, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

**b. General observations/commentary:**

The inspection of Dr. Lee's site revealed regulatory violations. A Form FDA 483, Inspectional Observations, was issued to this investigator for:

- i. Failure to ensure that informed consent was properly documented in the that the written informed consent used in the study was not dated by the subject or the subject's legally authorized representative at the time of the consent [21 CFR 50.27(a)]. Specifically, for three subjects, study staff dated the informed consent documents rather than ensuring that the subjects or their legally authorized representatives dated them.
- ii. Failure to ensure that the investigation was conducted according to the signed investigator statement and the investigational plan [21 CFR 312.60]. Specifically for:
  - a) Subjects having received concomitant prohibited non-study systemic antibacterials:
    - i) Subject #4450 received 5 doses of cefazolin between 10/11/2006 and 10/13/2006 as prophylaxis for an orthopedic procedure.
    - ii) Subject #4562 received erythromycin 250 mg po every 8 hours between 12/20/2006 and 12/26/2006, which was administered to improve gastric motility.

- b) Enrollment of subjects that did not meet eligibility criteria:
  - i) Subject #4781 had only gram negative diplococci and gram negative rods on baseline sputum gram stain.
  - ii) Subject #4206 did not have history of pneumonia acquired after 48 hours hospitalization or acquired within 7 days after being discharged from a hospitalization of  $\geq 3$  days duration.

Of note, when the FDA investigators reviewed line listings for protocol deviations at this site they noted that the protocol deviation log at the site included additional deviations that were not reported in the NDA line listings. Deviations involving seven subjects were not included in the NDA and encompassed issues ranging from failure to collect laboratory specimens to use of prohibited medications (See Appendix 1 – Site #38024 Protocol Deviation Log source document). Based on queries to the Applicant it appears that non-eligibility deviations were hand tabulated from these source documents for submission in the NDA, rather than having been captured in a dataset. In this case, it appears that one page of the log was not included in tabulations.

In addition, the FDA investigators noted a number of examples of cases in which the investigator had changed their assessment of clinical outcome of pneumonia (protocol primary endpoint) at either the end of therapy and/or test of cure visit, based on data query forms (DCF) from the CRO/sponsor, to an outcome assessment that seemed inconsistent with manner that the protocol stated the assessments were to be made (examples of these changes are summarized in Appendix 2). This issue was discussed with the review division medical officer. Given that the review division will be using all cause mortality as the primary efficacy endpoint for this study, the changes made to clinical outcome assessments for these subjects will not impact the review division's primary analysis.

c. **Assessment of data integrity:**

While multiple regulatory violations occurred at this site it does not appear that subject safety was compromised. The review division should determine whether subjects with protocol deviations that were noted in Section 1.b.ii. above, were appropriately categorized in the Applicant's analyses (i.e., assigned into correct study population and treatment outcome groups). Given that the review division will be using all cause mortality as the primary efficacy endpoint for this study, the import of the observations pertaining to missed inclusion of one page of protocol deviations and changes prompted by the Sponsor to the CIs assessment of clinical outcome at EOT and/or TOC is minimized. With the exception of issues summarized above, the overall efficacy and safety data from Dr Lee's site appear otherwise reliable.

**2. Visnja Skerk, MD, PhD**

University Clinic for Infectious Diseases "Dr. Fan Mihaljevic"  
Mirogojska 810000  
Zagreb, Croatia  
Protocol #0015, Site #09004

a. **What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.811 between 06/29/2009-07/03/2009. A total of 41 subjects were screened, 36 subjects were enrolled and 36 completed the study. A 100% review of informed consent forms was conducted. Records for 12 enrolled subjects and one screen failure were reviewed during the inspection. Records of enrolled subjects were reviewed to verify that eligibility criteria were met, that primary and secondary endpoint outcomes were accurately reported, that adverse events were accurately reported, and that study drug dosing was correct and appropriately reported. In addition, drug accountability records, IEC approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. **General observations/commentary:**

The inspection of Dr. Skerk's site did not reveal regulatory violations. A Form FDA 483, Inspectional Observations, was not issued.

c. **Assessment of data integrity:**

Based on preliminary communications with the FDA field investigator, data derived from Dr. Skerk's site are considered acceptable.

