CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-110

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-110 SUPPL # N/A HFD # 520

Trade Name VIBATIV

Generic Name Telavancin

Applicant Name Theravance, Inc.

Approval Date, If Known June of 2009

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 ☒ NO ☐

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

505(b)(1)

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 ☒ NO ☐

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.

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:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

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

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

YES ☐ 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?

YES ☐ 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 ☐ NO ☒

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

NDA#

NDA#

NDA#

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.)

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

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 ☐ NO ☐

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 ☐ NO ☐

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?

YES ☐ 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.

YES ☐ 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?

YES ☐ 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:

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 YES ☐ NO ☐

Investigation #2 YES ☐ 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 YES ☐ NO ☐

Investigation #2 YES ☐ 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"):

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 # YES ☐ ! NO ☐
! Explain:

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

(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?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(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.)

YES ☐ NO ☐

If yes, explain:

Name of person completing form: J. Christopher Davi, MS, Senior RPM, DAIOP
Title: Senior Regulatory Project Manager
Date: April 3, 2009

Name of Office/Division Director signing form: Wiley A. Chambers, MD
Title: Acting Division Ditrector, DAIOP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Kathrine Laessig
5/11/2009 10:25:59 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-110 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: December 19, 2006 PDUFA Goal Date: October 19, 2007

HFD-520

Trade and generic names/dosage form: Vibativ (telavancin for injection/intravenous infusion)

Applicant: Theravance, Inc. Therapeutic Class: 4010900 (Antibiotic)

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

X Yes. Please proceed to the next question.

No. PREA does not apply. Skip to signature block.

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) *previously approved* (please complete this section for supplements only): N/A

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Complicated Skin and Skin Structure Infections (cSSSI)

this an orphan indication?

Yes. PREA does not apply. Skip to signature block.

X No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

X No: Please check all that apply: ____Partial Waiver __X__Deferred ____Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

f studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr.__0__ Tanner Stage_____
Max_____ kg_____ mo._____ yr.__16__ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- X **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): December 31, 2012

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}
J. Christopher Davi, MS, RPM
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- ☐ **Yes. PREA does not apply. Skip to signature block.**
- ☐ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Sumathi Nambiar
5/31/2007 08:00:49 AM

1.3.3 DEBARMENT CERTIFICATION

b(4)

Brand Name: C) (Proposed)

Active Ingredient: Telavancin Hydrochloride

Strengths: (1) 250 mg (2) 750 mg

Proposed Indication: complicated Skin and Skin-Structure Infections (cSSSI)

In connection with this new drug application, Theravance certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act.

Rebecca Coleman Date: 01 Dec. 2006

Rebecca Coleman, PharmD.
Senior Director, Regulatory Affairs
Theravance, Inc.

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Title: Primary:
To evaluate the outcomes of pregnancy in women who were exposed to VIBATIV at any time during pregnancy.
Secondary:
To evaluate the effect of fetal exposure to VIBATIV on pregnancy outcomes, fetal/neonatal outcomes, and infant development and milestones through 12 months of age.

PMR/PMC Schedule Milestones:		
	Protocol Submission Date:	08/2009 (completed)
	Interim Report Date:	09/2010 and annually
	Study Completion Date:	06/2019
	Final Study Report Submission Date:	12/2019

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Only feasible to conduct post-approval and long term data needed

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 4.***

   - **Which regulation?**

     ☐ Accelerated approval
     ☐ Animal efficacy confirmatory studies
     ☐ Pediatric requirement
     ☒ FDAAA required safety study/clinical trial

   - **Describe the particular review issue leading to the PMR**

Adverse developmental outcomes (teratogenicity) observed in three animal species at clinically relevant doses

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

Potential adverse developmental outcomes (teratogenicity) in humans

- **If the PMR is a FDAAA safety study/clinical trial, does it:**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

N/A

4. If not required by regulation, characterize the review issue leading to this **PMC**

N/A

5. What type of study or clinical trial is required or agreed upon (describe)?

Develop and maintain a pregnancy registry

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

☒ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

☐ Subpopulation (list type)

☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
☐ Dose-response study performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

6. Is the PMR/PMC clear and feasible?

   ☒ Are the schedule milestones and objectives clear? Yes
   ☒ Has the applicant adequately justified the choice of schedule milestone dates? Yes
   ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility? Yes

---

CDTL or PMR/PMC Development Coordinator:
This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality. X

