

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022407Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 22-407

SUPPL # N/A

HFD # 520

Trade Name: VIBATIV

Generic Name: Telavancin

Applicant Name: Theravance, Inc.

Approval Date, If Known: June 21, 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

Type 9

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

e) Has pediatric exclusivity been granted for this Active Moiety?

NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

No

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Two Phase 3 clinical trials of identical design, Study 0015 and Study 0019, were submitted to support this application.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 NO

Investigation #2 NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 NO

Investigation #2 NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 0015 and Study 0019

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 60,237 YES

Investigation #2

IND # 60,237 YES

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

N/A

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

NO

=====
Name of person completing form: J. Christopher Davi, MS
Title: Senior RPM
Date: June 24, 2013

Name of Office/Division Director signing form: Katherine A. Laessig, MD
Title: Deputy Director, DAIP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

JOSEPH C DAVI
06/24/2013

KATHERINE A LAESSIG
06/25/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹		
NDA # 22-407 BLA # N/A	NDA Supplement # N/A BLA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Vibativ Established/Proper Name: Televancin hydrochloride Dosage Form: Injection		Applicant: Theravance Agent for Applicant (if applicable): N/A
RPM: J. Christopher Davi, MS, Sr. Regulatory Project Manager		Division: DAIP
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): N/A</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>September 13, 2013</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None CR Actions: November 23, 2009; December 21, 2010; and February 22, 2013

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<p>N/A</p>
<p>❖ Application Characteristics ³</p> <p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>REMS: <input checked="" type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p>N/A</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p>N/A</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<p>Yes</p>
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<p>Yes</p>
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<p><input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other CDER Office of Executive Programs</p>

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	No
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	No
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	N/A
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	N/A
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	N/A
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	No
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	Verified
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	N/A
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	N/A
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	N/A

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

N/A

N/A

N/A

N/A

N/A

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p>N/A</p>
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CONTENTS OF ACTION PACKAGE

<p>❖ Copy of this Action Package Checklist⁴</p>	<p>Included</p>
Officer/Employee List	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p>Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p>Included</p>
Action Letters	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>November 23, 2009 (Cycle 1) December 21, 2010 (Cycle 2) February 22, 2013 (Cycle 3) June 21, 2013 (Cycle 4)</p>
Labeling	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	<p>June 4, 2013</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>Included</p>
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	<p>N/A</p>

⁴ Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	X Medication Guide X Patient Package Insert X REMS
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Included: June 4, 2013
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Included: January 23, 2009
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	Included: January 4, 2013
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	Name approval cross referenced to NDA 22-110 (August 7, 2009)
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	DMPP: 5/30/13 PLT: 5/30/13 DRISK: 3/5/13 ODPD (DDMAC): 12/28/12 DCDP: 1/09/13
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	N/A
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	N/A
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	No
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>December 19, 2012</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	Included; Pediatric record ID# 1848
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	N/A (Not an original application)
❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Internal memoranda, telecons, etc.	Included
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	No meeting
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	No meeting
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	March 6, 2008
• EOP2 meeting (<i>indicate date of mtg</i>)	No meeting
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	None
❖ Advisory Committee Meeting(s)	
• Date(s) of Meeting(s)	November 29, 2012
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	Not available
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	N/A (Not an NME)
Division Director Summary Review (<i>indicate date for each review</i>)	November 23, 2009 (Cycle 1) December 21, 2010 (Cycle 2) February 22, 2013 (Cycle 3) June 21, 2013 (Cycle 4)
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	November 12, 2009 (Cycle 1) December 20, 2010 (Cycle 2) February 1, 2013 (Cycle 3) June 17, 2013 (Cycle 4)
PMR/PMC Development Templates (<i>indicate total number</i>)	None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	September 25, 2009 (Cycle 1) December 21, 2010 (Cycle 2)
• Clinical review(s) (<i>indicate date for each review</i>)	September 25, 2009 (Cycle 1) December 21, 2010 (Cycle 2) February 1, 2013 (Cycle 3) June 17, 2013 (Cycle 4)
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	N/A
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Page 27 of Cycle 1 Clinical Review (September 25, 2009) N/A
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	N/A
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	N/A
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	Submitted June 11, 2013
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	March 5, 2013 (Cycle 3)
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	June 7, 2013 (Cycle 4)

⁶ Filing reviews should be filed with the discipline reviews.

❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	August 26, 2009
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	September 30, 2009
Clinical Microbiology Review(s) (indicate date for each review)	December 23, 2012
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	None
Statistical Team Leader Review(s) (indicate date for each review)	October 2, 2009 (Cycle 1) January 18, 2013 (Cycle 3)
Statistical Review(s) (indicate date for each review)	October 2, 2009 November 6, 2012 (Supplemental Review) January 18, 2013 (Cycle 3)
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	September 25, 2009 (Cycle 1) December 3, 2010 (Cycle 2) December 20, 2012 (Cycle 3)
Clinical Pharmacology review(s) (indicate date for each review)	September 25, 2009 (Cycle 1) December 3, 2010 (Cycle 2) December 20, 2012 (Cycle 3)
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	None
• Supervisory Review(s) (indicate date for each review)	September 29, 2009 (Cross reference to NDA 22-110)
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	No carc
❖ ECAC/CAC report/memo of meeting	None
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	None
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	July 27, 2009 (Cycle 1) January 31, 2013 (Cross referenced to NDA 22-110) – Cycle 3
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See page 10 of May 31, 2013 CMC review
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	N/A
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>	Date completed: April 24, 2013 <input checked="" type="checkbox"/> Acceptable See page 13 of CMC Review
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	N/A
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	Not needed

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.



NDA 22-407

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Vice President, Regulatory Affairs and Quality
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

We acknowledge receipt on March 13, 2013, of your March 13, 2013, resubmission of your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vibativ (telavancin for injection).

We consider this a complete, class 2 response to our February 22, 2013, action letter. Therefore, the user fee goal date is September 13, 2013.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Maureen Dillon-Parker
Chief, Project Management Staff
Division of Anti-infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MAUREEN P DILLON PARKER
05/03/2013



NDA 22-407

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Vice President, Regulatory Affairs and Quality
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

We acknowledge receipt on July 12, 2012, of your July 12, 2012, resubmission of your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VIBATIV (telavancin hydrochloride) for injection.

We consider this a complete, class 2 response to our December 21, 2010, action letter. Therefore, the user fee goal date is January 12, 2013.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Maureen Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MAUREEN P DILLON PARKER
09/04/2012

From: [David, Jeannie C](#)
To: ["BColeman@theravance.com"](mailto:BColeman@theravance.com)
Cc: [Cuff, Althea](#); [Davi, Christopher](#)
Subject: RE: NDA 22407
Date: Wednesday, August 01, 2012 5:10:20 PM
Importance: High

Dear Ms. Coleman,

Per my voicemail today, please submit the establishment information provided below to NDA 22-407. For each site, we also request that you confirm that the site is ready for inspection.

Please confirm receipt of this email, and provide a timeline for your response.

I am covering for Ms. Althea Cuff while she is on leave. Please let me know if you have any questions.

Regards,

Jeannie

Jeannie David, M.S.
Regulatory Health Project Manager
Food and Drug Administration
Phone: (301) 796-4247

From: Coleman, Becky [mailto:BColeman@theravance.com]
Sent: Friday, July 27, 2012 04:59 PM
To: Cuff, Althea
Cc: Davi, Christopher
Subject: RE: NDA 22407

Ms. Cuff,

The information regarding the Stability and Sterility sites for the VIBATIV drug product remains the same also. Contact information is provided below.

Please feel free to contact me with any further questions.

Rebecca Coleman, Pharm.D.
Vice President, Regulatory Affairs and Quality
Theravance, Inc.

Phone:  (b) (6)

Microbiologic testing

 (b) (4)

(b) (4)

Stability testing

(b) (4)

From: Cuff, Althea [mailto:Althea.Cuff@fda.hhs.gov]
Sent: Friday, July 27, 2012 8:55 AM
To: Coleman, Becky
Subject: RE: NDA 22407

Ms. Coleman,

Thanks for the reply; Please also confirm the Drug Product Stability and Sterility sites.

Althea

From: Coleman, Becky [mailto:BColeman@theravance.com]
Sent: Thursday, July 26, 2012 5:45 PM
To: Cuff, Althea
Cc: Davi, Christopher
Subject: RE: NDA 22407

Ms. Cuff,

All information regarding the manufacturing facilities for telavancin drug substance and VIBATIV® drug product remain the same as has been submitted to NDA 22-110. Contact information is provided below.

Please feel free to contact me with any further questions.

Rebecca Coleman, Pharm.D.
Vice President, Regulatory Affairs and Quality
Theravance, Inc.

Phone: 650 808 6076

Drug Product Manufacturer

(b) (4)

(b) (4)

Drug Substance Manufacturer

(b) (4)

From: Cuff, Althea [<mailto:Althea.Cuff@fda.hhs.gov>]
Sent: Thursday, July 26, 2012 4:31 AM
To: Coleman, Becky
Subject: NDA 22407

Dear Ms. Coleman,

"Please provide a list of the manufacturing facilities involved in the manufacture of the drug substance and the drug product including the current contact name, address, phone and fax numbers, and email addresses for each establishment. Please state if any changes have been made to the manufacturing facilities since the approval of NDA 22-110, which is cross-referenced for CMC information in the current NDA." Please respond by Friday July 27.

Thanks,

Althea Cuff, MS
Regulatory Health Project Manager
Food & Drug Administration, CDER
Office of New Drugs Quality Assessment II
301-796-4061

Notice of Confidentiality:

This message contains confidential information intended exclusively for the intended recipient. This message should not be forwarded to any other party. Use or disclosure of information transmitted in error is prohibited. Please delete the message along with any attachments and alert the sender by return e-mail if this message was received in error.

Notice of Confidentiality:

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/s/

JEANNIE C DAVID
08/01/2012

Dr. Coleman,

Please see the following comments and information requests on the ADMORT dataset (NDA 22-407):

- For the METHOD variable (Specimen collection method), please clarify what are the specimen collection methods included in the following categories:
 - Other
 - Sputum method #1"
 - Sputum method #2
- For the PEA variable, please clarify whether PEA stands for "potentially effective antibiotic" or "prior effective antibiotic".
- For the PEA variable, what is the study window (in terms of study days) that this PEA flag captures?
- Please provide a variable that contains the drug name of the PEA.
- Please provide a variable that contains the study day that the PEA was first administered.
- Please provide a variable that contains the number of study days that the PEA was administered.
- Please include the variables INCREOT and INCREOTC that contains the clinical response at EOT.
- Please include variables that contain the study day that the EOT and TOC visits occurred.
- Are the serum creatinine and creatinine clearance variables based on local or central laboratory measurements?
- Please direct us to the location in the ADMORT dataset for the variable that contains information on the receipt of prior antimicrobial agents categorized as:
 - No prior therapy
 - ≤ 24 hours of prior antimicrobial therapy
 - > 24 hours of prior antimicrobial therapy

Please let me know if you have any questions.

J. Christopher Davi
Senior Regulatory Project Manager, DAIP

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

/s/

JOSEPH C DAVI
06/11/2012



NDA 22-407

MEETING MINUTES

Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Vice President, Regulatory Affairs and Quality
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VIBATIV (telavancin for injection).

We also refer to the meeting between representatives of your firm and the FDA on April 24, 2012. The purpose of the meeting was to discuss the status of the resubmission of the VIBATIV application.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Katherine A. Laessig, MD
Deputy Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES: Meeting Minutes
Preliminary responses from Agency dated April 23, 2011

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: Guidance

Meeting Date and Time: April 23, 2012
Meeting Location: CDER White Oak Campus

Application Number: 22-407
Product Name: VIBATIV
Indication: Nosocomial Pneumonia
Sponsor/Applicant Name: Theravance, Inc.

Meeting Chair: John K. Jenkins, MD, Director, OND

Meeting Recorder: J. Christopher Davi, MS, Senior Regulatory Project Manager

CDER participants: Division of Anti-Infective Products (DAIP) except where noted as Office of New Drugs (OND) and Office of Antimicrobial Products (OAP)

John K. Jenkins, MD, Director, OND
Edward M. Cox, MD, MPH, Director, OAP
John Farley, MD, MPH, Acting Director
Katherine A. Laessig, MD, Deputy Division Director
Sumathi Nambiar, MD, MPH, Deputy Director for Safety
Eileen Navarro-Almario, MD, Medical Reviewer
Benjamin Lorenz, MD, Medical Reviewer
Edward Nevius, PhD, Deputy Director, Office of Biometrics
Thamban Valappil, PhD, Team Leader, Biostatistics
Scott Komo, DrPH, Biostatistics Reviewer
J. Christopher Davi, MS, Senior Regulatory Project Manager

SPONSOR ATTENDEES: Theravance, Inc. (unless otherwise noted)

Rebecca Coleman, Pharm.D. Vice President, Regulatory Affairs and Quality, Theravance
Alan Hopkins, PhD, Vice President, Biometrics, Theravance
Steve Barriere, Pharm.D. Vice President, Clinical and Medical Affairs, Theravance
Josephine Torrente Regulatory Counsel to Theravance, Hyman Phelps McNamara
Chris Barnes, Sr., PhD, Director, Biometrics, Theravance
Philip Worboys, PhD, Drug Metabolism and PK, Theravance

BACKGROUND

Theravance (Sponsor) requested a Type-A meeting to discuss their resubmission for VIBATIV for the indication of nosocomial pneumonia (NP). Further, the Sponsor wished to discuss various aspects of a future advisory committee meeting for NDA 22-407. The Sponsor provided a briefing document to the Division April 10, 2012, and the Division provided preliminary responses to the questions in the Sponsor's briefing document on April 23, 2012 (appended). Discussion points generated from these responses are provided herein.

DISCUSSION

- With regard to item #1 of the appended responses, the Sponsor wished to clarify that the baseline characteristics necessary to demonstrate pneumonia for purposes of enrollment were taken from the 2005 ATS/IDSA criteria. The Division confirmed this to be the case.
- The Sponsor wished to clarify that if a subject were to present with two (2) of the baseline characteristics in addition to a positive chest X-ray, that this would suffice for purposes of demonstrating NP (i.e., the presence of all 3 criteria would not be necessary). The Division agreed with this assessment.
- With regard to item #6 (of the appended responses) the Division confirmed that among the several analytic populations listed, it is acceptable to include the ATS/IDSA group. However, the Division reminded the Sponsor that VIBATIV only has activity against Gram positive pathogens.
- The Sponsor indicated that they (Sponsor) recognized potential biases toward the “null” with the types of criteria being used to confirm that subjects actually had NP and that they would be taking steps to reduce this bias. The Division stressed that robust analyses to demonstrate the activity of the study drug should be conducted. The Sponsor was advised to focus on the adequacy of the specimens to ensure subjects have the disease under study. The Sponsor acknowledged this.
- The Sponsor indicated that there was value in the use of regression methods and companion Kaplan-Meier curves for screening purposes. The Sponsor asked the Division why the use of a hazard ratio of 1.6 (e.g., versus the 10% non-inferiority (NI) margin) might be problematic. The Division raised concerns in using a regression based approach and stated that the 10% NI margin, when translated into a hazard ratio can be problematic because of the use of post-hoc, data-driven covariates, and the critical assumptions required. Historical evidence of control treatment effect was estimated using a risk difference metric and the translation of the NI margin to a hazard ratio raises concerns.

- The Sponsor indicated that the hazard ratio of 1.6 was calculated from a 20% mortality rate that was discussed in the guidance. The Sponsor believed that a hazard ratio yielded more power than comparing mortality through day 28. The Division recommended the Sponsor use the Kaplan-Meier estimates at day 28 to estimate the difference in mortality.
- The Sponsor indicated that they would use the treatment group as a covariate to estimate the treatment effect using the hazard ratio. The Division will accept such an analysis as additional, but advised the Sponsor to ensure that they check that the proportionality of the hazards assumption is valid.
- The Sponsor asked the Division what type of sensitivity analysis was preferred for the missing or censored observations. The Division stated that the Sponsor should use methods that best demonstrate the robustness of the results. The Division mentioned that multiple imputation is a possible method that could be considered.
- The Division asked the Sponsor if they were including renal function covariates due to the observed differences in treatment effect with renal function. The Sponsor confirmed this, indicating that they felt the outcomes should be interpreted taking into account the patients' creatinine clearance and renal function. The Sponsor indicated that an important difference was noted between mixed Gram positive and Gram-negative infections, and that some patients received inadequate coverage for Gram-negative infections.
- With regard to the pending Advisory Committee meeting, the Sponsor asked if an additional meeting could be granted to discuss the various issues to be covered. The Division stated that this would be acceptable.

-End

ATTACHMENTS AND HANDOUTS

Preliminary responses to Sponsor dated April 23, 2012

Dr. Coleman,

The Division of Anti-Infective Products (DAIP) has reviewed your briefing document dated April 10, 2012, (NDA 22-407) and we have the following preliminary responses to the questions therein (*italics*):

1. Does the Agency agree that the baseline characteristic, respiratory sample, and chest radiographic evidence, taken together strongly suggest that the patients in Studies 0015 and 0019 had nosocomial pneumonia and were sufficiently ill to demonstrate a treatment benefit when given an effective antibiotic?

Agency Response: *The Division generally agrees with the use of ATS/IDSA criteria for the purpose of inclusion of appropriate patients in trials of HABP and VABP. The appropriateness of inclusion into the microbiologically evaluable population based on these criteria will be established in our review of your submission.*

In your submission, please provide additional analyses of the endpoints 28 day all-cause mortality and protocol-defined clinical response in the following patient populations:

- a. *Patients with respiratory samples only considered “reliable” using the microscopic criteria from sputum (WBCs >25, SECs <10/LPF), ETA (SECs <10/LPF), and samples from other invasive procedures.*
- b. *Patients with respiratory samples using methods with higher specificity and sensitivity:*
 - i. *Patients with reliable ETA samples and invasive procedures*
 - ii. *Patients with samples only from invasive procedures*

The above analyses should be conducted for all patients with a pathogen identified, for those with a gram-positive pathogen identified, for those with a gram-positive pathogen identified whose only active gram-positive therapy was telavancin or comparator, and for those with (and without) radiologic evidence of pneumonia.

2. Given censored mortality data, does the Agency accept the use of survival methods (i.e., Kaplan-Meier and Cox regression) for analyzing the mortality endpoint? Does the Agency agree that the data may be analyzed as described in the briefing document?

Agency Response: *Survival methods may be used to handle the missing mortality data. In addition, we recommend that you provide other sensitivity analyses that look at the impact of the missing mortality data. As the historical evidence of control treatment effect was estimated using a risk difference metric, we have concerns regarding the translation of the 10% NI margin on the risk difference scale to 1.6 on the hazard ratio scale.*

In your submission, please also provide an analysis based on the difference in Day-28 Kaplan-Meier estimates of mortality that do not control for any prognostic risk factors. These analyses should be conducted in the ITT, mITT (micro ITT with a gram-positive pathogen identified), and per-protocol populations.

3. Does the Agency agree that mortality rates should be analyzed conditional upon kidney function, represented by the variable *creatinine clearance at baseline*?

Agency Response: *In your submission, please provide an analysis based on the difference in Day-28 Kaplan-Meier estimates of mortality stratified by baseline creatinine clearance. One of the analyses should categorize baseline creatinine clearance into two categories (≤ 50 mL/min; > 50 mL/min). In addition, provide an analysis that groups subjects based on their baseline creatinine clearance into four categories (< 30 mL/min, 30-50 mL/min, 50-80 mL/min and > 80 mL/min).*

We consider these analyses reliable in patients with chronic kidney disease (i.e., creatinine clearance in patients with acute renal failure cannot be accurately estimated at a single time point using serum creatinine measurements). Patients who are classified as having chronic versus acute renal failure, therefore, may need to be analyzed in separate strata, using standardized criteria that can be verified from the study data. We recommend that you consider the labeling implications of a positive interaction between renal failure and mortality and propose instructions for use of telavancin in a manner that preserves a satisfactory risk benefit in HABP and VABP.

4. Does the Agency agree that it is more appropriate to analyze the biomarker groups (see Question 6) using the combined studies since the power ranges from 40% to 63% for the individual studies?

Agency Response: *In your submission, please provide separate analyses for the biomarker subgroups by trial as well as a pooled analysis stratified by trial. We have concerns regarding pooling the trials because the treatment effect for 28-day mortality rates does not appear to be consistent across the trials. Nonetheless, a closer assessment of the interaction between renal failure and mortality may allow us to consider approaches to the analysis of the primary endpoint. In addition, we are also concerned that the populations in these two trials appeared to be substantially different based on pre-treatment characteristics. There are differences between the two trials in the distribution of potential risk factors for mortality (e.g., diabetes mellitus and renal impairment/failure). There were more patients in Study 0015 with chronic renal failure, baseline CrCl < 50 mL/min, serum creatinine > 1.2 mg/dL, hemodialysis, diabetic status (yes), history of diabetes mellitus, ARDS, HABP, torsades, history of atrial fibrillation, and history of myocardial infarction.*

5. Does the Agency agree that aggregation by strata can help alleviate the imbalances noted in Study 0015 compared to Study 0019 through stratification with a direct adjustment for creatinine clearance level?

Agency Response: *Refer to our responses to Question #4*

6. Does the Agency agree that the ATS/IDSA group is appropriate for the primary mortality analysis and that aggregated analysis of the Gram-positive Only population provides supportive evidence of efficacy untainted by mixed infections, etc?

Agency Response: *In your submission, please provide analyses for the following populations:*

1. *All treated*
 2. *Patients with any gram positive pathogens isolated at baseline*
 3. *Patients meeting the ATS/IDSA criteria at baseline and having any gram positive pathogens isolated at baseline*
 4. *Patients with only gram positive pathogens isolated at baseline*
 5. *Patients meeting the ATS/IDSA criteria at baseline and having only gram positive pathogens isolated at baseline*
 6. *Patients with MRSA isolated at baseline*
 7. *Patients meeting the ATS/IDSA criteria at baseline and having MRSA isolated at baseline*
7. Does the Agency agree with our proposal to resubmit the NDA addressing the issues identified in the letter from Dr. Jenkins?

Agency Response: *Yes, the Division agrees.*

8. Can we anticipate a goal of 6 months for review of the resubmission? Could we expect to go to an Advisory Committee in month 4 or 5 of the review timeframe?

Agency Response: *Yes. The Division will coordinate with Theravance regarding the planning for the Advisory Committee meeting.*

Additional Comments:

We request you include a revised efficacy dataset in your resubmission that includes:

- *All of the variables in ADSL*
- *Additional mortality information that was submitted to the NDA after the initial submission. This information should include day of death, censoring time, and cause of death*
- *Flag to indicate patients who met ATS/IDSA criteria at baseline*
- *Flag to indicate patients with a gram-positive pathogen whose only active gram-positive therapy was telavancin or comparator*

- *Flag to indicate patients who had their pretreatment radiographs reviewed*
- *Variable to indicate radiological report type*
- *Variable to indicate the core radiology adjudication finding*
- *Variable to indicate receipt of prior antimicrobial agents categorized as*
 - *No prior therapy*
 - *≤24 hours of prior antimicrobial therapy*
 - *>24 hours of prior antimicrobial therapy*
- *Variable to indicate the method used to obtain the respiratory sample*
- *Variable to indicate whether the sample was considered “reliable” using the microscopic criteria from sputum (WBCs >25, SECs <10/LPF), ETA (SECs <10/LPF), and samples from other invasive procedures.*

We look forward to our discussion with you on April 24, 2012. If you have questions in the interim, please contact me at (301) 796- 0702.

J. Christopher Davi, MS
Senior Regulatory Project Manager
DAIP

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/s/

KATHERINE A LAESSIG
05/22/2012

Dr. Coleman,

The Division of Anti-Infective Products (DAIP) has reviewed your briefing document dated April 10, 2012, (NDA 22-407) and we have the following preliminary responses to the questions therein (*italics*):

1. Does the Agency agree that the baseline characteristic, respiratory sample, and chest radiographic evidence, taken together strongly suggest that the patients in Studies 0015 and 0019 had nosocomial pneumonia and were sufficiently ill to demonstrate a treatment benefit when given an effective antibiotic?

Agency Response: *The Division generally agrees with the use of ATS/IDSA criteria for the purpose of inclusion of appropriate patients in trials of HABP and VABP. The appropriateness of inclusion into the microbiologically evaluable population based on these criteria will be established in our review of your submission.*

In your submission, please provide additional analyses of the endpoints 28 day all-cause mortality and protocol-defined clinical response in the following patient populations:

- a. *Patients with respiratory samples only considered “reliable” using the microscopic criteria from sputum (WBCs >25, SECs <10/LPF), ETA (SECs <10/LPF), and samples from other invasive procedures.*
- b. *Patients with respiratory samples using methods with higher specificity and sensitivity:*
 - i. *Patients with reliable ETA samples and invasive procedures*
 - ii. *Patients with samples only from invasive procedures*

The above analyses should be conducted for all patients with a pathogen identified, for those with a gram-positive pathogen identified, for those with a gram-positive pathogen identified whose only active gram-positive therapy was telavancin or comparator, and for those with (and without) radiologic evidence of pneumonia.