**Note: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

3. **Galia Rahav, MD**

Sheba Medical Center  
Infectious Disease Unit  
Tel-Hashomer, 52621  
Israel  
Protocol #0019, Site #18004

a. **What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.811 between 07/05/2009-07/09/2009. A total of 54 subjects were screened, 54 subjects were enrolled and 53 completed the study. A 100% review of informed consent forms was conducted. Records for 10 enrolled subjects were reviewed in depth to verify that eligibility criteria were met, that primary and secondary endpoint outcomes were accurately reported, that adverse events were accurately reported, and that study drug dosing was correct and appropriately reported. In addition, drug accountability records, IEC approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. **General observations/commentary:**

The inspection of Dr. Rahav's site did not reveal regulatory violations. A Form FDA 483, Inspectional Observations, was not issued.

c. **Assessment of data integrity:**

Based on preliminary communications with the FDA field investigator, data derived from Dr. Rahav's site are considered acceptable.

**Note: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

4. **Martin Magana, MD**

Hospital Ignacio Morones Prieto

Avenida Venustiano Carranza No. 2395 Zona Universitaria, 78240, San Luis Potosi  
San Luis Potosi, Mexico

Protocol #0019, Site #40000

a. **What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.811 between 07/13/2009-07/17/2009. A total of 245 subjects were screened, 18 subjects were enrolled and 13 completed the study. A 100% review of informed consent forms was conducted. Records for 9 enrolled subjects were reviewed in depth to verify that eligibility criteria were met, that primary and secondary endpoint outcomes were accurately reported, and that adverse events were accurately reported. In addition, drug accountability records, IEC approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. **General observations/commentary:**

The inspection of Dr. Magana's site did not reveal regulatory violations. A Form FDA 483, Inspectional Observations, was not issued.

c. **Assessment of data integrity:**

Based on preliminary communications with the FDA field investigator, data derived from Dr. Magana's site are considered acceptable.

**Note: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

5. **Alejandro Ortiz, MD**

Hospital Civil "Fray Antonio Alcalde"

Calle Hospital No. 278 S.G.

44100, Guadalajara  
Jalisco, Mexico  
Protocol #0019, Site #40001

a. **What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.811 between 07/06/2009-07/10/2009. A total of 123 subjects were screened, 24 subjects were enrolled and 18 completed the study. A 100% review of informed consent forms was conducted. Records for 11 enrolled subjects were reviewed in depth to verify that eligibility criteria were met, that primary and secondary endpoint outcomes were accurately reported, and that adverse events were accurately reported. In addition, drug accountability records, IEC approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. **General observations/commentary:**

The inspection of Dr. Ortiz's site revealed regulatory violations. A Form FDA 483, Inspectional Observations, was issued to this investigator for:

- i. Failure to report to the sponsor adverse effects that may reasonably be regarded as caused by, or probably caused by, an investigational drug [21 CFR 312.64(b)]. Specifically, for failing to report:
  - a) "Hypothermic hyperventilation," which was documented in source records, for Subject #6090
  - b) Severe bronchospasm requiring urgent treatment for Subject #6094
- ii. Failure to conduct the study according to the signed investigator statement and the investigational plan [21 CFR 312.60]. Specifically, for:
  - a) Failure to obtain complete safety laboratories and/or ECGs for eight of eleven subjects for whom records were reviewed during the inspection.
  - b) Failure to document the significance of out of range laboratory values for nine of eleven subjects for whom records were reviewed during the inspection.
  - c) Enrolling one subject who did not meet study eligibility criteria (Subject #6095 was not hospitalized for 48 hours prior to being diagnosed with HAP).

c. **Assessment of data integrity:**

Reporting of safety data from this site was incomplete (several AEs not reported to sponsor and missing protocol required safety laboratories and ECGs); however, the efficacy and reported safety data appears to be reliable.

**6. Marcelo Rocha, MD**

Rua Prof. Annes Dias 285  
Pavilhã Pereira Filho – UTI 2nd Andar  
Irmandade da Santa Casa de Misericórdia de Porto Alegre  
Porto Alegre RS – 90020-090  
Brazil  
Protocol #0019, Site #05003

**a. What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.811 between 07/13/2009 and 07/17/2009. A total of 134 subjects were screened, 24 subjects were enrolled and 18 completed the study. A 100% review of informed consent forms was conducted. Records for 24 enrolled subjects were reviewed that primary and select secondary endpoint outcomes were accurately reported, and that adverse events were accurately reported. In addition, drug accountability records, IEC approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

**b. General observations/commentary:**

The inspection of Dr. Rocha's site did not reveal regulatory violations. A Form FDA 483, Inspectional Observations, was not issued; however, the field investigator did note in her preliminary summary to DSI that there were some irregularities in drug accountability records. For example, that documentation of temperature monitoring for the study drug stored at the site appeared to have been inaccurately documented in that there were measurements stated for days in the calendar year that do not exist (e.g. February 31<sup>st</sup>). Exhibits related to this observation will be assessed when the EIR is received by DSI, and if supported, a post-inspectional correspondence (VAI letter) will be issued to this investigator noting their failure to conduct the study according to the signed investigator statement and the investigational plan [21 CFR 312.60].

**c. Assessment of data integrity:**

Based on preliminary communications with the FDA field investigator, with the exception of some issues related to drug storage temperatures, data derived from Dr. Rocha's site are considered acceptable.

While DSI can not confirm study drug was stored at the site according to protocol requirements (2 °C to 8 °C), based on discussions with the FDA chemist reviewing this Application, it appears that additional stability information (accelerated storage condition testing) available for the product suggests that it is stable for at least 24 months at 25°C. Despite irregularities in documentation of storage conditions at the site, it is likely that it was adequately maintained within the parameters defined by the accelerated storage condition testing and that it maintained stability throughout the period of use at site.

**Note: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

7. [REDACTED] (b) (4)

**a. What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.810 between [REDACTED] (b) (4). The inspection was directed to assess the adequacy of CRO functions and data management for Theravance Study #0015 and Study #0019. The inspection focused on the firm's electronic raw data files for Study #0015 and Study #0019, reporting of protocol deviations related to adverse events and protocol requirements, study specific SOPs, contracts between the Sponsor and CRO, the Clinical Monitoring Plan, the Global Safety Plan, the Unblinded Clinical Monitoring Plan, Clinical Research Associates' training records and CVs, and the procedures related to monitoring of Clinical Investigators. There were no limitations to the inspection; however, complete records were not available for review at the CRO during the inspection as per contract most all of the essential trial records for these studies had been forwarded to Theravance on 06/11/2008.

**b. General observations/commentary:**

The inspection of [REDACTED] (b) (4) did not reveal regulatory violations. A Form FDA 483, Inspectional Observations, was not issued. A DVD containing Data Transfer Versions, the Protocol 0015 Raw DB (database), the Protocol 0019 Raw DB, and Documentation of Databases Changes was provided, as requested, to the FDA investigator during the inspection. The data contained on this DVD was consistent with data submitted in the NDA. In addition, the CRO's documentation of data transfer dates/data files transferred to Theravance is consistent with dates of data transfer receipt/data files received that were documented by the sponsor and reviewed during the FDA inspection of the sponsor.

**c. Assessment of data integrity:**

Based on the Establishment Inspection Report (EIR) and associated exhibits provided by the FDA investigator, [REDACTED] (b) (4) adequately fulfilled monitoring and data management obligations transferred to them by the Sponsor, Theravance, in the conduct of Protocol #0015 and Protocol #0019.

**8. Theravance, Inc.**

901 Gateway Boulevard  
South San Francisco, CA 94080

a. **What was inspected:**

This inspection was conducted in accordance with Compliance Program 7348.810 between 06/10/2009-06/25/2009. The inspection was directed to:

- Assess the adequacy of sponsor/monitor functions for Study 0015 and Study 0019.
- Evaluate a complaint received by the Agency, in which the complainant asserted that the sponsor had improperly manipulated study data to achieve desired outcomes for Study 0015 and Study 0019.

The inspection focused on the selection, monitoring and data validation of clinical investigators, monitoring procedures and activities, adverse event reporting, data collection and handling, test article accountability, composition of and role of the Independent Data Monitoring Committee (IDMC) that oversaw the studies, and contract responsibilities (CRO, data collection, and laboratory support) related to these studies. Sponsor/monitor files for five CIs (Patrick Lee, Visnja Skerk, Galia Rahav, Martin Magana, and Alejandro Ortiz) were reviewed in depth during the inspection.

In addition, for each study the following items were investigated:

- The date that the Sponsor first received unblinded data from (b) (4)
- The dates and content of each dataset transfer from (b) (4)
- Reasons that the Sponsor requested (b) (4) update or revision datasets (databases unlocked/relocked).