2. Given censored mortality data, does the Agency accept the use of survival methods (i.e., Kaplan-Meier and Cox regression) for analyzing the mortality endpoint? Does the Agency agree that the data may be analyzed as described in the briefing document?

Agency Response: *Survival methods may be used to handle the missing mortality data. In addition, we recommend that you provide other sensitivity analyses that look at the impact of the missing mortality data. As the historical evidence of control treatment effect was estimated using a risk difference metric, we have concerns regarding the translation of the 10% NI margin on the risk difference scale to 1.6 on the hazard ratio scale.*

In your submission, please also provide an analysis based on the difference in Day-28 Kaplan-Meier estimates of mortality that do not control for any prognostic risk factors. These analyses should be conducted in the ITT, mITT (micro ITT with a gram-positive pathogen identified), and per-protocol populations.

3. Does the Agency agree that mortality rates should be analyzed conditional upon kidney function, represented by the variable *creatinine clearance at baseline*?

Agency Response: *In your submission, please provide an analysis based on the difference in Day-28 Kaplan-Meier estimates of mortality stratified by baseline creatinine clearance. One of the analyses should categorize baseline creatinine clearance into two categories (≤ 50 mL/min; > 50 mL/min). In addition, provide an analysis that groups subjects based on their baseline creatinine clearance into four categories (< 30 mL/min, 30-50 mL/min, 50-80 mL/min and > 80 mL/min).*

We consider these analyses reliable in patients with chronic kidney disease (i.e., creatinine clearance in patients with acute renal failure cannot be accurately estimated at a single time point using serum creatinine measurements). Patients who are classified as having chronic versus acute renal failure, therefore, may need to be analyzed in separate strata, using standardized criteria that can be verified from the study data. We recommend that you consider the labeling implications of a positive interaction between renal failure and mortality and propose instructions for use of telavancin in a manner that preserves a satisfactory risk benefit in HABP and VABP.

4. Does the Agency agree that it is more appropriate to analyze the biomarker groups (see Question 6) using the combined studies since the power ranges from 40% to 63% for the individual studies?

Agency Response: *In your submission, please provide separate analyses for the biomarker subgroups by trial as well as a pooled analysis stratified by trial. We have concerns regarding pooling the trials because the treatment effect for 28-day mortality rates does not appear to be consistent across the trials. Nonetheless, a closer assessment of the interaction between renal failure and mortality may allow us to consider approaches to the analysis of the primary endpoint. In addition, we are also concerned that the populations in these two trials appeared to be substantially different based on pre-treatment characteristics. There are differences between the two trials in the distribution of potential risk factors for mortality (e.g., diabetes mellitus and renal impairment/failure). There were more patients in Study 0015 with chronic renal failure, baseline CrCl < 50 mL/min, serum creatinine > 1.2 mg/dL, hemodialysis, diabetic status (yes), history of diabetes mellitus, ARDS, HABP, torsades, history of atrial fibrillation, and history of myocardial infarction.*

5. Does the Agency agree that aggregation by strata can help alleviate the imbalances noted in Study 0015 compared to Study 0019 through stratification with a direct adjustment for creatinine clearance level?

Agency Response: *Refer to our responses to Question #4*

6. Does the Agency agree that the ATS/IDSA group is appropriate for the primary mortality analysis and that aggregated analysis of the Gram-positive Only population provides supportive evidence of efficacy untainted by mixed infections, etc?

Agency Response: *In your submission, please provide analyses for the following populations:*

1. *All treated*
 2. *Patients with any gram positive pathogens isolated at baseline*
 3. *Patients meeting the ATS/IDSA criteria at baseline and having any gram positive pathogens isolated at baseline*
 4. *Patients with only gram positive pathogens isolated at baseline*
 5. *Patients meeting the ATS/IDSA criteria at baseline and having only gram positive pathogens isolated at baseline*
 6. *Patients with MRSA isolated at baseline*
 7. *Patients meeting the ATS/IDSA criteria at baseline and having MRSA isolated at baseline*
7. Does the Agency agree with our proposal to resubmit the NDA addressing the issues identified in the letter from Dr. Jenkins?

Agency Response: *Yes, the Division agrees.*

8. Can we anticipate a goal of 6 months for review of the resubmission? Could we expect to go to an Advisory Committee in month 4 or 5 of the review timeframe?

Agency Response: *Yes. The Division will coordinate with Theravance regarding the planning for the Advisory Committee meeting.*

Additional Comments:

We request you include a revised efficacy dataset in your resubmission that includes:

- *All of the variables in ADSL*
- *Additional mortality information that was submitted to the NDA after the initial submission. This information should include day of death, censoring time, and cause of death*
- *Flag to indicate patients who met ATS/IDSA criteria at baseline*
- *Flag to indicate patients with a gram-positive pathogen whose only active gram-positive therapy was telavancin or comparator*

- *Flag to indicate patients who had their pretreatment radiographs reviewed*
- *Variable to indicate radiological report type*
- *Variable to indicate the core radiology adjudication finding*
- *Variable to indicate receipt of prior antimicrobial agents categorized as*
 - *No prior therapy*
 - *≤24 hours of prior antimicrobial therapy*
 - *>24 hours of prior antimicrobial therapy*
- *Variable to indicate the method used to obtain the respiratory sample*
- *Variable to indicate whether the sample was considered “reliable” using the microscopic criteria from sputum (WBCs >25, SECs <10/LPF), ETA (SECs <10/LPF), and samples from other invasive procedures.*

We look forward to our discussion with you on April 24, 2012. If you have questions in the interim, please contact me at (301) 796- 0702.

J. Christopher Davi, MS
Senior Regulatory Project Manager
DAIP

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/s/

JOSEPH C DAVI
04/23/2012



NDA 22-407

MEETING REQUEST GRANTED

Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Vice President, Regulatory Affairs and Quality
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VIBATIV (telavancin for injection).

We also refer to your March 13, 2012, correspondence requesting a Type-A meeting to discuss the presentation of VIBATIV for the treatment of nosocomial pneumonia at an Anti-Infective Drugs Advisory Committee meeting. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

Date: April 24, 2012
Time: 12:00 Noon to 1:00 PM, EST
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

CDER participants: Division of Anti-Infective Products (DAIP) except where noted as Office of New Drugs (OND) and Office of Antimicrobial Products (OAP)

John K. Jenkins, MD, Director, OND
Edward M. Cox, MD, MPH, Director, OAP
John Farley, MD, MPH, Acting Director
Katherine A. Laessig, MD, Deputy Division Director
Sumathi Nambiar, MD, MPH, Deputy Director for Safety
Janice K. Pohlman, MD, MPH, Lead Medical Officer
Eileen Navarro-Almario, MD, Medical Reviewer
Benjamin Lorenz, MD, Medical Reviewer
Lisa Lavange, PhD, Director, Office of Biometrics
Thamban Valappil, PhD, Team Leader, Biostatistics
Scott Komo, DrPH, Biostatistics Reviewer
David L. Roeder, MS, Associate Director for Regulatory Affairs, OAP
Maureen Dillon-Parker, Chief, Project Management Staff

Amy Bertha, Senior Regulatory Project Manager, OND
J. Christopher Davi, MS, Senior Regulatory Project Manager, DAIP

Please e-mail any updates to your attendees to christopher.davi@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email the enclosed Foreign Visitor Data Request Form, to christopher.davi@fda.hhs.gov at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with the following number to request an escort to the conference room: (301) 796-0702.

Submit background information for the meeting (three paper copies or one electronic copy to the application and 16 desk copies to J. Christopher Davi) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by April 10, 2012, we may cancel or reschedule the meeting.

Submit the 16 desk copies to the following address:

J. Christopher Davi, MS
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6121
10903 New Hampshire Avenue
Silver Spring, Maryland
*Use zip code **20903** if shipping via United States Postal Service (USPS).*
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Maureen Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective Drug Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	April 24, 2012; 12:00 Noon
MEETING ENDING DATE AND TIME	April 24, 2012; 1:00 PM
PURPOSE OF MEETING	Discuss plans for Advisory Committee Meeting
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	WO Bldg. 22, conference room 1415
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	J. Christopher Davi, MS, Sr. RPM, DAIP WO 22, Room 6121 (301) 796-0702
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

MAUREEN P DILLON PARKER
03/14/2012



NDA 022407

DISPUTE APPEAL – DENIED

Theravance, Inc.
Attention: Rebecca Coleman, Pharm. D.
Vice President, Regulatory Affairs and Quality
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

Please refer to your supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VIBATIV (telavancin) for injection, 250 mg and 750 mg, for the treatment of nosocomial pneumonia (NP).

We also refer to your December 6, 2011, request for formal dispute resolution, received on December 7, 2011, to the Office of New Drugs. The request for dispute resolution concerns the deficiencies described in the November 23, 2009, and December 21, 2010, complete response (CR) letters from the Division of Anti-infective Products (DAIP), explaining that the sNDA does not provide substantial evidence of safety and efficacy of telavancin in the treatment of NP. Your request for formal dispute resolution followed your August 24, 2011, appeal to the Office of Antimicrobial Products (OAP) and the subsequent denial of that appeal on October 14, 2011, by Edward Cox, M.D., M.P.H., Director, OAP. We also refer to the meeting held between FDA and Theravance on January 20, 2012, where the issues raised in your request for formal dispute resolution were discussed.

In your dispute resolution submission, you take the position that the data submitted in the sNDA demonstrate that telavancin is non-inferior (NI) to vancomycin on the pre-specified primary endpoint of cure rate in the treatment of NP and meet the statutory standard for approval of this new indication. You also state your view that it is inappropriate for the Agency to impose a requirement that you demonstrate efficacy based on a different primary endpoint, all-cause mortality, when your phase 3 trials were agreed to by the Agency before the trials were conducted. Further, you note that the Agency has not finalized its guidance to sponsors regarding its current thinking on appropriate endpoints and statistical analysis plans for clinical trials for evaluating drugs for the treatment of NP and has not initiated procedures to withdraw approval for antibacterial drugs with a NP indication that were approved based on a clinical cure endpoint. Despite your objections to the Agency's requirement that you demonstrate efficacy based on a mortality endpoint, you also claim that the data submitted in the sNDA meet the Agency's proposed NI margin of 10% for mortality. You request that I find that the available data are adequate to support approval and that the deficiencies cited in the two CR letters do not warrant the conduct of additional clinical trials prior to approval.

I have carefully reviewed the materials you submitted in support of your appeal, the reviews, meeting minutes, and decision memoranda prepared by FDA staff, the CR letters, and Dr. Cox's appeal denied letter. I have also consulted with staff in OAP, the Office of Biostatistics (OB), the Office of Regulatory Policy, Lisa LaVange, Ph.D., Director, OB, and Robert Temple, M.D., Deputy Center Director for Clinical Science.

I have completed my review of your request for formal dispute resolution and deny your appeal. Although I am denying your appeal, I recommend that you resubmit the application for further review by the Agency and presentation to an Anti-Infective Drugs Advisory Committee (AIDAC) meeting.

As you are aware, the Agency's current thinking on the appropriate use and interpretation of NI trials for the approval of antibacterial drugs, and for other drug classes, has evolved significantly over the past decade. The evolution in the Agency's approach to NI trials has been driven by a more complete understanding of the scientific issues that underlie the design, analysis, and interpretation of these trials. The Agency has engaged with various stakeholders throughout this process, and has sought input and communicated its evolving thinking through numerous public meetings and workshops, advisory committee meetings, and publication of draft and final guidance on the broad issue of NI trials, the use of NI trials in anti-infective drugs in general, and for specific anti-infective diseases.

The Agency's current thinking on the use of NI trials is based on the need to clearly establish the beneficial effect of the active comparator that will serve as the reference product in the trials to establish the efficacy and safety of the new, or test, drug. Information on the beneficial effect of the active control that can be assumed to be present in the NI trials is ideally derived from adequate and well-controlled trials comparing the reference drug to placebo or no treatment, and is commonly referred to as M1. Once M1 is established, the NI margin for a trial comparing a test drug to the reference drug can be established. This NI margin, in effect, represents a clinical judgment of how much of the beneficial effect of the reference drug could be "lost" by the test drug and still be considered to demonstrate efficacy of the test drug. The NI margin is some fraction of M1 and is commonly referred to as M2.

In many diseases, it is relatively simple to determine M1 and to develop an acceptable NI margin. Unfortunately, for a variety of reasons stated in Dr. Cox's October 14, 2011, letter, which I will not repeat here, reliable identification of M1 and development of an acceptable NI margin for antibacterial drugs have proven to be quite challenging. For some anti-infective indications, the Agency has determined that M1 cannot be reliably determined and an interpretable NI margin cannot be established. In such cases (e.g., acute bacterial sinusitis), the Agency has advised sponsors of the need to conduct superiority trials to support approval of a new drug. In other cases the Agency has been able to identify data that support a science-based determination of M1 and has used these data to develop a recommended NI margin.

In the case of NP (also known as hospital-acquired bacterial pneumonia [HABP], with a subset known as ventilator-associated bacterial pneumonia [VABP]), the Agency has been unable to find sufficient data to determine a reliable estimate of M1 for the endpoint of clinical cure, and therefore has been unable to recommend an evidence-based and interpretable NI margin. The Agency has identified data that we believe would support a reliable estimate of M1 for the endpoint of all-cause mortality. It was on the basis of this new understanding of the available scientific data that the Agency published for comment a draft guidance on development of drugs for the treatment of HABP/VABP in November 2010. In that draft guidance, the Agency recommends use of all-cause mortality as the primary endpoint and a NI margin of 10%.

The Agency's current inability to establish a science-based NI margin for clinical cure in NP does not mean that the Agency does not recognize the importance of clinical cure as one of the primary goals of antibacterial drug therapy in patients with NP and as an important endpoint to evaluate in clinical trials. The Agency also recognizes the limitations of using all-cause mortality as the primary endpoint for NP trials, which include the fact that some fraction of the deaths in the trial may not be related to the patient's pneumonia. Unfortunately, based on the available data, the Agency's current thinking is that a science-based and interpretable NI margin for clinical cure in NP cannot be determined. As you note, the Agency has not finalized the draft HABP/VABP guidance. At present, the Agency continues to evaluate comments from the public and from the AIDAC meeting held in November 2011 to discuss the draft guidance. Some of the issues you have raised in your dispute resolution submission are also being considered as the Agency works to finalize guidance for this indication.

The challenge the Agency faces anytime it makes a change in policy on the scientific or clinical requirements for approval is how to apply the new policy to applications from sponsors whose development programs were complete, or nearly complete, at the time of the policy change, as well as the impact of the policy change on drugs that were approved based on the old policy. You raise this dilemma as an issue of fairness in your dispute. The development program of telavancin in NP was agreed to with the Agency and the clinical trials were ongoing during the time the Agency was reconsidering its approach to the use of NI trials in approval of antibacterial drugs. The Agency's draft guidance on HABP/VABP was published after the phase 3 clinical trials for telavancin in NP were completed and after the sNDA was submitted. The Agency's evolving thinking in this area was considered during the review of your sNDA and referenced in the CR letters, which I view as appropriate. You view the application of this change in Agency policy as unfair and request that the Agency "grandfather" telavancin and approve it based on the previous approach of relying on clinical cure as the primary endpoint for approval of drugs for the treatment of NP.

The Agency's policy is that it must apply the most current thinking and science as it makes decisions on individual applications. To do otherwise would prevent the Agency from incorporating new science into its decision making and perpetuate past practices, which in some cases may have proven to be flawed or outdated. The Agency has also generally not revisited all past decisions once our policy on a given issue changes. The Agency may, however, revisit past decisions if it has concerns that the approved drug may be ineffective or unsafe for its intended use. You argue that since the Agency has not initiated procedures to withdraw approval of the NP indication for previously-approved antibacterial drugs that were approved based on a clinical cure endpoint; it should review the telavancin NDA in accordance with the approval standard applied to these antibacterial drugs. This argument is inconsistent with the need for the Agency to apply the most current science to its review of, and decisions on, new applications. A system that required the Agency to revisit every prior decision as science evolves and standards change would make the regulatory process impossibly cumbersome and burdensome on both the Agency and sponsors of approved applications. I also note that during our January 20, 2012, meeting representatives of Theravance and your counsel acknowledged that withdrawal of the NP indication from previously-approved antibacterial drugs was not your desired outcome.

The clinical development program for telavancin in NP has generated a large amount of data, which I believe must be carefully re-evaluated to support a decision on whether the new indication should be approved. These data may also help the Agency inform its thinking on the appropriate design, endpoints, and analysis for trials to support approval of antibacterial drugs in NP.

As you point out in your dispute resolution submission, telavancin met the pre-specified primary endpoint in both Study 0015 and 0019; i.e., it met the pre-specified NI margin for clinical cure. The trials were not designed or powered to assess all-cause mortality as a primary endpoint, and it is not surprising that the analysis of the all-treated population failed to meet the Agency's recommended 10% NI margin for this endpoint in Study 0015. You have argued that by pooling the two trials (which had identical protocols) and applying particular statistical methodologies to analyze the data, the pooled results meet the 10% NI margin. Thus, you argue that the available data support approval even when using the Agency's stated preference for all-cause mortality as the primary endpoint. There are, however, a number of complex scientific issues that must be addressed in evaluating the available data. These include:

1. the appropriateness of analyzing mortality as the primary efficacy endpoint to support approval when the trials were not designed for this purpose,
2. the appropriate population for the mortality analysis (e.g., the all-treated population, patients with a Gram-positive pathogen),
3. the appropriateness of combining the two trials for the mortality analysis given the observed differences in some baseline characteristics of patients between the two trials and the heterogeneous result of the analysis of all-cause mortality between the two trials,
4. whether to include or exclude patients with baseline renal failure in the analysis considering the warning in the current telavancin labeling regarding an increased risk of nephrotoxicity

- and decreased efficacy in patients with moderate to severe baseline renal impairment treated with telavancin for complicated skin and skin structure infections, and
5. how to interpret the “lean” toward increased mortality seen with telavancin in some of the mortality analyses (e.g., the all-treated analysis of Study 015).

While the Agency has stated its preference for all-cause mortality as the primary endpoint, I believe it is important that the Agency make use of all the available data to help it reach its decision on whether the benefits of telavancin outweigh its risks in the treatment of NP. Before making a new decision on whether the available data support approval, I believe it would be beneficial for you to resubmit the application for further Agency review and reconsideration of these complex issues. Your resubmission should include all new analyses that you believe are informative to the interpretation of the data, as well as responses to the deficiencies stated in the last CR letter. I also believe that this application should be presented for discussion at a public meeting of the AIDAC, so that the Agency can obtain expert advice on the complex scientific issues as well as input on whether the available data support a conclusion that the benefits of telavancin for NP outweigh its risks in some patient population. I recommend that you request a meeting with DAIP to discuss the plans for your resubmission.

In our meeting on January 20, 2012, you stated your willingness to participate in an AIDAC discussion of this sNDA; however, you expressed concerns that the presentations and questions to the committee not be a “stacked deck.” As I interpret your concerns, you want to ensure that the data will be presented to the committee in a fair manner. In particular, you were concerned that the Agency briefing documents and presentations not state that the only acceptable endpoint for approval is all-cause mortality with a NI margin of 10%, as recommended in the draft HABP/VABP guidance. While the Committee members are aware of the draft HABP/VABP guidance, the Agency background materials and presentations for the meeting can make clear that the guidance is not final, and that we are seeking their advice on the “totality of the data” from the current application, noting that the development program was completed before the draft guidance was issued. So, I believe we can have a “fair hearing” before the AIDAC, and I will work with the staff in OAP and OB to ensure that goal. I will also make every effort to attend the committee meeting, and ask that Drs. LaVange and Temple attend as well if their schedules allow.

In summary, I believe it is important for the Agency to reconsider this application in light of the challenging scientific issues that have been raised regarding interpretation of the available data. I believe it is important that our re-evaluation include input from the public and AIDAC and that we carefully consider their input before making a new decision on whether telavancin can be approved for the treatment of NP based on the currently available data. I hope that you will agree to resubmit the application and to work with OAP in planning for an AIDAC meeting during the new review cycle.

Questions regarding next steps as described in this letter should be directed to J. Christopher Davi, M.S., Senior Regulatory Project Manager, at (301) 796-0702.

If you wish to appeal this decision to the next level, your appeal should be directed to Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research. The appeal should be sent to the NDA administrative file as an amendment, and a copy should be sent to the Center’s Dispute Resolution Project Manager, Amy Bertha. Any questions concerning your appeal should be addressed to Ms. Bertha at (301) 796-1647.

Sincerely,

{See appended electronic signature page}

John Jenkins, M.D.
Director
Office of New Drugs

Center for Drug Evaluation and Research

cc:
Hyman, Phelps & McNamara, P.C.
Attention: Josephine M. Torrente
Regulatory Counsel
700 Thirteenth Street, NW Suite 1200
Washington, D.C. 20005-5929

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/s/

JOHN K JENKINS
02/17/2012



NDA 022407

MEETING MINUTES

Theravance, Inc.
Attention: Rebecca Coleman, Pharm.D.
Vice President, Regulatory Affairs and Quality
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VIBATIV (telavancin) for injection, 10 mg/kg IV q24h.

We also refer to the meeting between representatives of your firm and the FDA on January 20, 2012. The purpose of the meeting was to discuss the issues raised in your request for formal dispute resolution dated December 6, 2011.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1647.

Sincerely,

{See appended electronic signature page}

Amy Bertha
Acting Team Leader
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure

cc:
Hyman, Phelps & McNamara, P.C.
Attention: Josephine M. Torrente
Regulatory Counsel
700 Thirteenth Street, NW Suite 1200
Washington, D.C. 20005-5929

MEMORANDUM OF MEETING MINUTES

MEETING DATE: January 20, 2012
TIME: 1:00 pm – 2:30 pm, EST
LOCATION: White Oak Campus, Building 21, Room 1417
APPLICATION: NDA 022407
DRUG NAME: VIBATIV (telavancin) for injection, 10 mg/kg IV q24h
TYPE OF MEETING: Formal Dispute Resolution
MEETING CHAIR: John Jenkins, M.D.
MEETING RECORDER: Amy Bertha

FDA ATTENDEES:

John Jenkins, M.D.	Director, Office of New Drugs
RADM Sandra Kweder, M.D.	Deputy Director, Office of New Drugs
Amy Bertha	Acting Team Leader, Office of New Drugs
Robert Temple, M.D.	Deputy Director for Clinical Science
Edward Cox, M.D., MPH	Director, Office of Antimicrobial Products (OAP)
John Farley, M.D., MPH	Deputy Director, OAP, and Acting Director, Division of Anti-Infective Products (DAIP)
David Roeder	Associate Director for Regulatory Affairs, OAP
Janice Pohlman, M.D., MPH	Clinical Reviewer, Office of Scientific Investigations
Benjamin Lorenz, M.D.	Medical Officer, DAIP
Maureen Dillon-Parker	Supervisory Project Manager, DAIP
J. Christopher Davi	Senior Regulatory Health Project Manager, DAIP
Lisa LaVange, Ph.D.	Director, Office of Biostatistics, Office of Translational Science
Thamban Valappil, Ph.D.	Team Leader, Division of Biometrics IV
Scott Komo, Dr.PH	Biometrics Reviewer, Division of Biometrics IV
Denise Esposito	Deputy Director, Office of Regulatory Policy
Jay Sitlani	Regulatory Counsel, Division of Regulatory Policy I

EXTERNAL CONSTITUENT ATTENDEES:

Rick Winningham	Chairman and Chief Executive Officer, Theravance
Leonard Blum	Senior Vice President and Chief Commercial Officer, Theravance
Rebecca Coleman, Pharm.D.	Vice President, Regulatory Affairs and Quality, Theravance
Alan Hopkins, Ph.D.	Vice President, Biometrics, Theravance
Steve Barriere, Pharm.D.	Vice President, Clinical and Medical Affairs, Theravance
(b) (4)	Outside Medical Consultant (b) (4)
Josephine Torrente	Regulatory Counsel to Theravance, Hyman Phelps McNamara
Delia Stubbs	Regulatory Counsel to Theravance, Hyman Phelps McNamara

BACKGROUND:

Theravance submitted a formal dispute resolution request to the Office of Antimicrobial Products (OAP) on August 24, 2011, concerning the complete response action taken on December 21, 2010, specifically that the NDA does not provide substantial evidence to demonstrate the safety and efficacy of telavancin in the treatment of nosocomial pneumonia (NP). Dr. Edward Cox, Director, OAP, denied the appeal on October 14, 2011. Theravance submitted a formal dispute resolution request to the Office of New Drugs (OND) on December 6, 2011. Dr. John Jenkins, Director, OND is the deciding authority. In Theravance's December 6, 2011, dispute resolution submission, the company requested a meeting with the deciding official before he rendered his decision on this matter. The meeting was granted and took place on January 20, 2012.

MEETING OBJECTIVES:

The objective of this meeting was to discuss the issues surrounding the appeal.

DISCUSSION:

FDA and Theravance discussed the following issues:

- FDA asked Theravance to address why the company did not think it would be appropriate to hold an Advisory Committee (AC) meeting on this application given the complexity of the issues. Theravance agreed that an AC meeting to discuss this application would be appropriate, however they expressed concerns over how the questions would be posed to the committee, specifically in the areas of efficacy endpoints (i.e., mortality versus clinical cure) and analyses (i.e., pooling studies 0015 and 0019).
- Theravance designed their clinical trials with clinical cure as the primary endpoint. Theravance and FDA discussed their views on the appropriate non-inferiority (NI) margin for the clinical cure endpoint. Additionally, clinical cure and mortality as efficacy endpoints in trials for the treatment of NP were discussed.
- Theravance proposed to combine the results from studies 0015 and 0019, and to use the combined results to look at the mortality endpoint. The issues with combining these studies were discussed from a statistical perspective. Specifically, the difference in the baseline characteristics of the patients in both studies, what the appropriate analysis population would be (i.e., the all-treated population versus the Gram-positive pathogen population), and what potential bias pooling might introduce were discussed.

DECISIONS (AGREEMENTS) REACHED:

This meeting was not conducted with the expectation that decisions would be made or agreements reached at the meeting. The issues discussed will be taken into consideration when reaching a decision regarding the formal dispute resolution request which will be made within 30 days of the meeting date.

ATTACHMENTS/HANDOUTS:

Slides from Theravance presentation.

Jan 13, 2012

Question from FDA

Please explain why you do not think it is appropriate to hold an Advisory Committee Meeting on this application given the complexity of the issues.

Oct 20, 2011 FDA Letter

Issues for AIDAC

- The trials were originally designed with different primary endpoints and numerous subgroup analyses are being analyzed to evaluate a mortality endpoint
- Collection and evaluation of respiratory tract samples and radiographic evaluation for patients enrolled in the trials
- The role and effect of prior and/or concomitant antibacterial drug therapy, empiric therapy, and de-escalation of adjunctive antibacterial drug therapy in the interpretation of trial results.
- The appropriate analysis population, given that the spectrum of activity of telavancin is against Gram-positive organisms and that patients may have received prior or concomitant antibacterial drug therapy
- The role of supporting data from other indications and the role that such information may play in whether one trials vs. two trials can provide sufficient information to support the indication you seek
- The analysis of mortality data in patients with baseline renal failure and the definition of renal failure as applied in the clinical trials

Oct 20, 2011 FDA Letter

Issues for AIDAC

- The trials were originally designed with different primary endpoints and numerous subgroup analyses are being analyzed to evaluate a mortality endpoint
- Collection and evaluation of respiratory tract samples and radiographic evaluation for patients enrolled in the trials
- The role and effect of prior and/or concomitant antibacterial drug therapy, empiric therapy, and de-escalation of adjunctive antibacterial drug therapy in the interpretation of trial results.
- The appropriate analysis population, given that the spectrum of activity of telavancin is against Gram-positive organisms and that patients may have received prior or concomitant antibacterial drug therapy
- The role of supporting data from other indications and the role that such information may play in whether one trials vs. two trials can provide sufficient information to support the indication you seek
- The analysis of mortality data in patients with baseline renal failure and the definition of renal failure as applied in the clinical trials

Clinical Cure Rates AT/CE Populations

Study	Population	Telavancin n/N (%)	Vancomycin n/N (%)	Difference % (95% CI)
0015	AT	214/372 (57.5)	221/374 (59.1)	-1.6 (-8.6, 5.5)
	CE	118/141 (83.7)	138/172 (80.2)	3.5 (-5.1, 12.0)
0019	AT	227/377 (60.2)	228/380 (60.0)	0.2 (-6.8, 7.2)
	CE	139/171 (81.3)	138/170 (81.2)	0.1 (-8.2, 8.4)
Combined	AT	441/749 (58.9)	449/754 (59.5)	-0.7 (-5.6, 4.3)
	CE	257/312 (82.4)	276/342 (80.7)	1.7 (-4.3, 7.7)

28-Day Mortality Rates AT Population

Study	Population	Telavancin %	Vancomycin %	Difference % (95% CI)
0015 (n=746)	AT	25.9	20.1	5.8 (-0.3, 11.9)
0019 (n=757)	AT	22.3	24.3	-1.9 (-8.0, 4.2)
Combined (N=1503)	AT	24.2	21.8	2.25 (-2.0, 6.5)

Clinical Response Endpoint

- Prospectively defined and agreed-upon primary endpoint
- Studies powered and designed for the endpoint
- Investigators trained on the endpoint
 - Used objective criteria (Temp, WBC, oxygenation, PE, etc)
- Clinically relevant and intimately linked to purpose of antibiotic treatment (attributable results)
- Evaluation of clinical cure is a key component of the analysis of efficacy of telavancin

Conclusion

- In two adequate and well controlled studies telavancin was noninferior to vancomycin on clinical cure
- In a combined analysis of 28-day mortality (n=1503) telavancin was noninferior to vancomycin
- Further supportive information is available in the approved cSSSI pivotal studies
- Evaluation of telavancin's efficacy by an Advisory Committee should be informed by these findings

Rationale for Pooling

- Studies 0015 and 0019 were methodologically identical and conducted contemporaneously
- Statistical analysis plan called for combining studies for analysis of an efficacy endpoint (albeit not mortality)
- No significant difference between treatment groups of the pooled database on 30 of 31 baseline characteristics
- Confidence intervals for crude mortality rates overlap
- No evidence of differential informative censoring of data
- Multivariate regression analysis identified multiple baseline variables are related to vital status
- Adjusting for prognostic factors, there was no statistically significant interaction between study and treatment for mortality

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/s/

AMY E BERTHA
02/17/2012



NDA 022407

Theravance, Inc.
Attention: Rebecca Coleman, Pharm.D.
Vice President, Regulatory Affairs and Quality
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VIBATIV (televancin) for injection, 250 mg and 750 mg.

We acknowledge receipt on December 7, 2011, of your December 6, 2011, request for formal dispute resolution concerning the December 21, 2010, Complete Response letter to NDA 022407. You are requesting that the FDA approve VIBATIV for the treatment of nosocomial pneumonia or hospital-acquired pneumonia caused by susceptible strains of the following Gram-positive organisms: *Staphylococcus aureus* (including methicillin-resistant isolates) and penicillin susceptible *Streptococcus pneumoniae*. You are requesting that this approval be based on data already submitted to NDA 022407. We also refer to your formal dispute resolution request, received on August 25, 2011, to the Office of Antimicrobial Products (OAP), and the denial of the appeal by Dr. Edward Cox, Director, OAP on October 14, 2011.

Your appeal has been forwarded for review to Dr. John Jenkins, Director, Office of New Drugs (OND), Center for Drug Evaluation and Research. In your appeal you request a meeting to discuss the matter. We are granting your meeting request and have scheduled the following meeting.

Date: January 20, 2012
Time: 1:00 pm – 2:30 pm, EST
Location: 10903 New Hampshire Avenue
White Oak Building #22, Conference Room 1417
Silver Spring, MD 20903

CDER participants (invited):

Center for Drug Evaluation and Research

Robert Temple, M.D., Deputy Center Director for Clinical Sciences

Office of New Drugs

John Jenkins, M.D., Office Director

Beth Duvall, Associate Director for Regulatory Affairs

Amy Bertha, Senior Regulatory Health Project Manager

Office of New Drugs/OAP

Edward Cox, M.D., Office Director

John Farley, M.D., Office Deputy Director and Acting Director, Division of Anti-Infective Products
David Roeder, Associate Director for Regulatory Affairs
Katherine Laessig, M.D., Division Deputy Director, Division of Anti-Infective Products
Janice Pohlman, M.D., Team Leader, Division of Anti-Infective Products
Benjamin Lorenz, M.D., Medical Officer, Division of Anti-Infective Products
Maureen Dillon-Parker, Supervisory Project Manager, Division of Anti-Infective Products
J. Christopher Davi, Regulatory Health Project Manager, Division of Anti-Infective Products

Office of Translational Science/Office of Biostatistics

Lisa Lavange, Ph.D., Office Director
Thamban Valappil, Ph.D., Team Leader, Division of Biometrics IV
Scott Komo, Ph.D., Biometrics Reviewer, Division of Biometrics IV

Please e-mail me a list of your attendees at amy.bertha@fda.hhs.gov. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Please use the visitor main entrance in building 22. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Amy Bertha at (301) 796-1647 or Victor Vail at the OND Immediate Office main number (301) 796-0700.

Subsequent to the meeting, we will respond to the formal dispute request within 30 days of the meeting (February 19, 2012). We will contact you should we have any questions or require additional information. If you have any questions please call me at (301) 796-1647.

Sincerely,

{See appended electronic signature page}

Amy Bertha
Senior Regulatory Health Project Manager
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

cc:
Hyman, Phelps & McNamara, P.C.
Attention: Josephine M. Torrente
Regulatory Counsel
700 Thirteenth Street, NW Suite 1200
Washington, D.C. 20005-5929

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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

/s/

AMY E BERTHA
12/20/2011



NDA 022407

DISPUTE APPEAL – DENIED

Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Senior Director, Regulatory Affairs
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VIBATIV (telavancin) for injection, 250 mg and 750 mg.

We also refer to your August 24, 2011, request for formal dispute resolution, received on August 25, 2011, to the Office of Antimicrobial Products (OAP). The request for dispute resolution concerns the deficiency, stated in our November 23, 2009 and December 21, 2010, complete response (CR) letters, that the NDA does not provide substantial evidence to demonstrate the safety and efficacy of telavancin in the treatment of nosocomial pneumonia (NP). We also refer to the End-of-Review meeting held June 20, 2011.

I have carefully reviewed the materials you submitted in support of your appeal, the reviews and decision memoranda prepared by the Division of Anti-infective Products (DAIP) staff, the CR letters, and other pertinent material (e.g., materials from various Anti-infective Drug Advisory Committee meetings).

I have completed my review of your request for formal dispute resolution and deny your appeal.

The CR letter of December 21, 2010, for your NDA 22-407 that seeks an indication for treatment of patients with NP notes that there is a lack of substantial evidence to support the proposed NP indication. The deficiencies specifically enumerated in the CR letter are the following items:

1. The results of the two phase 3 clinical trials (Studies 0015 and 0019) submitted in this application do not provide substantial evidence to demonstrate the safety and efficacy of telavancin in the treatment of nosocomial pneumonia. While a substantial amount of missing mortality data has been recovered and provided for analysis, the analysis in the population of interest (i.e. patients with nosocomial pneumonia caused by Gram positive bacteria) in Study 0015 does not demonstrate noninferiority of telavancin relative to vancomycin. When the same analysis population was assessed in Study 0019, the observed treatment difference in 28-day all-cause mortality rates is 2.0% (telavancin: 24.3%; vancomycin: 22.3%) and the upper bound of the 95% CI is 10.0%, (-6.1%, 10.0%), and does not provide sufficient evidence for the noninferiority of telavancin to vancomycin.

2. In addition, the method of selection of patients did not provide adequate assurance that they had the disease being studied due to uncertainties with respect to interpretations of chest radiographs and adequacy of respiratory tract specimens.

3. Your analysis method that compares the telavancin-treated patients from your Phase 3 trials to the historical studies of patients receiving inadequate, inappropriate, and delayed therapy is problematic. Specifically, the baseline characteristics of the patients in the telavancin trials patients are not comparable to those in the historical control groups.

4. The pooling of patients across the two Phase 3 trials is not appropriate because subjects in study 0015 had more potential risk factors for mortality (e.g., diabetes mellitus and renal impairment/failure) than the subjects in study 0019.

5. The inclusion of post-hoc selected prognostic risk factors for mortality in the analyses is not acceptable because they may bias the results.

6. The diagnosis of renal failure was left to the discretion of the investigator, and in some cases it was unclear whether some of the patients may have had acute as well as chronic renal failure. For patients with potential risk factors, renal status should have been more specifically defined by standardized measures at entry and followed more closely for at least 28 days.

Before the application can be approved, it will be necessary for you to perform at least two adequate and well-controlled studies to demonstrate the efficacy and safety of telavancin in patients with hospital-acquired bacterial pneumonia.

The CR letter also provides advice on inclusion criteria for future clinical trials in patients with Hospital-Acquired Bacterial Pneumonia / Ventilator-Associated Bacterial Pneumonia (HABP/VABP) and on uniform study procedures for assessment of chest radiographs, respiratory samples, renal function, and the use of adjunctive antibacterial therapy.

I note that the initial request for formal dispute resolution dated April 27, 2011 was denied because an End of Review meeting after the December 21, 2010 CR letter had not been held with the division. The End of Review meeting was held on June 20, 2011 to discuss the division's findings for the application and further clarified the basis for your request for formal dispute resolution. The idea of discussing this application before a meeting of the FDA's Anti-Infective Drugs Advisory Committee was suggested; as you note in your request for formal dispute resolution, you do not believe that an Advisory Committee meeting is warranted.

In your April 27th, 2011, initial request, you raise a number of scientific issues surrounding the data in your submission:

1. You note that studies generally met their pre-specified endpoint based upon clinical response and there is adequate data to approve based upon a clinical response endpoint
2. You question the appropriateness of an endpoint based upon mortality
3. You argue that there is not adequate data to support a non-inferiority margin for an endpoint of mortality
4. You argue that the data in the application are adequate to support the approval of the application based upon a mortality endpoint

In addition, you also argue the following point:

II. D. FDA Refusal to Approve Telavancin on the Basis of Clinical Cure Is Inconsistent with Continued Marketing Approval for Other NP drugs Approved via Clinical Cure Noninferiority Studies

Updated thinking regarding clinical study design and conduct should be retrospectively applied to products whose development is essentially complete only when FDA believes that previous guidance would allow for ineffective or unsafe products to reach US patients. In this event, FDA would be expected to carefully examine the continued marketing of other drugs approved on the bases of the superseded standards, which FDA now views as inadequate to protect public health. Given the continued marketing of three products (linezolid, levofloxacin, and piperacillin/tazobactam) approved to the treatment of NP based on previous FDA guidance, this is not the case regarding recent changes in the guidance development of NP agents.

In your letter of August 24, 2011, you further emphasize your point II.D (as excerpted above),¹ and further state that because this is a primary issue in your argument, that you do not believe discussion of the application at an Advisory Committee meeting is appropriate.

In the way of additional background, discussions regarding the phase 3 clinical development program for telavancin for NP took place in July of 2004 at an End of Phase 2 meeting. The application was initially submitted in January 2009 and a CR letter was issued in November of 2009. This first of two CR letters stated that substantial evidence had not been provided to support the efficacy and safety of telavancin for NP. The letter asks for additional information including mortality data for patients in the NP trials, a scientific rationale for pooling patients in the two studies given the differing baseline characteristics, and provides advice regarding study enrollment criteria and study procedures.

During this same time period that telavancin has been under development for NP, there have been significant advances in our understanding of the science, and interpretation of noninferiority clinical trials and their use in the area of antibacterial drug development (a therapeutic area where noninferiority trials are the types of trials often performed). There had been discussions on the topic of noninferiority clinical trial designs for some indications for antibacterial drugs beginning in 2002. More substantial discussion, including product specific discussions on the application and interpretation of noninferiority clinical trials, have been topics of discussion at more recent FDA Advisory Committee meetings. At the September 12th, 2006 Anti-Infective Drugs Advisory Committee meeting, for a particular antibacterial drug seeking an indication for acute bacterial sinusitis, the issue of the interpretation of noninferiority trial designs was a key issue of discussion at the meeting; the absence of evidence to support a reliable estimate of the treatment effect of the active control drug in the condition being studied (i.e., an evidence base to support a noninferiority margin) was a key issue in the Committee discussions on the evaluation of efficacy. On December 14 and 15, 2006, a meeting of the Anti-Infective Drugs Advisory Committee discussed the antibacterial drug Ketek (telithromycin) for its approved indications (as of December 2006) in the setting of new safety information on adverse effects including hepatotoxicity, visual adverse effects, loss of consciousness, and exacerbations of myasthenia gravis. A critical part of these discussions was the issue of the

¹ Zosyn (piperacillin/tazobactam) was approved for nosocomial pneumonia in 1996 and a new dosing regimen was approved in 2003; Zyvox (linezolid) was approved for nosocomial pneumonia in 2000; Levaquin (levofloxacin) was approved for nosocomial pneumonia in 2002; Cipro IV (ciprofloxacin) has an indication for nosocomial pneumonia that was approved October 21, 1996.

appropriate use and interpretation of noninferiority trials and the importance of having a basis for determining a noninferiority margin in order to have a means of interpreting the trial results for assessing the benefit of the drug. The inability to assess benefit (because of the lack of support for an evidence-based noninferiority margin for the trials) in two of the conditions in the setting of new safety information led to a re-assessment of the risks and benefits of the product for its previously approved indication and the subsequent dropping of two of the indications from the product labeling along with the addition of a boxed Warning and a Medication Guide.² The new safety information was a key factor triggering the Advisory Committee discussion and the re-evaluation of the risks and benefits of Ketek.

The need for having a basis for the noninferiority margin to interpret an NI trial is, and has been, in our regulations at 21CFR 314.126 (b)(2)(iv), where for active treatment concurrent control trials, the following is stated:

(iv) Active treatment concurrent control. The test drug is compared with known effective therapy; for example, where the condition treated is such that administration of placebo or no treatment would be contrary to the interest of the patient. An active treatment study may include additional treatment groups, however, such as a placebo control or a dose-comparison control. Active treatment trials usually include randomization and blinding of patients or investigators, or both. If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective. The analysis of the study should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control drug.

A key point is that it is essential to understand the effect of the control drug in order to know if the study had the capacity to detect a difference in the treatments, if such a difference existed. Our Guidance for Industry: *E 10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001) (ICH E10) also discusses assay sensitivity, *the ability to distinguish an effective treatment from a less effective or ineffective treatment*. ICH E10 describes the importance of understanding the historical evidence of sensitivity of drug effects and that the noninferiority trial should be similar in design and conduct to the trials from which the evidence of drug effect has been derived (e.g., including such elements as a similar endpoint, similar time point for endpoint assessment, patients with the condition of interest with a similar disease severity).

FDA published a guidance for industry titled: *Antibacterial Drug Products: Use of Noninferiority Trials to Support Approval* (published in draft for public comment in October 2007 and then published in final in November of 2010). The document includes a section on providing evidence to support justification for active-controlled trial designed to show noninferiority. The guidance states that

² FDA Telithromycin information webpage, available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107824.htm>

NI trial designs are appropriate only when there is adequate evidence of a defined effect size for the control treatment so that the proposed NI margin can be supported. The time point of the assessment of the efficacy endpoint in the previous trials used to estimate the treatment effect is an important consideration for a proposed NI margin and NI trial design. For an NI trial to be informative, it is critical to have an adequately justified NI margin and to use appropriate efficacy endpoints.

In addition, this guidance document, *Antibacterial Drug Products: Use of Noninferiority Trials to Support Approval* also notes that the following and cites the guidance document on Special Protocol Assessment.³

Sponsors should re-evaluate all ongoing or completed NI trials that will be submitted in a new drug application for antibacterial indications to ensure that there is an adequate scientific basis for the established effect size of the active control and the proposed NI margin. This recommendation applies to trials that may have been previously reviewed by the Office of Antimicrobial Products under an SPA. If substantial scientific issues essential to determining the safety or efficacy of the drug have been identified for the NI trial design used, commitments from the FDA under a SPA may no longer be valid.

The Guidance for Industry, E9 Statistical Principles for Clinical Trials, September 1998 (ICH E9)⁴ states the following regarding non-inferiority margins.

It is vital that the protocol of a trial designed to demonstrate equivalence or noninferiority contain a clear statement that this is its explicit intention. An equivalence margin should be specified in the protocol; this margin is the largest difference that can be judged as being clinically acceptable and should be smaller than differences observed in superiority trials of the active comparator.

The excerpt above describes that the margin “*should be smaller than differences observed in superiority trials of the active comparator*”; this is similar to what is commonly referred to as M1, or the effect that the active control has over a placebo or inactive compound; an evidence-based assessment. The phrase “*this margin is the largest difference that can be judged as being clinically acceptable*” is what is commonly referred to as M2 which is the largest clinically acceptable difference (degree of inferiority or degree of loss of efficacy) of the test drug compared to the active control; a clinical judgment. As stated in ICH E9 in the excerpt above, M2 should be smaller than M1. In order to have an informative and interpretable non-inferiority trial M2 cannot be larger than M1. Typically one selects a noninferiority margin that is smaller than M1 in order to preserve a proportion of the valued effect of the control drug that has led to the decision to utilize an active controlled trial designed to show noninferiority. The concept of appropriate selection of a non-inferiority margin has been in Guidance since September 1998.

In addition to the above, there was an FDA Anti-Infective Drugs Advisory Committee meeting on July 16, 2008 discussing a product seeking an indication for NP, including ventilator-associated pneumonia (VAP). One of the topics of discussion at the meeting was the available data to support a noninferiority margin for a clinical trial in NP and VAP. The FDA presentation on this topic described the available

³ Guidance for Industry: Special Protocol Assessment. May 2002, available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080571.pdf>

⁴ Guidance for Industry: E9 Statistical Principles for Clinical Trials. September 1998. (ICH E9) available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073137.pdf>

data to support an NI margin for NP and VAP for a mortality endpoint, and also noted that we were not able to identify data to support an NI margin for an endpoint of clinical response.

As part of efforts to provide recommendations on clinical trial designs for studies in HAP / VAP and to have public discussions on the topic, FDA also held a co-sponsored public workshop with the Infectious Diseases Society of America on Clinical Trial Design for Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia on March 31 and April 1, 2009. Again as part of these discussions, similar to the July 2008 Advisory Committee meeting, FDA presented data that supported an NI margin for a mortality endpoint for NP and ventilator-associated pneumonia.

Subsequently, FDA published a draft guidance for public comment on recommended trial designs for clinical trials for patients with HAP/VAP that provided as an appendix a detailed evidence-based non-inferiority margin justification for a mortality endpoint for clinical trials of HAP / VAP.

On September 7, 2010, an application for an antibacterial drug was presented to the FDA's Anti-Infective Drugs Advisory Committee for two indications. The trials were originally designed with primary endpoints for which we were unable to support an evidence-based, reliable noninferiority margin. The Agency conducted and presented analyses that evaluated patient response at an earlier timepoint for which we were able to support a noninferiority margin. These analyses that the Agency performed and presented were important in the Advisory Committee's advice on the application and also were essential information in the ultimate approval of the drug.

In general, across a number of therapeutic areas, not just antibacterial drug indications, the topic of appropriate design and interpretation of noninferiority trials has been a topic of considerable interest and attention over the last several years. A draft guidance on the general topic of Non-Inferiority Clinical Trials was published for public comment in March of 2010.⁵ In addition, the use of non-inferiority clinical trials has also been the focus of a recent GAO report.⁶

Hence, the issues of appropriate design and interpretation of noninferiority clinical trials is an issue that is, and has been, in our regulations. The basic principles of appropriate use and interpretation of noninferiority clinical trials has been in guidance documents since before 2001. More recently, there have been a number of public discussions that have contributed to the advancing knowledge on the appropriate use and interpretation of noninferiority trials for evaluating antibacterial drugs in treating patients with different types of bacterial infections. There have been product specific discussions on the topic of appropriate use of noninferiority trials at public FDA Advisory Committee meetings since 2006. Specifically in the area of NP and HAP / VAP, there has also been a product specific FDA Advisory Committee meeting, a public workshop on clinical trial designs, and publication of a draft FDA guidance document for public comment.

You ask that we approve (1) telavancin for NP based upon the results from your clinical trials 0015 and 0019 and (2) also argue that telavancin should be approved because previously approved drugs with NP indications that were (at the time of their approval) based upon clinical response endpoints remain on the market.

⁵ Guidance for Industry: Non-Inferiority Clinical Trials. Draft. March 2010. available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf>

⁶ GAO 10-798. FDA's Consideration of Evidence from Certain Clinical Trials. July 2010. available at <http://www.gao.gov/new.items/d10798.pdf>

Trials 0015 and 0019 were originally designed as noninferiority trials with a clinical response endpoint. As described above, in order to be able to appropriately interpret a noninferiority trial, one needs to have a reliable, evidence-based estimate of the treatment effect for the endpoint being used to assess patient response in the clinical trial(s). In our work to identify data to support a noninferiority margin for trials in NP, HABP / VABP, we have not been able to identify an evidence-based noninferiority margin for a clinical response endpoint for NP, HABP/VABP. We have identified and described a noninferiority margin for a mortality endpoint for trials evaluating an antibacterial drug for treatment of patients with NP, HABP/VABP.