Dr. Scott Komo, the FDA statistician that participated in this inspection as an expert consultant, also requested that a number of the dataset versions that evolved over time be submitted to the NDA for further evaluation.

There were no limitations to the inspection

b. **General observations/commentary:**

The inspection of Theravance did not reveal regulatory violations. A Form FDA 483, Inspectional Observations, was not issued.

In addition, the Applicant's documentation of dates of data transfer/data files transferred from (b) (4) is consistent with data transfer dates/data files/file content that were documented by (b) (4) and reviewed during the FDA inspection of the CRO.

c. **Assessment of data integrity:**

Based on preliminary communications with the FDA field investigator, and subsequent follow-up discussions with Dr. Scott Komo, Theravance adequately fulfilled Sponsor/monitor obligations in the conduct of Protocol #0015 and Protocol #0019.

**Note: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

#### IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, Protocol #0015 and Protocol #0019 appear to have been conducted adequately and the data in support of the NDA appear reliable.

The final classification of the CRO, (b) (4), is No Action Indicated (NAI) and the final classification of the Clinical Investigator inspection of Dr Lee is Voluntary Action Indicated (VAI). While regulatory violations occurred at Dr. Lee's site, given that the review division will be using all cause mortality as the primary efficacy endpoint for this study, the import of the observations pertaining to missed inclusion of one page of protocol deviations and changes prompted by the Sponsor to the CI's assessment of clinical outcome at EOT and/or TOC are minimized.

The preliminary classification of the Sponsor inspection of Theravance is NAI. Issues identified in the complaint received by the Agency, in which the complainant asserted that the sponsor had improperly manipulated study data to achieve desired outcomes for Study 0015 and Study 0019, have been adequately investigated and determined to be unsupported.

The preliminary classification of the Clinical Investigator inspection of Dr. Ortiz is VAI. While regulatory violations occurred at this site, and reporting of safety data from this site was incomplete (several AEs not reported to sponsor and missing protocol required safety laboratories and ECGs), the efficacy and safety data that was reported appears to be reliable.

The preliminary classification of the Clinical Investigator inspection of Dr. Rocha is also VAI based on the site's failure to adequately document drug storage temperatures; however, safety and efficacy data derived from Dr. Rocha's site are considered acceptable.

The preliminary classifications of the Clinical Investigator inspections of Dr. Skerk and Dr. Rahav are NAI. Data from these sites is considered reliable in support of the NDA.

**Note:** Upon receipt and review of the EIRs for Theravance, Dr. Ortiz, Dr. Rocha, Dr. Skerk, and Dr. Rahav, an addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final classifications or additional observations of clinical and regulatory significance are discovered after reviewing the EIRs.

*{See appended electronic signature page}*

Jean M. Mulinde, M.D.  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

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**Summary of changes to clinical outcome assessments made as a result of database change forms (DCF) at Site #38024**

<b>Subject</b>	<b>EOT Source Document</b>	<b>EOT CRF</b>	<b>EOT NDA Line Listing</b>	<b>TOC Source Document</b>	<b>TOC CRF</b>	<b>TOC NDA Line Listing</b>	<b>DCF request/rationale/CI response for change</b>
4284	Fail	Fail Δ Cure	Cure	Fail	Fail Δ Cure	Δ Indet	EOT -Vanc given for cont therapy for suspected MRSA bacteremia (no evidence of positive culture) beginning day study drug discontinued. TOC – Request make clinical judgment on pneumonia at TOC based on clinical grounds rather than other concomitant antibiotics. CI changes to Indet, but adds comment “gram positive bacteremia could have been caused by pneumonia.”
4426	Indet Δ Fail	Indet Δ Fail Δ Indet	Indet	Indet Δ Fail	Indet (out of study window)	Indet	EOT – D10 subject noted to have only gram negative on sputum culture (from D9), progression of infiltrate and study drug stopped and started on gram negative coverage alone. Baseline culture had grown nl flora only. CI checks DCF that outcome is Fail. Second DCF checked by sub-inv checked that outcome should be Indet because of relapsed pneumonia due to gram negative and no antistaph antibiotics initiated (subject started on Tobramycin).
4449	Cure Δ Indet	Indet Δ Cure	Cure	Indet	Cure Δ Indet	Cure	TOC - Request make clinical judgment on pneumonia at TOC based on clinical grounds rather than other concomitant antibiotic usage (levofloxacin had been given for UTI between EOT and TOC visits). CI changes to Cure

**Summary of changes to clinical outcome assessments made as a result of database change forms (DCF) at Site #38024**

<b>Subject</b>	<b>EOT Source Document</b>	<b>EOT CRF</b>	<b>EOT NDA Line Listing</b>	<b>TOC Source Document</b>	<b>TOC CRF</b>	<b>TOC NDA Line Listing</b>	<b>DCF request/rationale/CI response for change</b>
4521	Cure Δ Indet	Cure Δ Indet	Cure	Indet	Indet	Cure	EOT/TOC - Request make clinical judgment on pneumonia at EOT/TOC based on clinical grounds rather than other concomitant antibiotic usage (levofloxacin had been given for UTI). CI changes to Cure at EOT and TOC.
4568	Cure Δ Indet	Indet	Cure	Indet	Indet	Cure	EOT/TOC - Request make clinical judgment on pneumonia at EOT/TOC based on clinical grounds rather than other concomitant antibiotic usage (keflex had been given for “wound drainage”). CI changes to Cure at EOT and TOC.
4591	-	Indet	Cure	Indet	Indet	Cure	EOT/TOC - Request make clinical judgment on pneumonia at EOT/TOC based on clinical grounds rather than other concomitant antibiotic usage (augmentin had been given for “abdominal wound infection”). CI changes to Cure at EOT and TOC.
Δ = change made to Fail = Failure, Indet = Indeterminate							



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/s/  
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JEAN M MULINDE  
08/26/2009

TEJASHRI S PUROHIT-SHETH  
08/26/2009

## DSI CONSULT: Request for Clinical Inspections

**Date:** April 3, 2009

**To:** Constance Lewin, M.D., M.P.H, Branch Chief, GCP1  
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2  
Division of Scientific Investigations, HFD-45  
Office of Compliance/CDER

**Through:** *Janice K. Pohlman, MD, Medical Team Leader*  
*Wiley A. Chambers, MD, Acting Division Director, DAIOP*

**From:** *J. Christopher Davi, MS, Senior Regulatory Project Manager*

**Subject:** **Request for Clinical Site Inspections**

### **I. General Information**

Application#: NDA 22-407  
Applicant: Theravance, Inc.  
Drug Proprietary Name: Vibativ (telavancin hydrochloride)  
NME or Original BLA: Yes  
Review Priority: Standard

Study Population includes < 17 years of age: No  
Is this for Pediatric Exclusivity: No

Proposed New Indication(s): Nosocomial Pneumonia

PDUFA: Yes  
Action Goal Date: November 26, 2009  
Inspection Summary Goal Date: August 28, 2009

**II. Protocol/Site Identification**

*Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.*

<b>Site # (Name,Address, Phone number, email, fax#)</b>	<b>Protocol ID</b>	<b>Number of Subjects</b>	<b>Indication</b>
Patrick Lee <b>Site # 38024</b> Baystate Medical Center 759 Chestnut St Springfield, MA 01199 413-794-9227	0015	45 patients enrolled	HAP/VAP Gram positive bacteria
Visnja Skerk <b>Site # 09004</b> Dr Fran Mihaljevic University Hospital For Infectious Disease Department of Urinary Tract Infections and Fever of Unknown Origin Mirogojska 8 Zagreb, 10000 385 1 4603 222	0015	36 patients enrolled	HAP/VAP Gram positive bacteria
Galia Rahav <b>Site # 18004</b> Sheba Medical Center Infectious Disease Unit Tel-Hashomer, 52621 972 3 5303 500	0019	54 patients enrolled	HAP/VAP Gram positive bacteria
Martin Magana <b>Site # 40000</b> Hospital Ignacio Morones Prieto Avenida Venustiano Carranza No. 2395 Zona Universitaria San Luis Potosi, SL 78240 52-444-834 2778	0019	18 patients enrolled	HAP/VAP Gram positive bacteria
Alejandro Ortiz <b>Site # 40001</b> Hospital Civil de Guadalajara Fray Antonio Alcalde Coronel Calderon #777 Colonia el Retiro Gualdalajara, Jalisco 44620 52-33-361 47501	0019	24 patients enrolled	HAP/VAP Gram positive bacteria

### **Site Selection/Rationale**

Studies 0015 and 0019 are two large, multi-center, randomized, double blind, active comparator studies comparing telavancin to vancomycin for the treatment of hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP) caused by suspected or demonstrated Gram positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA).