You argue that mortality is not an appropriate endpoint for clinical trials of HABP/VABP and that the data are not sufficient to support determination of a noninferiority margin for a mortality endpoint for clinical trials evaluating an antibacterial drug for treatment of patients with NP, HABP/VABP. I recognize the limitations of the available data that we have worked with in our identification of a noninferiority margin based upon a mortality endpoint for NP, HABP/VABP trials, but I believe that antibacterial drug therapy still has an important effect on mortality in patients with NP (HABP / VABP) and hence, it is reasonable to estimate a treatment effect on mortality. The limitations of the available data from which to estimate treatment effect that you note, and that there is some degree of extrapolation that is needed in applying the historical data to a present day trial, argues for some degree of caution (which may be handled through some degree of discounting) in using the historical data to quantitatively estimate treatment effect. In sum, there is, in my opinion, evidence to support a treatment effect for clinical trials of NP (HABP / VABP) for a mortality endpoint. Survival is an important patient outcome.

An additional issue for consideration is the appropriate population for evaluating the effect of telavancin for treatment of NP. Given that the spectrum of activity of telavancin is against Gram-positive bacteria, it would not be appropriate to evaluate the efficacy of telavancin against bacteria for which the drug is not active, especially in a noninferiority trial where patients are receiving adjunctive drug therapy (and appropriately so) for the treatment of these pathogens outside the spectrum of activity of telavancin. As you note in your April 27, 2011 letter, for analysis populations (for example, patients with mixed Gram-positive and Gram-negative infections) some antibacterial therapy directed against Gram-negative bacteria may have activity against Gram-positive bacteria, and this may confound the evaluation of patient outcomes. Another related issue that affects the appropriate analysis population is the role or effect of prior or concomitant antibacterial drug therapy. In addition, as noted in the CR letter, questions were also raised regarding the inclusion criteria and study procedures for enrollment into the trials.

Analyses of outcomes on multiple subsets of patients from the trial have been performed. For example, analyses excluding patients with only Gram-negative pathogen(s) at baseline, analysis of the subset of patients that had only a Gram-positive pathogen at baseline for the endpoint of mortality, analyses on patients with MRSA at baseline who did not receive other active agents against MRSA, and patients with Gram-positive patients without renal failure at baseline. In some analyses, the 95% confidence intervals (CI) extend beyond a 10% bound. In addition to the multiple analyses that have been performed with varying results across the multiple subsets, there is also the issue of some remaining mortality data that is missing. However, we do recognize the considerable efforts that Theravance undertook to go back to collect as much mortality data as possible.

There are a number of issues that have been identified in your application that would benefit from additional analysis and discussion at an FDA Advisory Committee meeting. They include, the question of appropriate analysis populations, that the trials were originally designed with a different

endpoint and numerous analyses and subset analyses have been performed, the impact of prior and/or concomitant/adjunctive antibacterial drug therapy, enrollment criteria for the trials and study procedures (please also see the bulleted list that follows on p. 9 of this letter. I do not find that the analyses of the existing data are sufficient to support approval of telavancin for NP. Your request for approval for NP based upon the existing analyses of the data for telavancin for NP is therefore denied.

You also raise a second issue and argue that telavancin should be approved because there are previously approved drugs with indications for NP that remain on the market. Advances in the science of clinical trials and methods for the assessments of safety and efficacy of drugs are inevitable. In some instances, these advances may lead us in a different direction than past practices. In general, when there have been advances in science over time, we have not systematically gone back and reviewed previously approved drugs unless a particular issue has arisen such as a significant new safety issue(s). As described for Ketek (telithromycin), the approved indications and the risk/benefit for the approved indications was evaluated, considering the benefit of the drug based on a contemporary assessment in view of the advancing science weighed against the new safety data characterizing risk. This re-evaluation in the setting of new safety findings led to two indications being dropped from the product labeling, the addition of a boxed Warning and a Contraindication statement, and the addition of a Medication Guide.

When there are advances in the science, we need to judge the application(s) that we have pending before us based upon the information that is presented to us and our best scientific understanding at that time. We cannot ignore significant recent scientific advances when making our approval decisions. We need to judge the application for telavancin based upon the information submitted to us and our current scientific knowledge in the area.

This issue of advancing science on the appropriate use and interpretation of noninferiority trials is not unique to telavancin, but is an issue that we have faced for other applications where scientific advances have led to significant questions about the interpretation of noninferiority trials presented in an application seeking approval. We have approached these similar situations for each of several applications that we have encountered during this same time period consistently. Therefore, your request for approval of telavancin because other previously approved drugs for NP that utilized a clinical response endpoint in the past continue to be marketed is denied.

I think that it would be valuable to discuss this application at a meeting of the FDA Anti-Infective Drugs Advisory Committee to address issues including:

- The trials were originally designed with different primary endpoints and numerous subgroup analyses are being analyzed to evaluate a mortality endpoint.
- Collection and evaluation of respiratory tract samples and radiographic evaluation for patients enrolled in the trials
- The role and effect of prior and/or concomitant antibacterial drug therapy, empiric therapy, and de-escalation of adjunctive antibacterial drug therapy in the interpretation of trial results
- The appropriate analysis population, given that the spectrum of activity of telavancin is against Gram-positive organisms and that patients may have received prior or concomitant antibacterial drug therapy
- The role of supporting data from other indications and the role that such information may play in whether one trial vs. two trials can provide sufficient information to support the indication you seek

- The analysis of mortality data in patients with baseline renal failure and the definition of renal failure as applied in the clinical trials

We appreciate the continued very professional discussions on these issues that we have had with you. We recognize the considerable challenges that have been faced over the last several years in the setting of advancing scientific knowledge in the field of antibacterial drug development. If it would be helpful to you, I would be happy to meet with you to further discuss my decision on this formal dispute resolution.

We also recognize the important public health need for continued development of new antibacterial drugs and we continue to work on the issues and challenges, many of which are derived from the biology of acute bacterial diseases, of clinical trials to evaluate new antibacterial drugs.

Questions regarding next steps as described in this letter should be directed to J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

If you wish to appeal this decision to the next level, your appeal should be directed to John Jenkins, M.D., Director, Office of New Drugs, Center for Drug Evaluation and Research. The appeal should be sent to the NDA administrative file as an amendment, and a copy should be sent to the Center's Dispute Resolution Project Manager, Amy Bertha. Any questions concerning your appeal should be addressed to Ms. Bertha at (301) 796-1647.

Sincerely,

{See appended electronic signature page}

Edward Cox, M.D., M.P.H.
Director
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

cc: Hyman, Phelps, McNamara, P.C.
Attention: Josephine Torrente
700 13th Street NW, Suite 1200
Washington, DC 20005-5929

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/s/

EDWARD M COX
10/14/2011



NDA 22-407

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Theravance, Inc.
Attention: Jovanna Nembhard
Senior Manager, Clinical Drug Safety
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Applicant:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Telavancin sterile lyophilized powder for Injection.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

¹ These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions regarding this letter, please contact Maureen Dillon-Parker, Chief, Project Management Staff, at (301) 796-0706. For any other issues regarding this NDA, please contact J. Christopher Davi, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Acting Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JOHN J FARLEY
09/30/2011



NDA 022407

ACKNOWLEDGE DISPUTE APPEAL

Theravance, Inc.
Attention: Rebecca Coleman, Pharm.D.
Vice President, Regulatory Affairs and Quality
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VIBATIV (televancin) for injection, 250 mg and 750 mg.

We acknowledge receipt on August 25, 2011, of your August 24, 2011, request for formal dispute resolution concerning the Agency's December 21, 2010, Complete Response letter to NDA 022407. You are requesting that the Agency approve VIBATIV for the treatment of nosocomial pneumonia or hospital-acquired pneumonia caused by susceptible strains of the following Gram-positive organisms: *Staphylococcus aureus* (including methicillin-resistant isolates) and penicillin susceptible *Streptococcus pneumoniae*. You are requesting that this approval be based on data already submitted to NDA 022407.

Your appeal has been forwarded for review to Dr. Edward Cox, Director of the Office of Antimicrobial Products, Center for Drug Evaluation and Research, and a response will be provided by September 24, 2011. We will contact you should we have any questions or require additional information.

If you have any questions, please call me at (301) 796- 0799.

Sincerely,

{See appended electronic signature page}

David Roeder
Associate Director for Regulatory Affairs
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

DAVID L ROEDER
08/26/2011



NDA 22-407

MEETING MINUTES

Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Vice President, Regulatory Affairs and Quality
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vibativ (telavancin) for injection.

We also refer to the meeting between representatives of your firm and the FDA on June 20, 2011. The purpose of the meeting was to discuss the complete response letters from the Agency dated November 23, 2009, and December 21, 2010.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Katherine A. Laessig, MD
Deputy Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: A
Meeting Category: End of Review

Meeting Date and Time: June 20, 2011
Meeting Location: CDER White Oak Campus

Application Number: 22-407
Product Name: Vibativ (telavancin for injection)
Indication: Nosocomial pneumonia (NP)
Sponsor/Applicant Name: Theravance, Inc.

Meeting Chair: Edward Cox, MD, MPH
Director, Office of Antimicrobial Products (OAP)

Meeting Recorder: J. Christopher Davi, MS, Senior Regulatory Project Manager,
Division of Anti-Infective Products (DAIP)

FDA ATTENDEES

Edward Cox, MD, MPH, Director, Office of Antimicrobial Products (OAP)
John Farley, MD, MPH, Acting Director, DAIP
Katherine A. Laessig, MD, Deputy Director, DAIP
Sumathi Nambiar, MD, MPH, Deputy Director, DAIP
Janice K. Pohlman, MD, MPH, Clinical Team Leader, DAIP
Benjamin Lorenz, MD, Clinical Reviewer, DAIP
Daphne Lin, PhD, Supervisory Mathematical Statistician, OTS
Thamban Valappil, PhD, Biostatistics Team Leader
Scott Komo, DrPH, Biostatistics Reviewer
Dakshina Chilukuri, PharmD, Acting Clinical Pharmacology Team Leader
Aryun Kim, PharmD, Clinical Pharmacology Reviewer
David L. Roeder, MS, Associate Director of Regulatory Affairs, OAP
J. Christopher Davi, MS, Senior Regulatory Project Manager, DAIP

SPONSOR ATTENDEES (Theravance, Inc.)

Steven Barriere, PharmD, Clinical and Medical Affairs
Rebecca Coleman, PharmD, Regulatory Affairs and Quality
Joanne DiGiorgioi, Regulatory Affairs
Alan Hopkins, PhD, Biostatistics
Rick Winningham, CEO, Theravance
Josephine Torrente, Hyman and Phelps
Frank Sasinowski, Hyman and Phelps
Laura Kovanda, Project Management, Astellas
Robert Reed, Regulatory Affairs, Astellas

BACKGROUND

The Division of Anti-Infective Products granted Theravance a Type A end of review (EOR) meeting to discuss the complete response letters issued by the Agency on November 23, 2009, and December 21, 2010. The meeting was a post-action meeting following the December 21, 2010, Complete Response letter. Discussion points are recorded herein.

DISCUSSION

FDA noted that there are complex scientific issues involved with the application and recommended that an Advisory Committee (AC) meeting might be the best forum in which to discuss these issues. At an AC meeting, both the FDA and Theravance could present their viewpoints.

Theravance indicated that an AC meeting was not their preferred approach. In their view, the question was not so much one of science, but one of regulatory policy. The Agency cautioned that regulatory and scientific issues may not necessarily be able to be separated, and that an AC meeting may be an appropriate way to address the remaining issues.

Theravance was concerned that a third review cycle with an AC meeting would cause considerable delay. The Agency responded that an AC meeting could be held outside of a formal review cycle (i.e., the meeting can be convened without the NDA being resubmitted).

Theravance noted that their non-inferiority (NI) margin was based on discussions with the Agency at the time the trial was designed, and they (Theravance) believed that the NI margin was relatively “conservative” compared to other products with nosocomial pneumonia (NP) indications.

The Agency noted that the scientific evidence evaluated to date supporting a NI margin for this indication is for all cause mortality as the primary endpoint. The Agency also noted that the topic of NI has been discussed at several public meetings. In 2006, FDA AC meetings were held to discuss gemifloxacin for acute bacterial sinusitis (ABS) and Ketek for ABS, acute bacterial exacerbation of chronic bronchitis (ABECB) and community acquired pneumonia (CAP), where having an evidence-based NI margin justification was one of the major points of the meetings.

Theravance stated that they (Theravance) formulated their NI justification based on guidance from the Division, and they wished to discuss the studies “as designed”. Theravance stated their position is that the “new standards” should not apply to telavancin and indicated that they wanted the Agency to consider these issues.

Theravance asked for some type of “regulatory flexibility,” indicating that the studies as they stand are “far-off” from being able to be viewed in the context of the M1/M2 argument. Theravance suggested a scenario where approval might be considered based on clinical response as the primary endpoint with mortality as a safety endpoint.

The Agency indicated that, if the application is taken to an AC meeting, possible topics for discussion might include:

- The need for one trial versus two trials
- Appropriate analysis for a trial with Vibativ, which only has Gram positive coverage
- The effect of potentially effective non-study antibacterial drugs (PENS) and appropriate de-escalation of adjunctive antibacterial drug therapy
- The use of mortality data in the analyses of their trials
- Poor outcome of patients with renal failure
- Discussion of M1 versus M2 with regard to the preservation of treatment effect
- Expecterated sputum results versus tracheal aspirate results in terms of their reliability

The meeting ended with an understanding that Theravance would consider this discussion in determining their next steps.

-End

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/s/

KATHERINE A LAESSIG
07/21/2011



NDA 22-407

MEETING REQUEST GRANTED

Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Vice President, Regulatory Affairs and Quality
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vibativ (telavancin hydrochloride for injection) 250 mg and 750 mg.

We also refer to your May 13, 2011, correspondence requesting a meeting to discuss the complete response letter from the Agency dated December 21, 2010. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

Date: June 20, 2011
Time: 11:30 AM to 12:30 PM, EST
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

CDER participants:

Edward M. Cox, MD, MPH, Office Director, Office of Antimicrobial Products (OAP)
John Farley, MD, Acting Division Director, Division of Anti-Infective Products (DAIP)
Katherine A. Laessig, MD, Deputy Director, DAIP
Janice K. Pohlman, MD, MPH, Medical Team Leader, DAIP
Benjamin Lorenz, MD, Medical Reviewer, DAIP
Thamban Valappil, PhD, Biostatistics Team Leader, DAIP
Scott Komo, DrPH, Biostatistics Reviewer, DAIP
Aryun Kim, PhD, Clinical Pharmacology Reviewer, DAIP
Kerry Snow, MS, Clinical Microbiology Reviewer, DAIP
David L. Roeder, MS, Associate Director of Regulatory Affairs, OAP
J. Christopher Davi, MS, Senior Regulatory Project Manager, DAIP

Please e-mail any updates to your attendees to J. Christopher Davi at christopher.davi@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with the following number to request an escort to the conference room: (301) 796-0702.

We acknowledge receipt of your background materials for this meeting on May 13, 2011. If the materials presented in the information package are inadequate to prepare for the meeting, we may cancel or reschedule the meeting.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Maureen Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	June 20, 2011 @ 11:30 AM
MEETING ENDING DATE AND TIME	June 20, 2011 @ 12:30 PM
PURPOSE OF MEETING	Post action discussion
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	WO Bldg. 22, Conference Room 1309
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	J. Christopher Davi, MS Sr. Regulatory Project Manager WO Bldg. 22, Room 6121 (301) 796-0702
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

MAUREEN P DILLON PARKER
06/09/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022407

Hyman, Phelps, McNamara, P.C.
Attention: Frank Sasinowski
700 13th Street NW, Suite 1200
Washington, DC 20005-5929

Dear Mr. Sasinowski:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VIBATIV (telavancin) for injection, 250 mg and 750 mg.

We acknowledge receipt on April 28, 2011, of your April 28, 2011, request for formal dispute resolution. The appeal concerns the complete response action taken on December 21, 2010, specifically the deficiency that the NDA does not provide substantial evidence of efficacy and that before the application can be approved, at least two additional adequate and well-controlled studies must be performed.

In accordance with the procedures for dispute resolution described in the *Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level"* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079743.pdf>), the appropriate course of action for a sponsor that disagrees with a decision is to first request reconsideration of the matter by the division before the issue may be appealed to the next higher management level. In instances where a sponsor disagrees with a complete response action, our practices have been that the sponsor requests a post-action meeting with the division to discuss the sponsor's concerns with the decision. If a sponsor chooses not to take the advice that the division provides at the post-action meeting, the sponsor may proceed with the formal dispute resolution process.

Since a post-action meeting has not been held between the Division of Anti-Infective Products (DAIP) and you following the December 21, 2011 complete response action, it would be inappropriate to consider this matter under formal dispute resolution at this time. We believe that there is value in your having a post-action meeting with the DAIP to discuss your concerns. This will provide an opportunity for further productive discussion on the data in your application for Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia (HABP/VABP).

Please submit a meeting request for a post-action meeting to the NDA administrative file. We will work to schedule this meeting as soon as a mutually agreed upon date can be found. Ed Cox, Director, Office of Antimicrobial Products (OAP), will attend that meeting in a non-

decisional capacity, so that he may hear your concerns directly. If you have any questions, contact J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

If, after this meeting, the issue is still not resolved to your satisfaction, you may appeal the matter to the Director of OAP. If you have any questions regarding the formal dispute resolution process, you may call me at (301) 796-1647.

Sincerely,

{See appended electronic signature page}

Amy Bertha
CDER Formal Dispute Resolution Project Manager
Office of New Drugs
Center for Drug Evaluation and Research

cc: Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Senior Director, Regulatory Affairs
901 Gateway Boulevard
South San Francisco, CA 94080

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/s/

AMY E BERTHA
05/10/2011



NDA 22-407

ACKNOWLEDGE CLASS 2 RESPONSE

Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Vice President, Regulatory Affairs and Quality
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

We acknowledge receipt on June 30, 2010, of your June 30, 2010, resubmission to your new drug application for VIBATIV (telavancin for injection) 250 mg and 750 mg.

We consider this a complete, class 2 response to our November 23, 2009, action letter. Therefore, the user fee goal date is December 30, 2010.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22407	ORIG-1	THERAVANCE INC	VIBATIV

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/s/

Frances V LESANE
08/03/2010



NDA 22-407

MEETING MINUTES

Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Senior Director, Regulatory Affairs
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VIBATIV (telavancin) for injection, 250 and 500 mg.

We also refer to the meeting between representatives of your firm and the FDA on May 25, 2010. The purpose of the meeting was to discuss your future complete response submission in response to our November 23, 2009, action letter.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Katherine A. Laessig, MD
Deputy Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures: Minutes from meeting
Agency's preliminary comments dated May 21, 2010
Sponsor's slide presentation



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: Pre-Class 2 Resubmission

Meeting Date and Time: May 25, 2010
Meeting Location: White Oak

Application Number: 22-407
Product Name: Vibativ (telavancin hydrochloride)
Indication: Nosocomial Pneumonia
Sponsor/Applicant Name: Theravance

Meeting Chair: Wiley A. Chambers, MD, Acting Division Director
Meeting Recorder: J. Christopher Davi, MS, Regulatory Project Manager

FDA ATTENDEES

Wiley A. Chambers, MD, Acting Division Director
Katherine A. Laessig, MD, Deputy Division Director
Janice K. Pohlman, MD, MPH, Medical Team Leader
Sumathi Nambiar, MD, MPH, Deputy Director for Drug Safety
Ryan Owen, PharmD, Clinical Pharmacology Reviewer
Thamban Valappil, PhD, Biostatistics Team Leader
Scott Komo, PhD, Biostatistics Reviewer
David L. Roeder, MS, Associate Director of Regulatory Affairs
J. Christopher Davi, MS, Senior Regulatory Project Manager

SPONSOR ATTENDEES

Steve Barriere, Pharm.D., Clinical and Medical Affairs
Rebecca Coleman, Pharm.D., Regulatory Affairs and Quality
Alan Hopkins, Ph.D., Biostatistics
Joanne DiGiorgio, Regulatory Affairs
Edie Smith, Project Management

(b) (4)

Rochelle Maher, Global Development (Astellas)
Robert Reed, Regulatory Affairs (Astellas)
Peter Potgeiter, MD, Clinical and Medical Affairs

BACKGROUND

The Sponsor requested a Type A meeting to discuss their Class 2 resubmission to the Agency's November 23, 2009, complete response letter. The Division provided preliminary answers to the questions provided in the Sponsor's briefing document on May 21, 2010 (appended). Discussion points generated from these answers are included herein.

DISCUSSION

- The Sponsor discussed the primary endpoint issue, indicating that if they switch the primary endpoint at this stage to mortality, it will be difficult for them to estimate M1 in terms of how it relates to placebo historically. The Sponsor felt that such an exercise would be good as a supplementary analysis, since the primary endpoint analysis wasn't pre-specified as such. However, the Division has already stated that the historical evidence for the determination of an NI margin can only be derived for a mortality endpoint.
- The Division addressed concerns about historical controls in general, and emphasized the need for establishing patient comparability with respect to baseline characteristics to be able to make any kind of inference based on the results. The Division cautioned that if the historical populations are not comparable to the current studies, then they are of little value.
- The Sponsor expressed the opinion that it is not necessarily critical that they "match" subjects from recent studies with their historic counterparts, but rather it should be demonstrated that disease severity was similar between the two populations (i.e., at least as severe on the inclusion/exclusion criteria).
- The Division acknowledged this, but stated that the issue lies in knowing what factors need to be compared to make sure that the patients are of similar disease severity. If many parameters for this determination remain unknown, then certain judgments cannot be made. Comparability of historical data to studies 0015 and 0019 with respect to age, severity, % of ventilated patients and other prognostic factors that are associated with mortality should be established. There are several potential uncertainties in the historical data including, but not limited to, observational/non-randomized patients, unknown clinical criteria for patient selection, unknown mortality reporting periods, patient management, lack of information on concomitant medications used, lack of information on documented pathogens, etc. It is recommended that these factors should be considered while establishing comparability in order to make valid comparisons of treatment effect.
- The Sponsor indicated that they would provide a detailed analysis in the resubmission to demonstrate that patients from Studies 0015 and 0019 were analogous to those in the historical controls.

- The Sponsor felt that any biases typically trended in the direction of underestimating the placebo mortality rate. Matching the patient populations may not hold as much weight, provided that the prevailing trend is toward the underestimation of M1. The Sponsor stated that if they could support the underestimation of M1 in a significant way, it may mitigate some of the Division's concerns.
- The Division acknowledged this, but expressed concern that the differences in patient management can impact the mortality rates. Furthermore, the Division emphasized the need for the NI margin justification to be based on the relevant patient population and pathogens. Historical evidence of control effect (M1) was estimated in patients with Gram negative pathogens, predominantly with *P. aeruginosa* and using non-randomized patients. However, telavancin has activity only against Gram positive pathogens that include *S. aureus*. The Division stressed that the active control effect should be estimated in patients with Gram positive pathogens, unless it can be demonstrated that the active control effect in both Gram positive and Gram negative organisms is similar.
- The Division indicated that the Sponsor should perform an analysis without adjusting for any covariates. Any covariate adjustment should have been pre-specified prior to unblinding the data. The Sponsor expressed concern that they had no opportunity to pre-specify any covariates, since the trials were designed based on a clinical response endpoint.
- The Division recommended that the primary analysis population should only include Gram positive pathogens identified at baseline. The Sponsor expressed concern that this will significantly reduce the sample size and would affect the statistical power. They also raised concern that this may affect randomization. The Sponsor felt this would doom the studies to failure.
- The Division acknowledged the issue about the loss in study power, but stated that it will not affect the randomization since it is based on a baseline characteristic. The Division cited concerns about the reliability of the treatment effect if patients with Gram negatives are included in the analysis, knowing that the drug has no activity against them. The Division noted however, that these are our recommendations and it is the Sponsor's choice regarding how they want to perform the statistical analysis.
- The Sponsor felt that the 10% non-inferiority (NI) margin for mortality was reasonable if the control mortality rate is more than 20%, but expressed concern about the implications with point estimates with a margin less than 10%.
- The Division stated that this has more to do with M2 and deciding on what non-inferiority margin is clinically acceptable for mortality endpoint. The Division added that the argument is not necessarily scientifically driven, but that many in the Division are currently of the opinion that 7% is a more reasonable non-inferiority margin.
- The Sponsor indicated that with a 7% NI, one almost gets to the point where a placebo controlled trial would be ethical.

- The Division re-stated that the choice of M2 is not scientifically driven but based on clinical judgment. It has more to do with the desire not to approve inferior drugs, particularly for products with a mortality endpoint.
- The Sponsor indicated that they would try to demonstrate that studies 0015 and 0019 stand alone at the 10% NI margin, and that when combined, they could possibly meet a 7% NI margin (i.e., if both studies trend in the proper direction). The Sponsor agreed that it is a judgment call as to where M2 ends up.
- The Division stated that there are differences in the baseline characteristics of the patients enrolled in studies 0015 and 0019 and combining them is not recommended. However, the Division would consider the pooled analysis as a sensitivity analysis.

ATTACHMENTS AND HANDOUTS

Agency's preliminary comments dated May 21, 2010
Sponsor's slide presentation

Dr. Coleman,

In anticipation of our meeting on May 25, 2010, for NDA 22-407, please see the following responses (*italics*) to the questions posed in your briefing document dated May 10, 2010:

1. The draft statistical analysis plan (Appendix 1) proposes a three-step approach to analysis of the mortality data in Studies 0015 and 0019. Please comment on the acceptability of this approach. Which of the analysis objectives can be used to support a conclusion regarding the efficacy of telavancin?

Agency Response:

We have several concerns with your proposal.

- a. *Relying on a historical control based on inadequate/delayed therapy studies without a thorough evaluation as to the comparability of the two groups (see response to question #2) is problematic. Without confidence that the two groups are comparable, this analysis is prone to potential biases. The comparability of the historical data to the data based on studies 0015 and 0019 should be assessed based on age, APACHE-II scores, % of ventilated patients, primary documented pathogens, adjunctive medications used, ancillary care and management etc. as these factors can significantly impact the treatment effect and make the comparison less reliable. For example, we might expect in this case for the historical control rate to be estimated from patients with *S. aureus* rather than from patients with *Pseudomonas aeruginosa*.*
- b. *Given the concerns with the comparability of the groups addressed in (a) we believe that some degree of discounting should be applied to any determination of an NI margin.*

The following issues/limitations should be considered to assess the appropriate discounting when estimating M1:

- *Differences in historical studies and its designs*
 - *Differences in baseline patient characteristics*
 - *Concomitant medications used*
 - *Distribution of measured and unmeasured prognostic factors that are potentially associated with mortality*
 - *Prevalence of documented bacterial pathogens*
 - *Mortality reporting time periods, which are aspects of clinical trials that can affect constancy.*
 - *Advances in medical technology, standard of care, and management.*
- c. *The comparison between telavancin and vancomycin is proposed to include post-hoc selected variables assumed to predict mortality; this is problematic because it is a data-driven analysis and can bias the results. We recommend not including any covariates in the primary analysis. We also recommend that the primary analysis population be the microbiological ITT population including only patients with Gram positive and mixed Gram positive/Gram negative bacterial*

infections at baseline assigned to the treatment groups as they were originally randomized.

2. Do the reviewers conclude that the populations enrolled in the telavancin NP studies are similar to the populations enrolled in published studies of other treatments for NP?

Agency Response:

We believe that there is currently insufficient information provided to determine if the patients in the current telavancin trials are similar to the patients in the historical inadequate/delayed therapy studies.

3. Do the reviewers conclude that the published data for other drugs approved for use in NP bolster the credibility of results in Studies 0015 and 0019?

Agency Response:

No.

4. Is the 10% NIM proposed for the analysis of non-inferiority for mortality in the telavancin studies justified by the supporting information provided?

Agency Response:

No. We do not agree with the proposed calculation of M1 based on the issues identified above. In addition, we continue to have concern with an M2 margin in this population that is as high as 10%.

5. Do the reviewers conclude that the overall adequacy of respiratory specimens provide sufficiently reliable information regarding the pathogens responsible for the bacterial pneumonias in these patients?

Agency Response: *The list of criteria to assess reliability of sputum and ETA microbiologic cultures for pathogen determination are generally accepted and therefore satisfactory, although the lack of standardization in quantitative methods for assessment between different institutions as described in previous meetings between the FDA and Theravance raise this issue as a concern. Subject to the review of additional data, at this time, we do not consider the adequacy of respiratory specimens to be a principle issue with this application.*

6. Do the reviewers conclude that the chest radiograph data are reliable and supportive of the clinical diagnosis of pneumonia for patients enrolled in the studies?

Agency Response: *As previously noted by you at the pre-NDA meeting, the assessment of chest X-rays was performed by treating physicians (investigators) and radiology reports were not obtained. Based on information presented in this package, it is estimated that radiographic reports are now available for approximately 72% of the patient population, with source documentation signed by the investigator (and/or radiologist) able to account for an additional 13% of reports and 15% of patient reports missing based on the retrospective retrieval of results from investigational*

sites. Confidence in the appropriate selection of patients at study entry could have been strengthened by an independent verification of the chest radiographs. Instead, during a treatment-blinded review of a random sample of CRFs, discrepancies between radiographic reports and CRF data were noted. In some cases, the reports were not consistent with a diagnosis of pneumonia.

We acknowledge your plan to use chest X-rays, along with at least two other clinical signs (fever, with temperature > 38°C, leukocytosis or leukopenia, and/or purulent secretions) as a means of identifying an analysis population more likely to have a diagnosis of nosocomial pneumonia. While we agree with measures to assure that the most appropriate patient population is studied and analyzed, the need for retrospectively assessing whether patients enrolled in the clinical trial actually had a diagnosis consistent with nosocomial pneumonia raises concern about overall conclusions reached based on trial analyses. Reliability of chest radiographs will need to be considered in any subsequent review of the data.

7. Do the reviewers conclude that the duration and extent of Gram-negative coverage did not differentially impact mortality in the two treatment groups in these studies?

Agency Response: During the first cycle review, determination of whether an anti-infective was considered to be “potentially effective” differed at times between our reviewers and your assessment. Therefore, additional review of data on the impact of the nature and extent of Gram negative bacterial coverage is necessary to conclude that this did not differentially impact mortality.

8. Do the reviewers conclude that a single study in NP with a positive result for all cause mortality, along with supportive data, qualifies as sufficient evidence under the statutory standard described in FDAMA 115?

Agency Response: In general, reliance on a single trial is generally limited to situations in which the trial has demonstrated statistically strong evidence of a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. We do not believe that such an effect was observed in the telavancin NP trials.

9. We intend to prepare an addendum to the ISE for NDA 22-407 that will focus on analysis of the mortality endpoint and include information responsive to the other issues cited in FDA comments on the application. An outline of the changes proposed in the application is provided in Appendix 2. Is the proposed organization and format of the resubmission acceptable?

Agency Response: Mortality analyses should be included in Module 2, Section 2.7.3.6 Synopsis of Clinical Studies (for both 0015 and 0019) and added to Module 5, Sections 5.3.5.1.0015 and 5.3.5.1.0019.

10. What is the role of the protocol-defined endpoint of clinical response? Can this supportive data appear in the product label, as with other drugs in the class?

Agency Response: Based on the available information identified to date, the primary efficacy endpoint for which we are able to justify an NI margin is the 28-day

mortality. Therefore it is unlikely that clinical response information would be included in product labeling at the present time.

We look forward to our discussion with you on May 25, 2010. If you have questions in the interim, please contact me at (301) 796-0702.

J. Christopher Davi, MS
Sr. Regulatory Project Manager
DAIOP

Telavancin NDA 22-407

25 May 2010

Question 1

The draft statistical analysis plan proposes a three-step approach to analysis of the mortality data in Studies 0015 and 0019. Please comment on the acceptability of this approach. Which of the analysis objectives can be used to support a conclusion regarding the efficacy of telavancin?

Analysis Objectives

1. Is telavancin treatment "effective" in the traditional sense of providing a clinical benefit that is greater than a placebo effect?
2. What is the estimate of the relative efficacy of telavancin and vancomycin treatments?
3. Is telavancin treatment "effective" in the sense of providing a benefit that is not substantially worse than vancomycin control treatment? (NI approach to 2)

Proportional Hazards Regression Analyses

- The objective of these analyses is to make the treatment groups comparable for purposes of comparing treatments in this dataset.
- Nine factors have been identified in our data for which there is a correlation with mortality in nosocomial pneumonia.
- Adjustments to the SAP are warranted since the primary endpoint was changed after NDA submission - no opportunity to prespecify.
- Important to understanding this complex disease

Analysis Population

mITT

- Integrity of randomization lost
 - Excludes half the study patients
- Avoid selection bias inherent with subpopulations defined using post-randomization events

ITT

- NIM based on ITT populations from historical studies
- All-cause mortality endpoint best assessed using full patient cohort

Question 4

Is the 10% NIM proposed for the analysis of non-inferiority for mortality in the telavancin studies justified by the supporting information provided?

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22407	GI-1	THERAVANCE INC	VIBATIV

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/s/

KATHERINE A LAESSIG
06/03/2010

Dr. Coleman,

In anticipation of our meeting on May 25, 2010, for NDA 22-407, please see the following responses (*italics*) to the questions posed in your briefing document dated May 10, 2010:

1. The draft statistical analysis plan (Appendix 1) proposes a three-step approach to analysis of the mortality data in Studies 0015 and 0019. Please comment on the acceptability of this approach. Which of the analysis objectives can be used to support a conclusion regarding the efficacy of telavancin?

Agency Response:

We have several concerns with your proposal.

- a. *Relying on a historical control based on inadequate/delayed therapy studies without a thorough evaluation as to the comparability of the two groups (see response to question #2) is problematic. Without confidence that the two groups are comparable, this analysis is prone to potential biases. The comparability of the historical data to the data based on studies 0015 and 0019 should be assessed based on age, APACHE-II scores, % of ventilated patients, primary documented pathogens, adjunctive medications used, ancillary care and management etc. as these factors can significantly impact the treatment effect and make the comparison less reliable. For example, we might expect in this case for the historical control rate to be estimated from patients with S. aureus rather than from patients with Pseudomonas aeruginosa.*
- b. *Given the concerns with the comparability of the groups addressed in (a) we believe that some degree of discounting should be applied to any determination of an NI margin.*

The following issues/limitations should be considered to assess the appropriate discounting when estimating M1:

- *Differences in historical studies and its designs*
 - *Differences in baseline patient characteristics*
 - *Concomitant medications used*
 - *Distribution of measured and unmeasured prognostic factors that are potentially associated with mortality*
 - *Prevalence of documented bacterial pathogens*
 - *Mortality reporting time periods, which are aspects of clinical trials that can affect constancy.*
 - *Advances in medical technology, standard of care, and management.*
- c. *The comparison between telavancin and vancomycin is proposed to include post-hoc selected variables assumed to predict mortality; this is problematic because it is a data-driven analysis and can bias the results. We recommend not including any covariates in the primary analysis. We also recommend that the primary analysis population be the microbiological ITT population including only patients with Gram positive and mixed Gram positive/Gram negative bacterial*

infections at baseline assigned to the treatment groups as they were originally randomized.

2. Do the reviewers conclude that the populations enrolled in the telavancin NP studies are similar to the populations enrolled in published studies of other treatments for NP?

Agency Response:

We believe that there is currently insufficient information provided to determine if the patients in the current telavancin trials are similar to the patients in the historical inadequate/delayed therapy studies.

3. Do the reviewers conclude that the published data for other drugs approved for use in NP bolster the credibility of results in Studies 0015 and 0019?

Agency Response:

No.

4. Is the 10% NIM proposed for the analysis of non-inferiority for mortality in the telavancin studies justified by the supporting information provided?

Agency Response:

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Agency Response: *The list of criteria to assess reliability of sputum and ETA microbiologic cultures for pathogen determination are generally accepted and therefore satisfactory, although the lack of standardization in quantitative methods for assessment between different institutions as described in previous meetings between the FDA and Theravance raise this issue as a concern. Subject to the review of additional data, at this time, we do not consider the adequacy of respiratory specimens to be a principle issue with this application.*

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sites. Confidence in the appropriate selection of patients at study entry could have been strengthened by an independent verification of the chest radiographs. Instead, during a treatment-blinded review of a random sample of CRFs, discrepancies between radiographic reports and CRF data were noted. In some cases, the reports were not consistent with a diagnosis of pneumonia.

We acknowledge your plan to use chest X-rays, along with at least two other clinical signs (fever, with temperature > 38°C, leukocytosis or leukopenia, and/or purulent secretions) as a means of identifying an analysis population more likely to have a diagnosis of nosocomial pneumonia. While we agree with measures to assure that the most appropriate patient population is studied and analyzed, the need for retrospectively assessing whether patients enrolled in the clinical trial actually had a diagnosis consistent with nosocomial pneumonia raises concern about overall conclusions reached based on trial analyses. Reliability of chest radiographs will need to be considered in any subsequent review of the data.

7. Do the reviewers conclude that the duration and extent of Gram-negative coverage did not differentially impact mortality in the two treatment groups in these studies?

Agency Response: *During the first cycle review, determination of whether an anti-infective was considered to be “potentially effective” differed at times between our reviewers and your assessment. Therefore, additional review of data on the impact of the nature and extent of Gram negative bacterial coverage is necessary to conclude that this did not differentially impact mortality.*

8. Do the reviewers conclude that a single study in NP with a positive result for all cause mortality, along with supportive data, qualifies as sufficient evidence under the statutory standard described in FDAMA 115?

Agency Response: *In general, reliance on a single trial is generally limited to situations in which the trial has demonstrated statistically strong evidence of a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. We do not believe that such an effect was observed in the telavancin NP trials.*

9. We intend to prepare an addendum to the ISE for NDA 22-407 that will focus on analysis of the mortality endpoint and include information responsive to the other issues cited in FDA comments on the application. An outline of the changes proposed in the application is provided in Appendix 2. Is the proposed organization and format of the resubmission acceptable?

Agency Response: *Mortality analyses should be included in Module 2, Section 2.7.3.6 Synopsis of Clinical Studies (for both 0015 and 0019) and added to Module 5, Sections 5.3.5.1.0015 and 5.3.5.1.0019.*

10. What is the role of the protocol-defined endpoint of clinical response? Can this supportive data appear in the product label, as with other drugs in the class?

Agency Response: *Based on the available information identified to date, the primary efficacy endpoint for which we are able to justify an NI margin is the 28-day*

mortality. Therefore it is unlikely that clinical response information would be included in product labeling at the present time.

We look forward to our discussion with you on May 25, 2010. If you have questions in the interim, please contact me at (301) 796-0702.

J. Christopher Davi, MS
Sr. Regulatory Project Manager
DAIOP

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22407

ORIG-1

THERAVANCE INC

VIBATIV

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/s/

JOSEPH C DAVI

05/24/2010



NDA 22-407

MEETING REQUEST GRANTED

Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Senior Director, Regulatory Affairs
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VIBATIV (telavancin for injection), 250 and 750 mg.

We also refer to your February 4, 2010, correspondence requesting a meeting to discuss your resubmission of your nosocomial pneumonia marketing application for VIBATIV. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

The meeting is scheduled as follows:

Date: May 25, 2010
Time: 4:00 PM to 5:00 PM, EST
Location: CDER White Oak Campus
10903 New Hampshire Avenue
Bldg. 22, conference room #1311
Silver Spring, MD 20993

FDA Participants:

Office of Antimicrobial Products (OAP):

Edward M. Cox, MD, MPH, Office Director
John Farley, MD, Deputy Office Director
David Roeder, MS, Associate Director, Regulatory Affairs

Division of Anti-Infective and Ophthalmology Products (DAIOP):

Wiley Chambers, MD, Acting Director
Katherine A. Laessig, MD, Deputy Director
Janice K. Pohlman, MD, MPH, Medical Team Leader
Thamban Valappil, PhD, Biostatistics Team Leader
Scott Komo, PhD, Biostatistics Reviewer

Charles Bonapace, PharmD, Clinical Pharmacology Team Leader
Ryan Owen, PhD, Clinical Pharmacology Reviewer
Fred Marsik, PhD, Clinical Microbiology Team Leader
Kerry Snow, MS, Clinical Microbiology Reviewer
Wendelyn Schmidt, PhD, Non-Clinical Pharmacology Team Leader
J. Christopher Davi, MS, Senior Regulatory Project Manager

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. Please e-mail me any updates to your attendees at christopher.davi@fda.hhs.gov, so that our security staff has sufficient advance time to prepare temporary visitor badges. Upon arrival at FDA, give the guards either of the following number: (301) 796-0702.

Provide the background information for the meeting (three copies to the application and 15 desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by May 3, 2010, we may cancel or reschedule the meeting.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager at (301) 796-0702.

Sincerely,
{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22407	GI-1	THERAVANCE INC	VIBATIV

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/s/

Frances V LESANE
04/21/2010



NDA 22-407

Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Senior Director, Regulatory Affairs
901 Gateway Drive
South San Francisco, CA 94080

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA) for Telavancin for Injection. We also refer to the meeting between representatives of Theravance and the FDA on March 15, 2010. The purpose of the meeting was to discuss the deficiency cited in the "Acknowledge Incomplete Response" letter from the Agency dated January 26, 2010.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Katherine A. Laessig, MD
Deputy Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures, (3): Minutes from meeting
 Pre-meeting comments from Agency dated March 12, 2010
 Sponsor's opening statement and presentation



MEMORANDUM OF TELECONFERENCE

MEETING DATE: March 15, 2010
MEETING TIME: Noon to 1:00 PM, EST
APPLICATION (DRUG): Telavancin for Nosocomial Pneumonia
SPONSOR: Theravance, Inc.
TYPE OF MEETING: Type B, post-action
MEETING CHAIR: Wiley Chambers, MD, Acting Division Director
MEETING RECORDER: J. Christopher Davi, MS, Senior Regulatory Project Manager

FDA PARTICIPANTS:

Wiley Chambers, MD, Acting Division Director
Katherine A. Laessig, MD, Deputy Division Director
Janice K. Pohlman, MD, Medical Team Leader
Charles Bonapace, PharmD, Clinical Pharmacology Team Leader
Ryan Owen, PhD, Clinical Pharmacology Reviewer
Fred Marsik, PhD, Clinical Microbiology Team Leader
Kerry Snow, MS, Clinical Microbiology Reviewer
Thamban Valappil, PhD, Statistical Team Leader
Scott Komo, PhD, Biometrics Reviewer
Victor Ng, Regulatory Project Manager
J. Christopher Davi, MS, Senior Regulatory Project Manager

INDUSTRY PARTICIPANTS:

Steve Barriere, PharmD, Clinical and Medical Affairs
Rebecca Coleman, PharmD, Regulatory Affairs and Quality
Ralph Corey, MD, Principal Investigator, Studies 0015 and 0019 (Duke University)
Joanne DiGiorgio, Regulatory Affairs
Alan Hopkins, PhD, Biostatistics

(b) (4)

Rochelle Maher, Project Management (Astellas)
Robert Reed, Regulatory Affairs (Astellas)
Edie Smith, Project Manager
Rick Winningham, CEO

MEETING OBJECTIVE:

The purpose of the meeting was to discuss the deficiency cited in the “Acknowledge Incomplete Response” letter from the Agency dated January 26, 2010.

SUMMARY OF DISCUSSION:

The Division of Anti-Infective and Ophthalmology Products (DAIOP) granted the Sponsor a meeting to discuss the deficiency cited in the “Acknowledge Incomplete Response” letter from the Agency dated January 26, 2010. DAIOP provided preliminary comments to the Sponsor on March 12, 2010 (appended). Discussion points generated from the preliminary comments are in provided herein.

DISCUSSION POINTS:

- The Sponsor provided an opening statement (appended).
- The Sponsor informed the Division that they did not believe that two new registrational trials were necessary.
- The Division acknowledged this point, stating that the Sponsor was free to resubmit the application if they (Sponsor) wished to do so.
- The Division asked the Sponsor if both M1 and M2 (i.e., treatment effect of active control versus placebo and clinically acceptable non-inferiority margin of test drug and active control) were at issue. The Sponsor confirmed that the derivation of M1 was problematic and they believed that the patient populations studied in 0015 and 0019 met very strict enrolment criteria, comparable to those in the historical studies.
- The Division asked the Sponsor if they knew of other NP studies that would help further underpin the adequacy of studies 0015 and 0019. The Sponsor stated that these supportive studies existed in the literature, but had been previously discounted by the Agency.
- The Division informed the Sponsor that any resubmission should include a description of why they (Sponsor) agree or disagree with the non-inferiority (NI) margin proposed by the Agency. Further, any resubmission should identify what M1 and M2 should be, and how the supportive historical study populations would match up to the current trials.
- The Division stated that the draft guidance document on NI margins needs to be considered and encouraged the Sponsor to comment back to the Agency on any issues with the NI margin determination in the guidance document.

- The Sponsor asked the Division to clarify concerns regarding the combining of evidence from studies of 0015 and 0019. The Division indicated that there was concern regarding the similarity of patient populations and lack of standardized microbiological evaluation of respiratory tract specimens, including tracheal aspirates.
- The Sponsor indicated that there was more standardization of bronchoscopically obtained microbiology specimens and pathogen determination, while evaluation of adequacy of tracheal aspirates was not used in clinical practice. The Division disagreed regarding evaluation of tracheal aspirates.
- The Division added that there are concerns regarding studies 0015 and 0019 because drugs administered for Gram negative coverage were given longer than they should have been, and may have had additional Gram positive coverage. This has confounded assessment of treatment effect of the study drug. The Sponsor acknowledged these concerns, but indicated that Gram negative coverage with aztreonam alone was rapidly becoming inadequate due to increasing antimicrobial resistance in Gram negative bacteria.
- The Division indicated that the Sponsor could initiate a trial, perhaps concurrently with re-submission. This would preferably be a superiority trial. The Sponsor acknowledged this, but believed there was too much uncertainty with the potential success of such an endeavour.
- The Division agreed to meet with the Sponsor again to discuss a strategy for any future resubmission.

Minutes Prepared by: *{See appended electronic signature page}*
J. Christopher Davi, MS
Senior Regulatory Project Manager

Concurrence by: *{See appended electronic signature page}*
Katherine A. Laessig M.D.
Deputy Division Director

Dr. Coleman,

In anticipation of our face to face meeting on March 15, 2010, please find below the Agency's responses (*italics*) to the questions posed in your briefing document dated February 26, 2010, for NDA 22-407:

1. The discussion at the Workshop focused on comparing differences in mortality rates at a fixed landmark time. Since the vital status of a small proportion of subjects are unavailable for the time point of interest, the use of analytical methods, such as Kaplan Meier estimates and hazard ratios obtained from proportional hazards regression models is proposed to account for the presence of censored data. Does the Agency agree with the approach?

Agency Response: The Kaplan Meier estimates at the land mark date (e.g., day 28) may be considered as one of the methods to address censored observations. However, this does not address the concern that censoring could be treatment related and not a random occurrence.

2. Although the mortality endpoint does not require investigator judgment the interpretation of the results is complicated because all-cause mortality does not always measure response to the pneumonia in this seriously ill patient population. Therefore, a multivariate regression was conducted using a proportional hazards model to identify prognostic factors related to death and test whether any of these factors were also treatment-effect modifiers. Does the agency agree with this approach?

Agency Response: We view these analyses as exploratory and hypothesis generating for designing future trials.

3. Based on the results of these analyses, Theravance believes that studies 0015 and 0019 are adequate and well controlled trials that are of adequate size to test for non-inferiority of telavancin versus vancomycin using the all-cause mortality at 28-days endpoint and a 10% non-inferiority margin. Please clarify why the agency believes the studies are inadequate.

Agency Response: As stated in the Complete Response letter, both trials were designed based on a clinical response endpoint, with all-cause mortality as a secondary endpoint. Scientific literature identified to date does not permit use of clinical response as a primary endpoint, due to lack of data to estimate the treatment benefit of active control antibacterial therapy relative to placebo. A justification for [possible] use of a 7% NI margin based on all-cause mortality was developed by the Agency based on historical literature. Since the Complete Response letter was issued, a substantial amount of missing mortality data has been recovered. However, on the surface, the patients enrolled in these trials differ from those in the historical studies that provided justification for the NI margin.

Specifically, the patient populations enrolled in trials used for the justification had a high likelihood of diagnosis of NP based on the presence of signs such as fever, leukocytosis, and purulent respiratory secretions, along with pulmonary infiltrates on chest radiograph. These features were not present in a substantial number of patients enrolled in 0015 and 0019.

4. Theravance believes that the small differential mortality overall seen between telavancin and vancomycin appears to be attributable to patients with acute renal failure (ARF) at baseline, as described in our reply to the complete response letter. Segregating this risk into patients with and without pre-existing ARF, provides a large population of patients (without pre-existing ARF) in whom the two treatments are non-inferior based upon all-cause mortality at 28 days as an endpoint. Does the Agency have any comments regarding the methods of analysis or this finding?

Agency Response: The trials were designed to demonstrate non-inferiority for all subjects. However, we recognize and are concerned with the observed increase in mortality for ARF patients who received telavancin compared with those who received vancomycin. This observation warrants further exploration in future trials.

5. In addition, Theravance used inclusion criteria suggested by FDA to define an additional analysis population in studies 0015 and 0019 (the CXR+2F analysis group, or the ATS/IDSA criteria for nosocomial pneumonia; i.e. patients with the highest probability of having pneumonia). In this population, non-inferiority using all-cause mortality at 28 days as an endpoint again is demonstrated between the two treatment groups.