The two studies were of identical design, but conducted independently. Approximately 750 patients were randomized and treated in each study. Two hundred and one centers participated in Study 0015 and 250 centers participated in Study 0019. Many centers enrolled fewer than 5 patients. In Study 0015, only 30% of patients were from the US, while in Study 0019, only 15% of patients were from the US.

Clinical trials for this indication have some inherent difficulties in design and interpretation. The populations being treated may be heterogeneous (i.e. young trauma patients versus elderly patients with heart problems), diagnostic criteria may be non-specific, and clinical response (cure, failure) difficult to objectively define. Patients may require concomitant antibacterial therapy with drugs that have activity against Gram negative bacteria which may overlap the Gram positive activity of the study drug.

Currently, clinical trial design for this indication is the topic of ongoing public discussion and was recently the topic of discussion at a public workshop with input from IDSA/ATS/ACCP/SCCM/FDA held in Silver Spring on March 31 and April 1 of 2009.

For Study 0015, the Lee (Site #38024) and Skerk (Site #09004) sites were the largest enrolling sites. Each site made up < 10% of the study population. Study 0015 had one investigative site (Towfigh #38020 with 13 patients) that participated in this study but was excluded from NDA 22-110 cSSSI study efficacy analysis due to data integrity issues. The sites to be inspected are as follows:

- Site #38024: there were only 3/21 telavancin-treated and 9/24 vancomycin-treated patients who were clinically evaluable. Overall results from this site did however favor the comparator.
- Site # 09004: there were 15/16 clinically evaluable patients with 14 cures for telavancin and 19/20 clinically evaluable patients with 16 cures for vancomycin. Few protocol deviations were noted for this site.

For Study 0019, with only 15% of patients from the US, three foreign sites (including two sites in Mexico) were selected for inspection. Again, given the large number of centers participating, no one center had an overwhelming effect on the results. Two sites in Mexico were chosen due to the lack of reported protocol deviations.

- Site #18004 (Rahav, Israel): the largest enroller in this study with 54 patients. Only 21 patients were clinically evaluable and all were treatment successes (12 telavancin and 9 vancomycin); overall in the all-treated population, the results favored vancomycin.
- Site #40001 (Ortiz, Mexico): enrolled 24 patients. Clinical evaluability rates were relatively low, with 6/13 telavancin-treated and 6/11 vancomycin-treated patients clinically evaluable.

- Site #40000 (Magana, Mexico): enrolled 18 patients. Five of seven patients treated with telavancin were clinically evaluable (all cures) and 6/10 vancomycin treated patients were clinically evaluable (5 cures).

NDA 22-110 had 2 cycles of inspections during its review and the company performed an extensive internal audit due to concerns about study monitoring procedures. Efficacy data for three sites was excluded from analysis due to data integrity issues (1 identified by DSI and 2 by Theravance). ECG safety data was excluded for 2 sites identified by DSI for not performing required ECG at protocol-specified times. There was also some difficulty in determination of clinical outcome (primary endpoint) based on issues of outcome definitions and design of the case report form.

Issues of concern for inspection include:

- Adherence to enrollment criteria (onset occurred after 48 hours of hospitalization or transfer to chronic care facility, adherence to inclusion criteria, chest radiograph interpretation (differences between investigator and radiologist interpretation, and following protocol if patients had received prior antimicrobials)
- Accurate accounting of concomitant medications, particularly systemic antibacterial agents
- Documentation of microbiological results
- Outcome assessment following protocol-specified definitions and changes in outcome determination after query by the CRO
- Collection of safety laboratories and ECGs at appropriate timepoints

**NDA 22-407 is in the EDR**

The date of the submission is January 23, 2009.

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): see discussion above

**International Inspections:**

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify): geographic/regional differences in diagnosis (depending on criteria used). Study 0019 had only 15% of randomized patients from the US.

**Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.**

**III. Tables of Specific Data to be Verified (if applicable)**

*If you have specific data that needs to be verified, please provide a table for data verification, if applicable.*

Should you require any additional information, please contact J. Christopher Davi, MS at 301-796-0702 or Janice Pohlman, MD at 301-796-0788 or Fred Sorbello, DO at 301-796-0816.

Concurrence: (as needed)

Janice K. Pohlman, MD Medical Team Leader

Wiley A. Chambers, MD Acting Division Director (for foreign inspection requests or requests for 5 or more sites only)

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Wiley Chambers  
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