Does the FDA agree that the CXR+2F population represents an acceptable additional analysis population in which to test for the non-inferiority of telavancin versus vancomycin using an endpoint of all-cause mortality at 28 days?

Agency Response: Yes. The utility of this analysis is valuable as a sensitivity analysis for evaluating consistency of effect to that observed in the primary analysis population.

6. Please clarify the agency's concerns regarding combining evidence from studies 0015 and 0019.

Agency Response: There were significant differences in prognostic factors and baseline severity for the study populations in Studies 0015 and 0019. Due to differences in patient co-morbidities, lack of adequate microbiological data, and other uncertainties with the data, the studies should not be combined to make inferences on mortality. Furthermore, the mortality rate difference between treatment arms does not appear to be the same in studies 0015 and 0019.

March 15, 2010 FDA Meeting

We appreciate the opportunity to meet with Agency representatives from the Office and the Division related to the NDA application for the NP indication for Televancin. We also thank you for the preliminary meeting comments, received on March 12th, which have been useful in our preparations for the discussion today.

Over a number of years Theravance has acted in good faith to obtain and incorporate input related to the design and conduct of Studies 0015 and 0019 for NP and the submission of the NDA, including input from multiple meetings and correspondence. The studies were designed and conducted in a manner consistent with FDA guidance and scientific standards in place at the time. To our knowledge, these 2 studies are among the largest conducted in this indication and entailed substantial efforts from the investigators and infectious disease and critical care communities, and ourselves. We believe we share, with FDA, a responsibility to the seriously ill patients involved, their caregivers, and those who conducted this research effort to fully assess these study data.

We acknowledge the Complete Response letter we have received indicates that a primary endpoint of all-cause mortality may be preferred to the current standard of clinical cure primary endpoint for NP. We note that these discussions remain ongoing and have not yet reached conclusion and that the Agency guidance related to use of a clinical cure primary endpoint continues to be in effect.

It is our position that even though all-cause mortality was a secondary endpoint in studies 0015 and 0019, evaluation of this endpoint is reasonable from a scientific and regulatory standpoint.

- Each study achieved the prospectively defined primary endpoint for clinical cure
- The studies are adequately powered to evaluate an endpoint of all-cause mortality at a non-inferiority margin of 10%. We believe this threshold is reasonable and clinically justified.
- Theravance has gathered additional mortality status data beyond the protocol defined study period in follow up to the Agency request and sufficient data are available for analysis

- Post-hoc analysis for all-cause mortality is justified as this variable is not subject to interpretive bias by the investigator or sponsor
- Mortality incidence for the vancomycin comparator arm in each study is consistent with the data from other studies in patients with NP
- A number of additional analyses can be conducted to assess the robustness of the all-cause mortality endpoint results

It is our position that studies 0015 and 0019 are adequate and well-controlled studies that provide substantial evidence of safety and efficacy when assessed against an appropriate all-cause mortality margin for non-inferiority, as well as the clinical response data. We believe the regulatory threshold for approvability is achieved and do not believe further studies are warranted.

Our objective is to obtain your input to identify an approach to submission of a Complete Response that would support a full evaluation of each study using an all-cause mortality endpoint.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22407	GI-1	THERAVANCE INC	VIBATIV

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/s/

KATHERINE A LAESSIG
04/09/2010

Dr. Coleman,

In anticipation of our face to face meeting on March 15, 2010, please find below the Agency's responses (*italics*) to the questions posed in your briefing document dated February 26, 2010, for NDA 22-407:

1. The discussion at the Workshop focused on comparing differences in mortality rates at a fixed landmark time. Since the vital status of a small proportion of subjects are unavailable for the time point of interest, the use of analytical methods, such as Kaplan Meier estimates and hazard ratios obtained from proportional hazards regression models is proposed to account for the presence of censored data. Does the Agency agree with the approach?

Agency Response: The Kaplan Meier estimates at the land mark date (e.g., day 28) may be considered as one of the methods to address censored observations. However, this does not address the concern that censoring could be treatment related and not a random occurrence.

2. Although the mortality endpoint does not require investigator judgment the interpretation of the results is complicated because all-cause mortality does not always measure response to the pneumonia in this seriously ill patient population. Therefore, a multivariate regression was conducted using a proportional hazards model to identify prognostic factors related to death and test whether any of these factors were also treatment-effect modifiers. Does the agency agree with this approach?

Agency Response: We view these analyses as exploratory and hypothesis generating for designing future trials.

3. Based on the results of these analyses, Theravance believes that studies 0015 and 0019 are adequate and well controlled trials that are of adequate size to test for non-inferiority of telavancin versus vancomycin using the all-cause mortality at 28-days endpoint and a 10% non-inferiority margin. Please clarify why the agency believes the studies are inadequate.

Agency Response: As stated in the Complete Response letter, both trials were designed based on a clinical response endpoint, with all-cause mortality as a secondary endpoint. Scientific literature identified to date does not permit use of clinical response as a primary endpoint, due to lack of data to estimate the treatment benefit of active control antibacterial therapy relative to placebo. A justification for [possible] use of a 7% NI margin based on all-cause mortality was developed by the Agency based on historical literature. Since the Complete Response letter was issued, a substantial amount of missing mortality data has been recovered. However, on the surface, the patients enrolled in these trials differ from those in the historical studies that provided justification for the NI margin.

Specifically, the patient populations enrolled in trials used for the justification had a high likelihood of diagnosis of NP based on the presence of signs such as fever, leukocytosis, and purulent respiratory secretions, along with pulmonary infiltrates on chest radiograph. These features were not present in a substantial number of patients enrolled in 0015 and 0019.

4. Theravance believes that the small differential mortality overall seen between telavancin and vancomycin appears to be attributable to patients with acute renal failure (ARF) at baseline, as described in our reply to the complete response letter. Segregating this risk into patients with and without pre-existing ARF, provides a large population of patients (without pre-existing ARF) in whom the two treatments are non-inferior based upon all-cause mortality at 28 days as an endpoint. Does the Agency have any comments regarding the methods of analysis or this finding?

Agency Response: *The trials were designed to demonstrate non-inferiority for all subjects. However, we recognize and are concerned with the observed increase in mortality for ARF patients who received telavancin compared with those who received vancomycin. This observation warrants further exploration in future trials.*

5. In addition, Theravance used inclusion criteria suggested by FDA to define an additional analysis population in studies 0015 and 0019 (the CXR+2F analysis group, or the ATS/IDSA criteria for nosocomial pneumonia; i.e. patients with the highest probability of having pneumonia). In this population, non-inferiority using all-cause mortality at 28 days as an endpoint again is demonstrated between the two treatment groups.

Does the FDA agree that the CXR+2F population represents an acceptable additional analysis population in which to test for the non-inferiority of telavancin versus vancomycin using an endpoint of all-cause mortality at 28 days?

Agency Response: *Yes. The utility of this analysis is valuable as a sensitivity analysis for evaluating consistency of effect to that observed in the primary analysis population.*

6. Please clarify the agency's concerns regarding combining evidence from studies 0015 and 0019.

Agency Response: *There were significant differences in prognostic factors and baseline severity for the study populations in Studies 0015 and 0019. Due to differences in patient co-morbidities, lack of adequate microbiological data, and other uncertainties with the data, the studies should not be combined to make inferences on mortality. Furthermore, the mortality rate difference between treatment arms does not appear to be the same in studies 0015 and 0019.*

7. While two studies can be employed to provide confirmation of a treatment effect a single study with supportive data has also served as the basis for a conclusion regarding efficacy. In particular, a single study with supportive data has been deemed adequate when the study endpoint is a measure of mortality. Data supportive of a nosocomial pneumonia indication could be the findings with regard to clinical response or the efficacy demonstrated in complicated skin and skin structure infection. At the HAP/VAP Workshop, not all participants agreed with the use of the mortality endpoint. Rather, the evaluation of the antibiotic course of treatment directly on the signs and symptoms of pneumonia was deemed more direct evidence of efficacy was mortality.

What is the Agency's perspective on the use of a single study, with supportive data, to demonstrate efficacy in the treatment of nosocomial pneumonia, when the endpoint utilized is all-cause mortality?

Agency Response: *In general, reliance on a single trial is generally limited to situations in which the trial has demonstrated statistically strong evidence of a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. Such an effect was not observed in either of the telavancin NP trials. Additionally, the lack of consistency across important subsets is a concern regarding generalizability (e.g., baseline renal function, see response to question #4).*

8. Theravance intends to resubmit further support for review of this application, based largely on the additional data and analyses provided in our reply to the Complete Response Action letter and consistent with any feedback from the Agency. Does the Agency concur?

Agency Response: *No. The data based on studies 0015 and 0019 are unlikely to provide adequate and reliable evidence to demonstrate non-inferiority of telavancin compared with vancomycin using a mortality endpoint. Additional trial(s) are strongly recommended.*

We look forward to meeting with you on March 15, 2010. If you have questions in the interim, please contact me at (301) 796-0702.

J. Christopher Davi, MS

Senior Regulatory Project Manager, DAIOP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22407	ORIG-1	THERAVANCE INC	VIBATIV

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/s/

JOSEPH C DAVI
03/12/2010



NDA 22-407

MEETING GRANTED

Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Senior Director, Regulatory Affairs
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VIBATIV (telavancin for injection), 250 and 750 mg.

We also refer to your February 4, 2010, correspondence requesting a meeting to discuss the Agency's January 26, 2010, communication regarding your incomplete response. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

The meeting is scheduled as follows:

Date: March 15, 2010
Time: 12:00 Noon to 1:00 PM, EST
Location: CDER White Oak Campus
10903 New Hampshire Avenue
Bldg. 22, conference room #1309
Silver Spring, MD 20993

CDER participants:

Edward M. Cox, MD, MPH, Office Director, OAP
John Farley, MD, Deputy Office Director, OAP
Wiley Chambers, MD, Acting Director, DAIOP
Katherine A. Laessig, MD, Deputy Director, DAIOP
Janice K. Pohlman, MD, MPH, Medical Team Leader
Thamban Valappil, PhD, Biostatistics Team Leader
Scott Komo, PhD, Biostatistics Reviewer
Charles Bonapace, PharmD, Clinical Pharmacology Team Leader
Ryan Owen, PhD, Clinical Pharmacology Reviewer
Fred Marsik, PhD, Clinical Microbiology Team Leader
Kerry Snow, MS, Clinical Microbiology Reviewer
Wendelyn Schmidt, PhD, Non-Clinical Pharmacology Team Leader

David Roeder, MS, Associate Director, Regulatory Affairs
J. Christopher Davi, MS, Senior Regulatory Project Manager

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. Please e-mail me any updates to your attendees at christopher.davi@fda.hhs.gov, so that our security staff has sufficient advance time to prepare temporary visitor badges. Upon arrival at FDA, give the guards either of the following number: (301) 796-0702.

Provide the background information for the meeting (three copies to the application and 15 desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to prepare for the meeting or if we do not receive the package by March 2, 2010, we may cancel or reschedule the meeting.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Frances LeSane
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22407	GI-1	THERAVANCE INC	VIBATIV

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/s/

Frances V LESANE
02/22/2010



NDA 22-407

ACKNOWLEDGE INCOMPLETE RESPONSE

Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Senior Director, Regulatory Affairs
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

We acknowledge receipt on December 22, 2009, of your December 21, 2009, submission to your new drug application (NDA) for VIBATIV (telavancin) for injection, 250 mg and 750 mg.

We do not consider this a complete response to our action letter. Therefore, the review clock will not start until we receive a complete response. The following deficiency from our action letter still needs to be addressed:

- While we acknowledge that additional mortality data and analyses have been provided to support pooling the two phase 3 clinical trials (Studies 0015 and 0019), even if this is acceptable, the two pooled studies would equate to only one adequate and well-controlled trial and would not constitute substantial evidence of efficacy. The adequacy and similarity of populations across studies for purposes of pooling has not yet been determined, and is a review issue.

As stated in our November 23, 2009, Complete Response letter to you, design of the new clinical trial(s) for the NP indication, should take into account the following:

- a. The study population should contain patients with a high likelihood of having the disease of interest. Therefore, the inclusion criteria for enrolled patients should include evidence of a new or progressive infiltrate on chest radiograph with at least two of the following features: fever $> 38^{\circ}\text{C}$, leukocytosis or leukopenia, and purulent lower respiratory tract secretions.
- b. Chest radiograph interpretation should be performed by a blinded healthcare provider, preferably a radiologist or pulmonologist, not directly involved in assessment of the patient for enrollment or during subsequent care.

- c. Uniform criteria should be applied to identify the quality of sputum and endotracheal aspirate specimens for culture and subsequent pathogen identification.
- d. The use of adjunctive antibacterial therapy should be minimized and rapid de-escalation criteria should be included in the study protocol.

We encourage you to request a meeting with us to discuss these issues.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We acknowledged receipt of your proposal for pediatric studies with this submission.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Katherine A. Laessig, MD
Deputy Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22407	ORIG-1	THERAVANCE INC	VIBATIV

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/s/

KATHERINE A LAESSIG
01/26/2010

Dr. Coleman,

Following is the FDA response to Theravance's submission of July 22, 2009 for NDA 22-407:

Follow-up Window for Mortality:

Assessment of the primary endpoint should be performed at a timepoint at which the outcome of interest reflects the clinical effect of the drug rather than underlying co-morbidities. Based on FDA review of the literature and the discussion at the public workshop¹, the clearest evidence of treatment effect was based on all-cause mortality. However, the historical literature did not provide a uniform timepoint for the assessment of mortality. Discussion at the workshop focused on the timepoint of 28 days after randomization/initiation of therapy. However, because the treatment duration varies from patient-to-patient, there is also consideration that a specified timepoint after end of therapy should be used for the mortality assessment.

Ideally the timing of the assessment would be prospectively defined. However, at the present time there is not a clear consensus on what the appropriate timing of assessment of all-cause mortality should be. There are strengths and weaknesses for use of either time from randomization or time from end of therapy. Therefore, given data that is available, FDA plans to assess outcomes at both of these timepoints and present the results at the planned Advisory Committee meeting for consideration, along with the identified strengths and weakness of both timepoints.

Updated Data Set:

For the two window periods (initiation of therapy to Study Day 28 and initiation of therapy to EOT + 28 days), provide the following for each study:

- Narratives of patients who died within either of the windows and for whom narratives were not previously submitted.
- An updated dataset similar to ADDTH28 (from your 3/26/09 submission) that contains the additional deaths.

In addition to the variables already included in ADDTH28, the dataset should also include the following variables:

- Study Day of death
- Flag for patients who died from initiation of therapy to Study Day 28
- Flag for patients whose death occurred on therapy
- Flag for patients whose death occurred from EOT to Study Day 28
- Flag for patients whose mortality status is not known up to Study Day 28
- Flag for patients whose mortality status is not known up to EOT + 28 days.

¹ Issues in the Design of Clinical Trials for Antibacterial Drugs for Hospital-Acquired Pneumonia (HAP) and Ventilator-Associated Pneumonia (VAP). A public Workshop co-sponsored by the Food and Drug Administration, the Infectious Diseases Society of America, the American Thoracic Society, the Society of Critical Care Medicine, and the American College of Chest Physicians. March 31 and April 1, 2009 in Silver Spring, MD.

- Latest Study Day that patient was known to be alive for patients whose mortality status was not known up to the end of the window (i.e. Day 28 post initiation of therapy and EOT + 28 days).
- Flag to indicate that subject received treatment
- Randomized and Actual treatment groups
- Flag to indicate that only Gram negative pathogens were isolated at baseline
- A separate table for each study similar to Table 1 of your 3/26/09 submission:
 - For the table summarizing the Study Day 28 window, the categories should be:
 - Deaths between Start of Study Drug and Day 28
 - Deaths on therapy
 - Deaths from EOT to Study Day 28
 - For the table summarizing the EOT + 28 days window, the categories should be:
 - Deaths between Start of Study Drug and EOT + 28 days
 - Deaths on therapy
 - Deaths from EOT to EOT + 28 days
 - Deaths from TOC to EOT + 28 days
- For each window, provide a listing of the patients by study in which mortality status is not known up to the end of the window. In addition, for each subject, provide the randomized treatment group, actual treatment group, and last Study Day that mortality status is known.

Please provide an estimated timeframe for your response to these information requests. If you have questions, contact me at (301) 796-0702.

J. Christopher Davi, MS
Senior Regulatory Project Manager

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/s/

JOSEPH C DAVI
07/31/2009

Davi, Christopher

From: Davi, Christopher
Sent: Tuesday, July 21, 2009 4:36 PM
To: 'Coleman, Becky'
Subject: Information Request (NDA 22-407)

Becky,

Please see the following clinical/statistical information request:

- **For NDA 22-407 Study 0015 and Study 0019, please submit (or direct us to the location in the application) the minutes for the closed session of the IDMC and the analyses provided to the IDMC for review.**

Thank you, and let me know if you have questions

Chris

***J. Christopher Davi, MS
Senior Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
FDA Center for Drug Evaluation and Research
christopher.davi@fda.hhs.gov
(301) 796-0702***

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/s/

Christopher Davi
7/21/2009 04:54:05 PM
CSO

Davi, Christopher

From: Davi, Christopher
Sent: Wednesday, June 17, 2009 4:03 PM
To: 'Coleman, Becky'
Subject: Information Requests (NDA 22-407)

Attachments: AR-M620U_20090617_155353.pdf



AR-M620U_200906
17_155353.pdf (...)

Dr. Coleman,

Please see the attached information requests from the clinical review team.

Regards,

Chris Davi

J. Christopher Davi, MS
Senior Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
FDA Center for Drug Evaluation and Research
christopher.davi@fda.hhs.gov
(301) 796-0702

Dr. Coleman,

Please see the following information requests from the clinical review team for NDA 22-407:

1. Provide a justification for the algorithm described in Section 8.2.9.2 of the 0015 Clinical Study Report regarding the assessment of the adequacy of concomitant Gram-negative therapy in patients with no baseline pathogens. As the use of concomitant Gram-negative therapy was left to the Investigator's discretion and there is no mandatory requirement for all study patients to be treated at baseline with Gram-negative antibacterial coverage as described in Section 6.4.8.1 of the same Study Report, the scientific rationale for the algorithm is unclear.
2. Provide a rationale for the discrepant assessments of the adequacy of concomitant Gram-negative therapy for the following two patients who were not administered Gram-negative coverage at baseline:
 - Patient 0019-38051-6533 had negative blood and respiratory cultures at baseline and was not administered baseline Gram-negative coverage, but was assessed as having received 'adequate Gram-negative therapy'.
 - Patient 0019-50001-6711 had negative blood and respiratory cultures at baseline and was not administered baseline Gram-negative coverage, but was assessed as having received 'inadequate Gram-negative therapy'.
3. Provide a rationale for the designation of "never received adequate Gram-negative therapy" for the following two patients, in which the investigator ticked "no Gram-negative coverage required" on the data clarification sheets in the case report forms:
 - 0015-05001-4319
 - 0019-50000-6667
4. Provide a rationale for the designation of "initial inadequate Gram-negative therapy" for patient 0019-05000-6151, who was treated with piperacillin-tazobactam from Study Day 2 until demise.
5. In reference to the determination of potentially effective non-study antibiotics (PEAT) as described in Section 6.7.1.4.2 of the 0015 Clinical Study Report, provide a justification for excluding from the assessment of PEAT the non-study antibiotics that exhibit Gram-negative activity against baseline Gram-negative respiratory pathogens that are part of a mixed infection.
6. Provide an efficacy analysis for clinical and microbiological outcomes at EOT and TOC in the AT, CE, and ME populations limited to patients at highest likelihood for having NP (ie., patients with fever ($>38^{\circ}\text{C}$), leukocytosis, purulent respiratory tract specimens, and CPIS ≥ 6 at the pre-treatment/baseline visit). Provide a separate analysis in which patients with axillary temperatures do not

have one degree Celsius added to the recorded value on the CRF, and base the assessment of fever and CPIS scoring using the recorded temperature value.

7. Provide an estimate of the number of study subjects who do not have radiologists' interpretations/reports for all chest x-rays performed at pre-treatment, on study, and EOT study visits. Explain the reason(s) for missing radiologists' interpretations/reports for all chest x-rays performed at pre-treatment, on study, and EOT study visits.
8. Explain the process of chest x-ray interpretation.
9. Provide a line listing of all study subjects who did not have radiographic evidence of NP.
10. Based on a review of CRFs, oral thrush and urinary fungal infections that developed during study drug treatment were not included as adverse events for some patients (Examples: 0015-05001-4066 and 0015-02024-4215). Provide an estimate of the number of study subjects for which such adverse events were not captured and provide a rationale for not including them as treatment-emergent adverse events.
11. Provide narratives for all patients that fulfill the criteria for Hy's Rule for hepatotoxicity.

If you have questions, please contact me at (301) 796-0702.

J. Christopher Davi, MS
Senior Regulatory Project Manager, DAIOP

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/s/

Christopher Davi
6/17/2009 04:21:26 PM
CSO

Davi, Christopher

From: Davi, Christopher
Sent: Friday, June 12, 2009 8:58 AM
To: 'Coleman, Becky'
Subject: NDA 22407 information request (data set)

Dr. Coleman,

The review team has requested that you identify the data set used to generate the ATTAIN protocol deviation log table for study 0015 (Appendix 15 of the clinical study report). If you have any questions, please let me know.

Regards,

Chris Davi

J. Christopher Davi, MS
Senior Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
FDA Center for Drug Evaluation and Research
christopher.davi@fda.hhs.gov
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Christopher Davi
6/12/2009 09:01:50 AM
CSO

Davi, Christopher

From: Davi, Christopher
Sent: Tuesday, June 09, 2009 1:38 PM
To: 'Coleman, Becky'
Subject: NDA 22-407 (Requests for Clarification on Agency's Inquiry)

Attachments: AR-M620U_20090609_132156.pdf



AR-M620U_20090609_132156.pdf (...)

Dr. Coleman,

In response to your request for clarification on the inquiries originally forwarded by the Agency on April 30, 2009, please see the attached PDF file. Let me know if you have any questions.

Regards,

Chris Davi

J. Christopher Davi, MS
Senior Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
FDA Center for Drug Evaluation and Research
christopher.davi@fda.hhs.gov
(301) 796-0702

NDA 22-407, N-008

Response to Theravance's request for clarification on items contained in FDA information request of April 30, 2009.

1. Theravance requests clarification regarding sensitivity analysis using CPIS scores.

FDA response: FDA agrees that CPIS analyses and datasets should only include patients with VAP.

2. Theravance requests clarification on the statement "...how the algorithmic categorization by organism morphology impacted pathogen status of organisms." and confirmation that FDA is looking for a description of the methodology for identification of respiratory pathogens.

FDA response: FDA confirms that the primary purpose of the information requested was to describe the methodology used for identification of respiratory pathogens.

It was unclear based on the algorithm in SAP Section 9.1 Classification of Infecting Organism copied below, how organism morphology was used in determination of pathogen status:

"Organisms will be algorithmically categorized as cocci, bacilli, or cocobacilli as follows: All Gram-positive respiratory pathogens are categorized as cocci. All Gram-negative respiratory pathogens, other than *H. influenzae*, are categorized as bacilli. *H. influenzae* is categorized as coccobacilli.

The above classifications apply to all instances of the given organism. That is, the classifications are considered inherent characteristics of the organism, and remain constant across patients; individual patient circumstances are not considered case-by-case. In this sense, the mapping functions as a thesaurus."

3. Theravance requests clarification regarding definition of clinical failure and analysis population.

FDA Response:

The FDA clinical failure definition of clinical failure included premature discontinuation of study medication due to adverse event. Therefore, if patients discontinued treatment and did not require additional antibacterial therapy, they would not be clinical failures.

FDA Analysis Populations:

- **cMAT**: Patients with infections due to only Gram negative pathogens should be excluded from the cMAT and mMAT. Patients with mixed Gram positive / Gram negative infections should not be excluded from the cMAT or mMAT (regardless of adequacy of Gram negative bacterial coverage).

- **CE:**
 - The definition should be based on those included in the study protocol, however a sensitivity analysis using the ATS/IDSA criteria (i.e. progressive infiltrate and two of three of the following fever $> 38^{\circ}\text{C}$ (as measured), leukocytosis or leucopenia, and purulent secretions) should also be performed.
 - All-cause mortality should be a criterion for failure in all analysis populations.
 - **PEAT:** The duration of PEAT should be minimized. If data collected cannot differentiate between 24 and 48 hours of treatment, sensitivity analyses should be performed using one versus two calendar days of PEAT.
4. Theravance would appreciate feedback regarding change of endpoint to a hybrid based on clinical failures, failures due to discontinuations for adverse event, and deaths and the impact of change in endpoint definition on any non-inferiority margin justification.

FDA Response: As discussed at the FDA/IDSA HAP/VAP workshop held on 3/31/09-4/01/09, historical evidence will only allow interpretation of noninferiority studies for antibacterial drugs in the treatment of NP and VAP that use all-cause mortality as the primary endpoint. Currently, there is no historical evidence to scientifically justify a NI margin based on a clinical response endpoint for this indication. Hence, due to the lack of an evidence-based scientific justification for your proposed NI margin of (b) (4) using clinical response as the primary endpoint, it is not possible to interpret the efficacy results based on clinical response for Studies 0015 and 0019. Assessing the noninferiority of telavancin compared to vancomycin in the two studies will depend on the analysis of the all-cause mortality data.

In relation to all-cause mortality, you have chosen to pool the populations of Studies 15 and 19 due to concerns about the lack of statistical power for each study individually. However, in analyzing the mortality data that you provided in your response to the Division's information request of February 25, 2009, pooling of the two clinical trial populations for mortality analyses is not recommended. There are serious concerns about the differential mortality rates in these studies for various mortality reporting periods. In Study 0015, telavancin-treated patients had a higher mortality rate for deaths between start of study drug and EOT + 28 days in the AT population compared to vancomycin-treated patients, and the difference was statistically significant. Similarly, a higher mortality rate was observed for telavancin-treated patients for deaths between EOT and EOT + 28 days compared to vancomycin-treated patients, and the difference was statistically significant. In Study 0019, there were no statistically significant differences in the mortality rates across the telavancin and vancomycin treatment arms in the AT population for either of those mortality reporting periods. Additionally, there are substantial differences between the two populations with respect to baseline demographic and medical history characteristics that preclude pooling. For example, in evaluating the

telavancin-treated patients in the AT population in Study 15 compared to the telavancin-treated patients in the AT population in Study 19, there are more telavancin-treated patients in Study 15 with chronic renal failure, baseline CrCl < 50 mL/min, hemodialysis, diabetic status (yes), history of diabetes mellitus, ARDS, and torsades compared to the telavancin-treated patients in Study 19. In contrast, there are more telavancin-treated patients in Study 19 with serum creatinine \leq 2 mg/dL and immunocompromise compared to the telavancin-treated patients in Study 15, and there are fewer telavancin-treated patients in Study 19 with chronic renal failure, baseline CrCl < 50 mL/min, hemodialysis, diabetic status (yes), history of diabetes mellitus, ARDS, and torsades compared to Study 15. Many of these parameters can potentially affect the risk for mortality, and all of the cross-study differences described are statistically significant. Thus, pooling of both study populations for mortality analysis is not appropriate. The mortality data relevant to each study should be assessed and analyzed individually.

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/s/

Christopher Davi
6/9/2009 01:41:47 PM
CSO

Davi, Christopher

From: Davi, Christopher
Sent: Tuesday, June 09, 2009 1:46 PM
To: 'Coleman, Becky'
Subject: IR to Theravance (NDA 22-407)

Dr. Coleman,

Please see the following information request from the clinical/statistical review team:

- ***We appreciate your reply to our information request of February 25, 2009, which provided a revised mortality analysis that identified 160 pooled telavancin-treated patients and 147 pooled vancomycin treated patients who died. As the revised analysis includes 10 additional telavancin and 7 additional vancomycin deaths compared to the mortality analysis provided in your original NDA submission, we are requesting that you provide narratives for the additional telavancin and vancomycin deaths. We also request an updated electronic safety dataset for adverse events (including treatment-emergent adverse events and serious adverse events) that includes these additional patients.***
- ***Please provide Kaplan-Meier curves for patient deaths thru EOT+28 days. Also provide these seperately by patient baseline creatinine clearance categories.***

Please advise on an estimated turn-around time for this information. If you have any questions, please contact me.

Regards,

Chris Davi

***J. Christopher Davi, MS
Senior Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
FDA Center for Drug Evaluation and Research
christopher.davi@fda.hhs.gov
(301) 796-0702***

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/s/

Christopher Davi
6/9/2009 01:57:12 PM
CSO

Davi, Christopher

From: Davi, Christopher
Sent: Monday, May 18, 2009 9:17 AM
To: 'Coleman, Becky'
Subject: NDA 22-407 (PK information request)

Dr. Coleman,

The Clinical Pharmacology reviewer has the following information request:

Please submit the datasets and codes/scripts from the population pharmacokinetic analysis (Report 08-6424-pop-PK-03) for reviewers to recreate modeling and simulations. Please include:

- All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
- NONMEM model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

Please let me know if you have any questions, and when you anticipate submitting your reply.

Regards,

Chris Davi

J. Christopher Davi, MS
Senior Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
FDA Center for Drug Evaluation and Research
christopher.davi@fda.hhs.gov
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/s/

Christopher Davi
5/18/2009 09:22:58 AM
CSO

Davi, Christopher

From: Davi, Christopher
Sent: Thursday, April 30, 2009 2:39 PM
To: 'Coleman, Becky'
Subject: FW: Information request for NDA 22-407

Attachments: Communication March 6 2008.pdf; 2_22407IR.doc



2_22407IR.doc (52
KB)

Dr. Coleman,

Please see the attached information request (word file) and referenced communication (PDF) for NDA 22-407. After you have had an opportunity to review the information requests, please advise on when you anticipate being able to provide a response to the Division.

Best regards,

Chris Davi

J. Christopher Davi, MS
Senior Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
FDA Center for Drug Evaluation and Research
christopher.davi@fda.hhs.gov
(301) 796-0702

Dr. Coleman,

Please see the following information requests from the review team for NDA 22-407:

1. Provide a line listing (by study and randomized treatment group) for patients who were granted eligibility waivers by the helpline physicians, specify the inclusion/exclusion criteria that were waived, and the reason(s) that the waiver was granted. [CRF page 4]
2. Based on review of some case report forms (CRFs), it became apparent that some Inclusion Criteria which were checked (CRF, page 1, e.g. respiratory rate > 30 breaths/ minute or pulse \geq 120 beats/minute) could not be confirmed based on information provided in the Clinical Signs and Symptoms of Pneumonia assessed within 24 hours Pre-Treatment (CRF, page 12). Data clarification in response to query for the CRFs stated the information was "correct as is since value used to qualify patient was different than one assessed at pre-treatment". Please explain these discrepancies. In the absence of recorded data on the CRF, we are unable to ascertain whether the patient fulfilled the specified criteria. [Patient example: 0019-06017-6436]
3. Provide a sensitivity analysis of clinical and microbiological outcomes at end of therapy (EOT) and test of cure (TOC) for all randomized patients in the All-Treated (AT), modified AT (MAT), clinically evaluable (CE), and microbiologically evaluable (ME) populations (stratified by study and treatment group) who had fever ($> 38^{\circ}\text{C}$) or hypothermia (rectal/core temperature $< 35^{\circ}\text{C}$), purulent sputum or other deep respiratory specimen, and elevated total peripheral WBC count $> 10,000$ cells/ mm^3 , $> 15\%$ immature neutrophils (band forms) regardless of total peripheral WBC count, or leukopenia with total WBC count < 4500 cells/ mm^3 at pre-treatment. Provide a separate similar sensitivity analysis in which all patients with only axillary temperatures at pre-treatment are excluded.
4. The Study Procedures section of the protocol indicates that oral, tympanic, or rectal temperatures were to be used to measure body temperature. Explain why a checkbox for an axillary temperature (AxT) was included on the CRF and used for data analysis.

Describe when the decision was made to add one degree Celcius to the recorded axillary temperature on the CRF and for data analysis. Provide scientific evidence supporting the validity of adding one degree Celcius to all axillary temperatures, since this conclusion is not supported by the reference cited in your clinical study report (*Am J Crit Care* 1995;4:286-292). The reference states that "AxT does not correlate well with core temperature, and this method should not be used clinically to assess for presence or absence of fever". Explain why Inclusion Criterion 2 b on page 1 of the CRF specifies hypothermia based on rectal/core temperature $< 35^{\circ}\text{C}$, but does not specify use of a rectal/core temperature to assess fever $> 38^{\circ}\text{C}$.

5. Provide a sensitivity analysis comparing CPIS and APACHE II scores calculated at all study visits by study and randomized treatment arm based on the actual recorded axillary temperature and based on the modified axillary temperature (determined by your methodology of adding one degree Celcius to all axillary temperatures). Provide an electronic dataset that includes the above information as well as identifies the method used (oral, rectal axillary, or tympanic) for all recorded temperatures for all patients at all study visits.
6. According to the Clinical Study Reports, the evaluation of clinical response at EOT defines cure as “signs and symptoms of pneumonia improved to the point that no further antibiotics for pneumonia were required, and baseline radiographic findings improved or did not progress”. Provide a line listing of all study patients who were assessed as clinical cures at EOT but did not have a chest x-ray or CT scan performed at the EOT visit. Include the patient identification number; the study in which the patient was enrolled, the randomized treatment group, the study day of all radiographic assessments for each patient, the study day of the EOT visit, the radiographic assessment for each visit, and the patient’s clinical evaluability. Explain why the EOT drug discontinuation evaluation (page 33A) of the CRF did not include reference to “baseline radiographic findings improved or did not progress” as part of primary reason #1 for discontinuing study medication. Primary reason #1 relates only to resolution of signs and symptoms.

Provide a line listing of all study subjects (including identification number, study number, and treatment group) who had radiographic imaging (Chest x-ray or CT scan) at Test of Cure. Include the study day of all radiographic assessments for each patient, the study day of the EOT and TOC visit, the radiographic assessment for each visit, the patient’s clinical evaluability status, and the clinical outcome at EOT and TOC.

7. In reviewing some CRFs, we have noted MRSA reported as the pre-treatment respiratory tract pathogen on the CRF, an accession number on the CRF that matches that of the central microbiology laboratory, but central laboratory identification reported as MSSA. No explanation for the discrepancy was provided on the CRFs or in the data clarification notes. (Example: Patients 0019-40001-6803 and 0015-07002-4239). Please explain this discrepancy between the CRF documentation and the data recorded in the electronic datasets, and clarify which source of microbiologic identification information is accurate for analysis. Provide corrected electronic datasets if necessary.
8. Provide a line listing of patients (by study and randomized treatment group) where there was a discrepancy between the identification of microbiological isolates between the local and central microbiology laboratory.

Include subject identification, specimen type (source), organism, study visit, the nature of the discrepancy, and the pathogen(s) included in the microbiological analyses.

Were Gram stains of respiratory specimens sent to the central microbiology laboratory for confirmation of local microbiology laboratory results?

Were interpretive criteria used to assess adequacy of tracheal aspirates, and if not why not?

Why are microbiological isolates obtained at subsequent study visits being classified as superinfecting pathogens when they are not being specifically treated clinically?

9. Sponsor's Determinations While Blinded (Statistical Analysis Plan, Section 9, Clinical Study Report, Section 6.7.1.4)

Determination of Patient Evaluability (SAP 9.7)

Provide a line listing of patients (by study) who had changes made by the Theravance medical monitor to analysis population status. Include patient (subject) identification number, treatment group as randomized, analysis population(s) affected along with the change made, the primary (clinical) outcome at test-of-cure, and rationale for the change.

Classification of Infecting Organisms (SAP 9.1)

- Provide a list of organisms considered to be respiratory pathogens.
 - Provide a list of organisms considered to be blood pathogens
 - Provide additional details (clarification) about how the algorithmic categorization by organism morphology impacted pathogen status of organisms. Were the Gram stain results from the microbiological specimen used in the determination of pathogen status of an organism?
10. Explain why a significant amount of laboratory safety data is missing at TOC (above the level expected based on mortality rates). Explain the impact of the missing TOC safety laboratory data on the overall assessment of the safety profile for the drug.
11. Provide a line listing of patients (by study and randomized treatment group) who were permitted to enroll despite receiving > 24 hours of prior antimicrobial therapy because of a resistant pathogen, along with the identification and susceptibility profile of that pathogen.

12. Prior to the pre-NDA meeting between FDA and Theravance on March 6, 2008, the FDA provided definitions for the analysis populations (communication March 5, 2008). For each study, provide analyses of clinical response at TOC as well as all-cause mortality for the analysis populations as specified in the 3/5/08 communication. In addition, provide a dataset similar to ADSL that includes flags for these populations.

Please provide an estimated date for a response to this information request as soon as you are able to do so. If you have questions, please contact me at (301) 796-0702.

J. Christopher Davi, MS, Senior Regulatory Project Manager
Division of Anti-Infective and Ophthalmology Products

Dr. Coleman,

In anticipation of our Pre-NDA meeting on March 6, 2008, for IND 60,237, please see the following responses from the Division of Anti-Infective and Ophthalmology Products (DAIOP) as they relate to the questions posed on page 5 of your February 6, 2008, briefing document:

1. Is the proposal for analysis of the Phase 3 Studies, as outlined in the Statistical Analysis Plan (Telavancin IND 60,237 SN 231, submitted 12 November 2007) acceptable?

Agency Response: *The clinical and statistical review team has the following comments regarding FDA analysis:*

- *The clinical response definitions are not outlined in the statistical analysis plan*
 - *FDA definition of clinical cure:*
 - *signs and symptoms of the primary infection have resolved or improved to the point that no further antibiotics for pneumonia are required AND*
 - *the baseline chest radiographic findings improved or did not progress*
 - *FDA definition of clinical failure:*
 - *primary treatment failure (lack of resolution or progression of pneumonia) after minimum of 72 hours of study medication treatment*
 - *relapsed pneumonia prior to TOC*
 - *premature discontinuation of study medication due to adverse event*
 - *death after minimum of 72 hours of study treatment due to any cause (not attributable mortality), up to 28 days after end-of-therapy (EOT)*
 - *Indeterminate:*
 - *inability to determine outcome*
- *Please describe a scenario(s) in which a patient is assessed by the investigator as "indeterminate" at EOT and subsequently a "clinical cure" at TOC*
- *FDA Analysis Populations:*
 - *All-treated (AT): all patients who received any amount of study drug (as randomized)*
 - *Clinically modified all-treated (cMAT): patients in the all-treated population who meet the clinical definition of HAP and do not have only Gram negative organisms isolated from baseline microbiological cultures*
 - *Microbiological modified AT (mMAT): patients in the AT population who have a baseline respiratory pathogen isolated excluding patients with only Gram negative organisms and those with mixed Gram positive/negative organisms who are not receiving adequate antimicrobial coverage for the Gram negative pathogen*
 - *Clinically evaluable (CE): AT population with sufficient adherence to protocol with conditions outlined by Theravance (statistical analysis plan submitted to IND 60,237) with the following exceptions/clarifications:*

- *Meets inclusion criterion of signs and symptoms and chest radiograph consistent with pneumonia or else was approved for enrollment by study hotline monitor – please explain how a patient not meeting these inclusion criteria could be enrolled in a HAP study*
- *Meets inclusion criteria regarding availability of appropriate specimens – patients with negative microbiological cultures should be included in the CE population*
- *Patient did not receive effective concomitant systemic antibiotic therapy for >24 hours prior to study enrollment or any time before TOC, unless the patient was enrolled due to clinical failure after at least 72 hrs of antimicrobial treatment or the pathogen demonstrated in vitro resistance to the prior antimicrobial*
- *If the patient was not a failure at EOT, then TOC assessment was made between Study Day 7P and 14 P, inclusive*
- *All-cause mortality up to 28 days after EOT*
- *Microbiologically evaluable (ME): patients in the CE population who also have a Gram positive baseline respiratory pathogen.*
- *Consideration should be given to including co-primary analysis populations using the cMAT and CE populations as defined above.*
- *Baseline pathogen window:
The window for obtaining specimens for baseline microbiology should be the 24 hour period prior to randomization with the exception of patients enrolled due to clinical failure after >72 hours of antimicrobial therapy and/or demonstrated in vitro resistance to the previously administered antimicrobial agent. The antimicrobial agent administered and corresponding susceptibility result of the resistant pathogen should be linked and provided in a dataset.*
- *Concomitant potentially effective antibiotic therapy (PEAT) from initiation of study drug treatment through EOT:
The duration of PEAT should not be greater than 24 hours since ≥ 24 hours of antimicrobial therapy has been demonstrated to diminish sensitivity of microbiological culture for some respiratory pathogens (i.e., Streptococcus pneumoniae)^{1,2}.*
- *If you would like to include patients receiving concomitant antimicrobial therapy for up to 3 days, please submit evidence (i.e., published literature) for consideration, regarding the lack of effect of this type of concomitant antimicrobial therapy on clinical status and respiratory cultures. The*

¹ Musher DM, Montoya R, Wanahita, A. Diagnostic Value of Microscopic Examination of Gram-Stained Sputum and Sputum Cultures in Patients with Bacteremic Pneumococcal Pneumonia. *Clinical Infectious Disease* 2004;39:165-169.

² Souweine B, et al. Diagnostic Accuracy of Protected Specimen Brush and Bronchoalveolar Lavage in Nosocomial Pneumonia: Impact of Previous Antimicrobial Treatments. *Critical Care Medicine* 1998;26:236-244.

antimicrobial agent classified as PEAT and corresponding susceptibility result of the patient's pathogen(s) should be linked and provided in a dataset.

- ~~*Including both prior and concomitant potentially effective antimicrobial agents in the definition of PEAT is confusing. Please provide clarification or consider the pre-study and on-study antimicrobial treatment situations separately.*~~
- *The study protocol states that sputum and endotracheal aspiration specimens have >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per low power field (10X objective).*
 - *How are organisms classified as pathogen versus colonizer in these and other types of specimens? If quantitative microbiology results are used for other types of specimens (i.e., bronchoalveolar lavage, protected specimen brush), the quantity used for pathogen determination should be specified.*
 - *Please provide the list of organisms which are considered to be respiratory pathogens in Study 0015 and 0019.*
 - *There should be a dataset submitted with the NDA containing Gram stain results which can be linked to the pathogen status of organisms isolated from the corresponding specimen.*
- *Microbiological analyses should be performed separately where central and local microbiology laboratory results for determination of pathogen identification and antimicrobial susceptibility are combined and where only central microbiology results are used.*
- *Chest radiographic reports should be submitted with the patient's case report form.*
- *The non-inferiority margin justification is still under review.*
- *The superiority analysis should be based on response rates in the AT population (or perhaps the MAT as described above). Ultimately, superiority claims are a labeling issue based on efficacy and safety criteria and overall benefit to risk assessment. In order for a claim to be made regarding the superiority of telavancin to vancomycin for treatment of infection due to methicillin-resistant *Staphylococcus aureus*, superiority would have to be demonstrated for the primary efficacy endpoint in both HAP trials.*
- *The *Streptococcus pneumoniae* multi-drug resistant strain (MDRSP) designation referring to the agents listed in the briefing package (penicillins, second-generation cephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole) was developed in the context of treatment of community-acquired pneumonia, not hospital-acquired pneumonia which is likely to be treated with different antimicrobial agents. What data (in vitro, clinical) are available regarding telavancin activity against penicillin-resistant *S**

pneumoniae? Was activity based on penicillin resistance as defined by MIC \geq 2 μ g/mL?

2. Please comment on the implications for our product of any conclusions reached following the recent IDSA/FDA workshop regarding the development of products for community acquired pneumonia.

Agency Response: The discussion at the IDSA/FDA workshop on development of antimicrobial products for community-acquired pneumonia has no direct implications for the telavancin HAP submission.

3. Please comment on the plan for an eCTD for the HAP indication and advise the Sponsor regarding any implications for the ongoing review of the cSSSI indication.

Agency Response:

Referencing Previously Submitted Documents

If a document was submitted in electronic format with the eCTD backbone files, you should not submit additional copies when referencing the previously submitted document. Instead, you should include the information by reference by providing in the text of the document (1) the application or master file number, (2) the date of submission (e.g., letter date), (3) the document name, and (4) the page number of the referenced document along with a hypertext link to the location of the information (see section II.Q of this guidance). If a document replaces or appends a document previously submitted with an eCTD backbone file, then you should include this information in the appropriate eCTD backbone file. The details on how to include this information in the eCTD backbone file are provided in the associated specifications for eCTD backbone files.

If a document was previously submitted in either paper or electronic format without the proper eCTD backbone files, you should reference the document as with any paper submission. In the text of the document, you should include (1) the application or master file number, (2) the date of submission (e.g., letter date), (3) the document name, (4) the page number, and (5) the submission identification (e.g., submission serial number, volume number, electronic folder, and file name) of the referenced document. In such cases, providing an electronic copy of the previously submitted documents can increase the utility of the submission. These documents, like all documents in the submission, should be appropriately described in the eCTD backbone files. These files are considered new in the eCTD backbone files. When referring to documents that are part of other applications, please remember to include the appropriate letters of authorization with the submission (e.g., 21 CFR 314.420(d)).

We look forward to meeting with you on March 6, 2008. If you have any questions, please contact me at (301) 796-0702.

Regards,

J. Christopher Davi, MS
Regulatory Project Manager
DAIOP

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/s/

Christopher Davi
5/1/2009 09:33:37 AM
CSO

Davi, Christopher

From: Davi, Christopher
Sent: Monday, April 27, 2009 11:04 AM
To: 'Coleman, Becky'
Subject: Information Request (NDA 22-407)

Attachments: AR-M620U_20090427_105331.pdf



AR-M620U_200904
27_105331.pdf (...)

Dr. Coleman,

Please see the attached information request from the Division of Scientific Investigations (DSI). Please let me know Theravance's timeframe for being able to reply to this request.

Regards,

Chris Davi

J. Christopher Davi, MS
Senior Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
FDA Center for Drug Evaluation and Research
christopher.davi@fda.hhs.gov
(301) 796-0702

The following line listings are requested, by Site, for subjects enrolled in Study 0015 at Sites #02011, 09004, #38020, #38024, #38148, and #38270

CRF Page(s)	Content	Items
1	Inclusion Criteria	All
2/2A-3/3A	Exclusion Criteria	All
4, 4A	Pre-treatment	Eligibility section, prior antimicrobial therapy section
5	Pre-treatment	BhCG Serum Pregnancy Test
6/6A	Pre-treatment	Renal Status section
7	Glasgow Coma	All
8	APACHE Chronic Health/Diabetes Cardiac Comorbidity	All
9	Respiratory Insufficiency/Failure	All
10-11	Med/Surg History	All
12	Diag HAP/Vent Status/SiandSx	All
13, 16, 18, 30	Radiography/oxygenation	All
14/14A, 17/17A, 32/32A, 36/36A	Sputum Culture	All
15	Blood Culture	All
19-25	Daily Assessment signs and symptoms	All
26-29	Study Medication Log	All
31	EOT Signs and Symptoms	All
33/33A	EOT	Was treatment unblinded, date
35	TOC	Clinical Signs and Symptoms section
39	Prior Antimicrobials	All
40	Concomitant medications	All
	Death report	All
Unblinded Pharmacy Record 1-2	Dose Modification Record	All
Unblinded Vancomycin Level Record 1-2	Vancomycin levels	All

Similarly, the equivalent line listings are requested, by Site, for subjects enrolled in Study 0019 at Sites #05003, #18004, #34002, #38069, #40000, and #40001

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/s/

Christopher Davi
4/27/2009 11:10:09 AM
CSO

Davi, Christopher

From: Davi, Christopher
Sent: Thursday, April 16, 2009 10:13 AM
To: 'Coleman, Becky'
Subject: NDA 22-407

Becky,

The clin/stat review team has asked that I forward to you the following information request:

- Please submit the raw data sets for your hospital-acquired pneumonia studies (0015 and 0019) and SAS programs used to generate derived variables.

Please let me know if you have any questions.

Regards,

Chris

*J. Christopher Davi, MS
Senior Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
FDA Center for Drug Evaluation and Research
christopher.davi@fda.hhs.gov
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/s/

Christopher Davi
4/17/2009 09:38:25 AM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-407

Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Vice President
Regulatory Affairs and Quality
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

Please refer to your new drug application (NDA) dated January 23, 2009, received January 26, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for VIBATIV™ (telavancin) for injection, 250 mg and 750 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application was considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is November 26, 2009.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to initiate labeling discussions and, if necessary, discuss any postmarketing commitment requests by October 9, 2009.

During our filing review of your application, we identified the following potential review issues:

1. The justification of the non-inferiority margin that you provided based on clinical response and all-cause mortality as primary endpoints.
2. Extent of the missing safety laboratory data.

We are providing the above comments to give you preliminary notice of potential review issues.

Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. Treatment-blinded case report forms for deaths, serious adverse events, discontinuations due to adverse events, and random sample of patients (random sample lists for studies 0015 and 0019 to be forwarded separately).
2. Provide an analysis of clinical cure rates in clinically evaluable subgroups, similar to that presented in Section 5.2.9.2.1 of the ISE, for Studies 0015 and 0019 separately.
3. Submit a rationale for assuming applicability of foreign data in the submission to the U.S. population, given the difference in clinical response rates in the pooled studies between geographic groups (i.e., 10% treatment difference favoring telavancin in Group 1 versus 1% and 3% treatment differences favoring vancomycin in Groups 2 and 3, respectively).

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. We acknowledge receipt of your request for a full deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you of our decision.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Acting Division Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Wiley Chambers
4/6/2009 01:51:39 PM

Dr. Coleman,

Please see the clarifications below (*bold italicized*) in response to your request on March 2, 2009:

We ask for clarification of the Information Request received 02/26/09 (Requests 1, 4, 5, and 12):

1. **1. In the Summary of Clinical Safety, you report there were a substantial proportion of patients with missing WBC counts from the central lab at baseline.**

FDA Request: In view of the missing laboratory data described, please provide an electronic dataset that includes the USUBJID numbers for each subject whose laboratory data was affected, the study site and location, study number, actual treatment group, the individual laboratory tests per subject whose results were missing, and the corresponding study visit and study day for each missing test.

Request for clarification:

The request discusses missing central laboratory WBC counts at baseline and then requests a dataset. We would like to confirm whether the dataset should include patients:

- with any missing baseline central laboratory data
- with any missing central laboratory data (any visit)

FDA Response: Provide a dataset that includes any missing central lab data (including baseline and other study visits).

2. **4. Provide the define.xml data in .pdf format.**

Request for clarification:

The define.xml file cannot readily be converted to .pdf format owing to the complexity of the links integral to the file. The define.xml can be simply converted to a PDF file from within our browser, but we cannot guarantee that all links will work within the file. Is there an alternative way to address the issue behind this request?

FDA Response: Provide a PDF file containing data definitions that can be printed using Microsoft Word even if the links are non-functional.

3. **5. Provide an electronic dataset that includes all concomitant procedures performed for study subjects. Include the name of the procedure, the indication for the procedure, and whether the procedure was performed due to an adverse event.**

Request for clarification:

Please clarify what procedures the reviewer is interested in.

In these studies of hospital-acquired pneumonia it was anticipated that patients would have multiple types and severities of comorbid conditions. Concomitant medical procedures were not prospectively collected except as they were recorded in the

narrative section of serious adverse event reports. Given the variability in type and number of comorbid conditions amongst the patients enrolled, any comparison between the two treatment groups would be subject to reporting bias. Also randomization was not controlled for the presence of comorbid conditions which may be associated with specific procedures.

FDA Response: Provide an electronic dataset that would include information regarding subjects who required concomitant procedures due to cardiac, hematologic, hepatic, or renal adverse events so that a table as below could be completed:

<i>Subject ID#</i>	<i>Treatment group</i>	<i>Age/Race/Gender</i>	<i>Study Day of Procedure</i>	<i>Indication for Procedure</i>	<i>Concomitant Procedure</i>

Examples of adverse events that should be captured include anemia, renal failure, hepatic necrosis, and torsades de pointes; examples of procedures that should be included in the table include blood transfusions, initiation of dialysis/CVVH, liver biopsy/resection, and pacemaker placement.

4. **12. In the ADLABS dataset, provide flags for the following information:**
1. • **Flag to indicate “normal baseline” test value**
 2. • **Flag to indicate “fulfills Hy’s Rule of hepatotoxicity”**
 3. • **Flag to indicate “at least 2 grade increase in toxicity”**

Request for clarification:

Like the Phase 3 program in complicated skin and skin structure infections studies reported in NDA 22-110, the nosocomial pneumonia program (Studies 0015 and 0019, NDA 22-407) did not utilize a grading system for evaluating changes in laboratory results. Those assessed as adverse events by the local investigator were assessed as mild, moderate, or severe based on clinical judgement.

Laboratory data were analyzed as specified in the protocol-

Continuous laboratory measurements will be summarized at each visit using univariate descriptive statistics (mean, median, etc.); observed values and changes from baseline will be summarized. Labs will also be summarized in terms of pre- to post-treatment shifts relative to lab normal ranges (normal-->low, normal-->normal, normal-->high, etc.).

Please confirm that this additional analysis should be undertaken. If so, please advise which laboratory parameters should be graded and what grading scale the reviewer would recommend we use for these data (nosocomial pneumonia).

FDA Response: Provide the following:

1. Revised laboratory datasets (adlabcs2, adlabpcs, adlabplt, adlabs) with demographic and analysis population variables removed. Information to be retained in the revised datasets should include USUBJID, PROTVERC, ACTTRTC, and all laboratory test information.

2. Using the NCI Common Toxicity Criteria, provide a unique dataset that includes toxicity grading for the following laboratory tests: ALT, AST, alkaline phosphatase, total bilirubin, calcium, CPK, creatinine, glucose, magnesium, phosphorous, proteinuria, sodium, uric acid, hemoglobin, platelets, leukocytes, neutrophils, PT, INR. Include the study number, actual treatment received, subject ID number, a flag for subjects with a normal baseline result, a flag for subjects with an abnormal baseline result, a flag to indicate subjects with at least a 2 grade increase in toxicity post-baseline, the study day that the test was done, the windowed study visit (ie, baseline, EOT, TOC, etc), the analysis window in which a laboratory tests occurred, and a flag to indicate the maximum post-baseline toxicity grade and the maximum on-treatment value. In addition, include a flag to indicate subjects who fulfill Hy's Rule of hepatotoxicity ($ALT \geq 3 \times ULN$ and $T\ Bilirubin > 2 \times ULN$ with $Alk\ phos < 2 \times ULN$).

3. As noted in the central laboratory manual, some of the tests for which toxicity grading has been requested are not listed in the central laboratory chemistry panel. Please specify which tests of those listed above, were not performed and explain the rationale for not including those tests in the safety assessment.

If you have questions, please contact me at (301) 796-0702.

J. Christopher Davi, MS
Senior Regulatory Project Manager
Division of Anti-Infective and Ophthalmology Products

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/s/

Christopher Davi
3/10/2009 01:59:25 PM
CSO

Dr. Coleman,

With regard to NDA 22-407, please see the following information requests from the clinical review team:

1. In the Summary of Clinical Safety, you report there were a substantial proportion of patients with missing WBC counts from the central lab at baseline.

In view of the missing laboratory data described, please provide an electronic dataset that includes the USUBJID numbers for each subject whose laboratory data was affected, the study site and location, study number, actual treatment group, the individual laboratory tests per subject whose results were missing, and the corresponding study visit and study day for each missing test.

2. Provide 28 day post-therapy mortality data for all subjects in both Phase 3 studies. This data is of particular interest for subjects who had their Follow-up/TOC visit prior to 28 days post-therapy, in order to account for any deaths that occurred between the Follow-up/TOC visit and Day 28 post-therapy.
3. Provide the final report on the study site audits.

Dataset Issues:

4. Provide the define.xml data in .pdf format.
5. Provide an electronic dataset that includes all concomitant procedures performed for study subjects. Include the name of the procedure, the indication for the procedure, and whether the procedure was performed due to an adverse event.
6. Provide an electronic dataset that includes only subjects who received potentially effective non-study antibiotics (PENSAB) from the time of randomization through TOC. Include the USUBJID numbers for each subject, the study site and location, actual treatment group, the potentially effective non-study antibiotics administered, the duration of such treatment (number of days), the indication for PENSAB, and a rationale for how the PENSAB classification affected CE and ME analysis evaluability for each subject.
7. Provide an electronic dataset that includes all subjects who experienced a hypersensitivity reaction. Include the USUBJID numbers for each subject, the study number, actual treatment administered, description of the clinical manifestations of the event, duration of the event, action taken with respect to study drug, the interventions employed to alleviate the reaction, and the outcome of the event. Provide individual patient narratives unless already provided in the NDA submission.

8. In the ADAE datasets, provide new data columns that indicate the adverse event duration (days), study day of onset of the AE and the adverse event time period (ie, on study drug or post-treatment).
9. In the ADANTMIC and ADCONMED datasets, provide new data columns that indicate the duration (days) of concomitant antibiotics and concomitant medications.
10. In the ADCOV dataset, add new data columns that indicate "Baseline renal risk: prior/concomitant nephrotoxic drugs" and identify the suspect drugs and their duration of administration.
11. In the ADLABS dataset, include lab data results in both standard and conventional units (example: total bilirubin results in both mg/dL and $\mu\text{mol/L}$)
12. In the ADLABS dataset, provide flags for the following information:
 - Flag to indicate "normal baseline" test value
 - Flag to indicate "fulfills Hy's Rule of hepatotoxicity"
 - Flag to indicate "at least 2 grade increase in toxicity"
13. In the ADSL dataset, add a flag to indicate whether the radiologic assessments were provided by the radiologist or by the investigator (or investigator's designate).
14. In the vs.xpt tabulations, include flags for the following:
 - Diastolic BP <50
 - Diastolic BP >105
 - Systolic BP <90
 - Systolic BP >180
 - Pulse >120
 - Pulse <50
 - Temperature < 35.6 °C
 - Temperature >40.5 °C
15. Study drug duration (in number of days) for the safety datasets.

If you have questions, please contact me at (301) 796-0702.

J. Christopher Davi, MS
Regulatory Project Manager
DAIOP

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/s/

Christopher Davi
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CSO



NDA 22-407

NDA ACKNOWLEDGMENT

Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Vice President
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Telavancin Hydrochloride

Date of Application: January 23, 2009

Date of Receipt: January 29, 2009

Our Reference Number: NDA 22-407

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 30, 2009 in accordance with 21 CFR 314.101(a).

Please note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application.

You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank*, to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at: http://internet-dev.fda.gov/cder/regulatory/FDAAA_certification.htm. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information on registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call J. Christopher Davi, MS, Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Frances LeSane
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Frances LeSane
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IND 60,237

Theravance, Inc.
Attention: Rebecca Coleman, PharmD
Senior Director, Regulatory Affairs
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

Please refer to your Investigational New Drug Application (IND) for telavancin for injection. We also refer to the meeting between representatives of your firm and the FDA on March 6, 2008. The purpose of the meeting was to discuss a future marketing application submission for telavancin in the hospital acquired pneumonia (HAP) indication.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

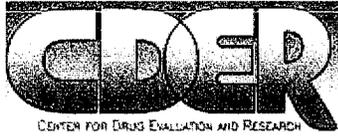
If you have any questions, call J. Christopher Davi, MS, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures: Minutes from meeting



MEMORANDUM OF MEETING

MEETING DATE: March 6, 2008
MEETING TIME: 3:00 to 4:00 PM, EST

APPLICATION (DRUG): IND 60,237 (telavancin for injection)

SPONSOR: Theravance, Inc.

TYPE OF MEETING: Pre-NDA, HAP indication
MEETING CHAIR: Wiley A. Chambers, MD, Acting Division Director, DAIOP
MEETING RECORDER: J. Christopher Davi, MS, Regulatory Project Manager

**FDA PARTICIPANTS, Division of Anti-infective and Ophthalmology Products, DAIOP
(unless otherwise noted):**

Edward M. Cox, MD, MPH, Director Office of Antimicrobial Products (OAP)
Wiley Chambers, MD, Acting Division Director
Katherine A. Laessig, MD, Deputy Division Director
Sumathi Nambiar, MD, MPH, Medical Team Leader
Janice K. Pohlman, MD, MPH, Medical Reviewer
Thamban Valappil, PhD, Team Leader, Biometrics
Scott Komo, DrPH, Reviewer, Biostatistics
David L. Roeder, MS, Associate Director of Regulatory Affairs, OAP)
J. Christopher Davi, MS, Regulatory Project Manager

INDUSTRY PARTICIPANTS (Theravance, Inc):

Michael Kitt, MD, Senior VP, Development
Steve Barriere, MD, Senior Director, Clinical
David Friedland, MD, Senior Director, Clinical
Alan Hopkins, PhD, Biometrics
Fred Genter, PhD, Biostatistics
Joanne DiGiorgio, Regulatory Affairs
Becky Coleman, PharmD, Senior Director, Regulatory Affairs
Rick Winningham, CEO, Theravance
Edie Smith, Project Management, Theravance

Astellas

Robert Reed, Director of Regulatory Affairs
Rochelle Maher, Drug Development and Project Management
Nkechi Azie, Medical Director

MEETING OBJECTIVE:

- To discuss a future marketing application submission for telavancin in the hospital acquired pneumonia (HAP) indication.

SUMMARY OF DISCUSSION:

The Division of Anti-Infective and Ophthalmology Products (DAIOP) granted Theravance (Sponsor) a meeting to discuss their HAP NDA submission. DAIOP provided preliminary comments to the Sponsor on March 5, 2008 (appended). Discussion points generated from the preliminary comments are provided herein.

- The Sponsor discussed a previous meeting with the Agency (end of Phase 2) and recalled the Agency's recommendation to rely on the clinical investigator's assessment regarding determination of outcome rather than use a clinical events committee.
- The Sponsor acknowledged that the Agency would be doing their own analysis. The Sponsor indicated that they are currently unblinded and have submitted preliminary study results to the Agency.
- The Sponsor stated that the definitions for clinical cure are in the protocol, but not in the statistical analysis plan (SAP). The Sponsor indicated that they (Sponsor) agreed with the Agency's definition of clinical cure, but that they had questions regarding the definition of failure.
- The Sponsor expressed concern about the clinical failure definition, as it relates to all cause mortality and not attributable mortality as suggested by the Sponsor. The Sponsor described a scenario where a patient with an injury (e.g., head trauma) who develops HAP should not necessarily be considered a failure if the patient was to die from the head trauma. The Division stated that there may be contributing factors, unrelated to the infection, and that these would likely even out between the groups due to randomization.
- The Sponsor expressed a desire to devise a sensitivity analysis similar, or identical to the sensitivity analysis that will be conducted by the Agency. The Sponsor indicated that their approach in the determination of outcome was based on the investigator's assessment and that they (Sponsor) made no attempt to alter outcomes.
- The Sponsor indicated that they planned to provide a secondary analysis on gram negative performance.
- The Division questioned the Sponsor regarding including Gram negatives in the all-treated populations as telavancin does not have Gram negative activity. The Division added that such an analysis would potentially confound the outcome, particularly in a non-inferiority setting, and make the study drug look more similar to the comparator.

- The Sponsor indicated that they would have difficulty going back and changing the populations. The Sponsor added that the study was an “all-comers” study, and that their approach with regard to the analysis was agreed upon with the Division at the End of Phase 2.
- The Division acknowledged the Sponsor’s concerns. The Division acknowledged the Sponsor’s 28 day time window, but cited problems with differential follow-up.
- The Sponsor stated that they understood the Division’s concern surrounding potentially effective antibiotic therapy (PEAT), and that they would make clear in the submission the definition(s) of PEAT relative to prior to starting study drug and while on study drugs.
- The Sponsor discussed the adequacy of specimens, indicating that they made efforts to ensure this, however the Sponsor stated that there is debate on the role of quantitative cultures. The Sponsor indicated that some sites obtained broncho-alveolar lavage (BAL) specimens, and that some sites had only sputum. The Sponsor informed the Division that there will be a spectrum of specimen types in this regard (i.e., quantitative methods between sites were different).
- The Sponsor informed the Division that if an organism was on the respiratory pathogen list, they were included in the analysis. The Sponsor added that there was a Gram positive and a Gram negative listing of organisms, and if an organism was isolated (and on either of the lists) it was considered a “pathogen”.
- The Sponsor informed the Division that they did not obtain chest radiology reports. The Sponsor attributed this to the fact that the study was not designed to include adjudication, but rather relied upon the investigator’s assessment. The Sponsor added however that the treating physician’s assessment of the X-ray is included in the case report forms (CRF).
- The Division questioned the Sponsor as to why they would not provide such radiology reports, as there can be differences between “real time” assessments and radiology reports. The Division expressed a preference for radiology reports, and the Sponsor stated that the reports could be provided.
- The Sponsor asked the Division when they would receive feedback from the Division regarding the NI justification provided by the Sponsor. The Division stated that the NI justification will be reviewed during review of the NDA.
- The Sponsor asked the Division if they (Division) wished to see microbiological data from the HAP study (i.e., separate from the cSSSI micro data) in the NDA. The Division stated that the preference would be for the presentation of HAP microbiological data only.

- The Sponsor asked the Division if they (Sponsor) could combine data from the two HAP studies for purposes of the integrated summary of safety (ISS). The Sponsor also stated that the safety data from the HAP studies would not be combined with the cSSSI studies. The Division stated that this would be acceptable.

Minutes Prepared by: *{See appended electronic signature page}*
J. Christopher Davi, MS
Regulatory Project Manager

Concurrence by: *{See appended electronic signature page}*
Wiley A. Chambers, M.D.
Acting Division Director

Dr. Coleman,

In anticipation of our Pre-NDA meeting on March 6, 2008, for IND 60,237, please see the following responses from the Division of Anti-Infective and Ophthalmology Products (DAIOP) as they relate to the questions posed on page 5 of your February 6, 2008, briefing document:

1. Is the proposal for analysis of the Phase 3 Studies, as outlined in the Statistical Analysis Plan (Telavancin IND 60,237 SN 231, submitted 12 November 2007) acceptable?

Agency Response: The clinical and statistical review team has the following comments regarding FDA analysis:

- *The clinical response definitions are not outlined in the statistical analysis plan*
 - *FDA definition of clinical cure:*
 - *signs and symptoms of the primary infection have resolved or improved to the point that no further antibiotics for pneumonia are required AND*
 - *the baseline chest radiographic findings improved or did not progress*
 - *FDA definition of clinical failure:*
 - *primary treatment failure (lack of resolution or progression of pneumonia) after minimum of 72 hours of study medication treatment*
 - *relapsed pneumonia prior to TOC*
 - *premature discontinuation of study medication due to adverse event*
 - *death after minimum of 72 hours of study treatment due to any cause (not attributable mortality), up to 28 days after end-of-therapy (EOT)*
 - *Indeterminate:*
 - *inability to determine outcome*
- *Please describe a scenario(s) in which a patient is assessed by the investigator as "indeterminate" at EOT and subsequently a "clinical cure" at TOC*
- *FDA Analysis Populations:*
 - *All-treated (AT): all patients who received any amount of study drug (as randomized)*
 - *Clinically modified all-treated (cMAT): patients in the all-treated population who meet the clinical definition of HAP and do not have only Gram negative organisms isolated from baseline microbiological cultures*
 - *Microbiological modified AT (mMAT): patients in the AT population who have a baseline respiratory pathogen isolated excluding patients with only Gram negative organisms and those with mixed Gram positive/negative organisms who are not receiving adequate antimicrobial coverage for the Gram negative pathogen*
 - *Clinically evaluable (CE): AT population with sufficient adherence to protocol with conditions outlined by Theravance (statistical analysis plan submitted to IND 60,237) with the following exceptions/clarifications:*
 - *Meets inclusion criterion of signs and symptoms and chest radiograph consistent with pneumonia or else was approved for enrollment by study hotline monitor – please explain how a patient not meeting these inclusion criteria could be enrolled in a HAP study*
 - *Meets inclusion criteria regarding availability of appropriate specimens – patients with negative microbiological cultures should be included in the CE population*
 - *Patient did not receive effective concomitant systemic antibiotic therapy for >24 hours prior to study enrollment or any time before TOC, unless the patient was enrolled due to clinical failure after at least 72 hrs of antimicrobial treatment or the pathogen demonstrated in vitro resistance to the prior antimicrobial*
 - *If the patient was not a failure at EOT, then TOC assessment was made between Study Day 7P and 14 P, inclusive*
 - *All-cause mortality up to 28 days after EOT*

- *Microbiologically evaluable (ME): patients in the CE population who also have a Gram positive baseline respiratory pathogen.*
- *Consideration should be given to including co-primary analysis populations using the cMAT and CE populations as defined above.*
- *Baseline pathogen window:
The window for obtaining specimens for baseline microbiology should be the 24 hour period prior to randomization with the exception of patients enrolled due to clinical failure after >72 hours of antimicrobial therapy and/or demonstrated in vitro resistance to the previously administered antimicrobial agent. The antimicrobial agent administered and corresponding susceptibility result of the resistant pathogen should be linked and provided in a dataset.*
- *Concomitant potentially effective antibiotic therapy (PEAT) from initiation of study drug treatment through EOT:
The duration of PEAT should not be greater than 24 hours since ≥ 24 hours of antimicrobial therapy has been demonstrated to diminish sensitivity of microbiological culture for some respiratory pathogens (i.e., Streptococcus pneumoniae)^{1,2}.*
- *If you would like to include patients receiving concomitant antimicrobial therapy for up to 3 days, please submit evidence (i.e., published literature) for consideration, regarding the lack of effect of this type of concomitant antimicrobial therapy on clinical status and respiratory cultures. The antimicrobial agent classified as PEAT and corresponding susceptibility result of the patient's pathogen(s) should be linked and provided in a dataset.*
- *Including both prior and concomitant potentially effective antimicrobial agents in the definition of PEAT is confusing. Please provide clarification or consider the pre-study and on-study antimicrobial treatment situations separately.*
- *The study protocol states that sputum and endotracheal aspiration specimens have >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per low power field (10X objective).*
 - *How are organisms classified as pathogen versus colonizer in these and other types of specimens? If quantitative microbiology results are used for other types of specimens (i.e., bronchoalveolar lavage, protected specimen brush), the quantity used for pathogen determination should be specified.*
 - *Please provide the list of organisms which are considered to be respiratory pathogens in Study 0015 and 0019.*
 - *There should be a dataset submitted with the NDA containing Gram stain results which can be linked to the pathogen status of organisms isolated from the corresponding specimen.*
- *Microbiological analyses should be performed separately where central and local microbiology laboratory results for determination of pathogen identification and antimicrobial susceptibility are combined and where only central microbiology results are used.*
- *Chest radiographic reports should be submitted with the patient's case report form.*
- *The non-inferiority margin justification is still under review.*
- *The superiority analysis should be based on response rates in the AT population (or perhaps the MAT as described above). Ultimately, superiority claims are a labeling issue based on efficacy and safety criteria*

¹ Musher DM, Montoya R, Wanahita, A. Diagnostic Value of Microscopic Examination of Gram-Stained Sputum and Sputum Cultures in Patients with Bacteremic Pneumococcal Pneumonia. *Clinical Infectious Disease* 2004;39:165-169.

² Souweine B, et al. Diagnostic Accuracy of Protected Specimen Brush and Bronchoalveolar Lavage in Nosocomial Pneumonia: Impact of Previous Antimicrobial Treatments. *Critical Care Medicine* 1998;26:236-244.

and overall benefit to risk assessment. In order for a claim to be made regarding the superiority of telavancin to vancomycin for treatment of infection due to methicillin-resistant Staphylococcus aureus, superiority would have to be demonstrated for the primary efficacy endpoint in both HAP trials.

- *The Streptococcus pneumoniae multi-drug resistant strain (MDRSP) designation referring to the agents listed in the briefing package (penicillins, second-generation cephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole) was developed in the context of treatment of community-acquired pneumonia, not hospital-acquired pneumonia which is likely to be treated with different antimicrobial agents. What data (in vitro, clinical) are available regarding telavancin activity against penicillin-resistant S pneumoniae? Was activity based on penicillin resistance as defined by MIC \geq 2 μ g/mL?*
2. Please comment on the implications for our product of any conclusions reached following the recent IDSA/FDA workshop regarding the development of products for community acquired pneumonia.

Agency Response: The discussion at the IDSA/FDA workshop on development of antimicrobial products for community-acquired pneumonia has no direct implications for the telavancin HAP submission.

3. Please comment on the plan for an eCTD for the HAP indication and advise the Sponsor regarding any implications for the ongoing review of the cSSSI indication.

Agency Response:

Referencing Previously Submitted Documents

If a document was submitted in electronic format with the eCTD backbone files, you should not submit additional copies when referencing the previously submitted document. Instead, you should include the information by reference by providing in the text of the document (1) the application or master file number, (2) the date of submission (e.g., letter date), (3) the document name, and (4) the page number of the referenced document along with a hypertext link to the location of the information (see section II.Q of this guidance). If a document replaces or appends a document previously submitted with an eCTD backbone file, then you should include this information in the appropriate eCTD backbone file. The details on how to include this information in the eCTD backbone file are provided in the associated specifications for eCTD backbone files.

*If a document was previously submitted in either paper or electronic format **without the proper eCTD backbone files**, you should reference the document as with any paper submission. In the text of the document, you should include (1) the application or master file number, (2) the date of submission (e.g., letter date), (3) the document name, (4) the page number, and (5) the submission identification (e.g., submission serial number, volume number, electronic folder, and file name) of the referenced document. In such cases, providing an electronic copy of the previously submitted documents can increase the utility of the submission. These documents, like all documents in the submission, should be appropriately described in the eCTD backbone files. These files are considered new in the eCTD backbone files. When referring to documents that are part of other applications, please remember to include the appropriate letters of authorization with the submission (e.g., 21 CFR 314.420(d)).*

We look forward to meeting with you on March 6, 2008. If you have any questions, please contact me at (301) 796-0702.

Regards,

J. Christopher Davi, MS
Regulatory Project Manager
DAIOP

Linked Applications

Sponsor Name

Drug Name

IND 60237

THERAVANCE INC

TD-6424

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/s/

WILEY A CHAMBERS

06/18/2008