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Title: Emerging resistance

PMR/PMC Schedule Milestones:		
	Protocol Submission Date:	01/2010
	Interim Report Submission:	03/2011, then annually
	Study Completion Date:	12/2014
	Final Study Report Submission Date:	05/2015

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Only feasible to conduct post-approval

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 4.***

- **Which regulation?**
  - ☐ Accelerated approval
  - ☐ Animal efficacy confirmatory studies
  - ☐ Pediatric requirement
  - ☒ FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

Likelihood for development of antibacterial resistance

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

Development of antibacterial resistance making the drug ineffective

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☒ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  - ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

5. What type of study or clinical trial is required or agreed upon (describe)?

A prospective study over a five year period after introduction of telavancin to the market to determine if resistance to Vibativ is occurring in the target population of bacteria that are in the approved Vibativ package insert

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

☐ Subpopulation (list type)

☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
Surveillance study to evaluate development of anti-bacterial resistance

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
☐ Dose-response study performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

6. Is the PMR/PMC clear and feasible?

☒ Are the schedule milestones and objectives clear? Yes
☒ Has the applicant adequately justified the choice of schedule milestone dates? Yes
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility? Yes

CDTL or PMR/PMC Development Coordinator:
This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality. ☒

Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Title: Effect of Renal Function on Biological Activity

PMR/PMC Schedule Milestones:

Protocol Submission Date:	01/2010
Study Completion Date:	02/2011
Final Study Report Submission Date:	06/2011

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Small subpopulation affected

2. If required, characterize the **PMR**. Check all that apply and add text where indicated. ***If not a PMR, skip to 4.***

- **Which regulation?**
  - ☐ Accelerated approval
  - ☐ Animal efficacy confirmatory studies
  - ☐ Pediatric requirement
  - ☐ FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

  ☐ Analysis of spontaneous postmarketing adverse events?
  Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  ☐ Analysis using pharmacovigilance system?
  Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
  Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

Decreased efficacy noted in patients with moderate and severe renal impairment

5. What type of study or clinical trial is required or agreed upon (describe)?

A comparative study evaluating results obtained with the current analytical assay for determining concentrations of telavancin in plasma and results obtained with a bioassay method for patients with normal renal function, severe renal impairment and end stage renal disease receiving hemodialysis

Required

☐ Pharmacoepidemiologic study (list risk to be evaluated)

☐ Registry studies
☐ Primary safety study or clinical trial (list risk to be evaluated)

☐ Subpopulation (list type)

☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing studies
☐ Additional data or analysis required for a previously submitted or expected study (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
☐ Dose-response study performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
Bioassay in patients with renal impairment

6. Is the PMR/PMC clear and feasible?

☒ Are the schedule milestones and objectives clear? Yes
☒ Has the applicant adequately justified the choice of schedule milestone dates? Yes
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility? Yes

CDTL or PMR/PMC Development Coordinator:
This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality. X

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22110	ORIG 1	THERAVANCE INC	TELAVANCIN

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

/s/

SUSMITA SAMANTA
09/01/2009

SUMATHI NAMBIAR
09/01/2009

ACTION PACKAGE CHECKLIST

Application Information			
BLA # N/A NDA # 22-110	BLA STN# N/A NDA Supplement # N/A	If NDA, Efficacy Supplement Type N/A	
Proprietary Name: Televancin Established Name: Vibativ Dosage Form: Injection/Intravenous Infusion		Applicant: Theravance, Inc.	
RPM: J. Christopher Davi, MS, Senior Regulatory Project Manager, Division of Anti-Infective and Ophthalmology Products		Division: DAIOP	Phone: (301) 796-0702
NDAs: NDA Application Type: 505(b)(1) Efficacy Supplement: N/A		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): N/A	

❖ User Fee Goal Date ❖ Action Goal Date (if different)	September 16, 2009 September 11, 2009
❖ Actions	
• Proposed action	AP: September 11, 2009
• Previous actions *(specify type and date for each action taken)*	AE: October 19, 2007 CR: February 20, 2009
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	X Requested in AP letter ☐ Received and reviewed
Application Characteristics	

Review priority: Standard
Chemical classification (new NDAs only): New Molecular Entity (NME) 4010900
NDAs, BLAs and Supplements: Fast Track

NDAs: Subpart H
- ☐ Accelerated approval (21 CFR 314.510)
- ☐ Restricted distribution (21 CFR 314.520)

Subpart I
- ☐ Approval based on animal studies

NDAs and NDA Supplements

Other comments: None

Application Integrity Policy (AIP)	
• Applicant is on the AIP	No

• This application is on the AIP	No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	N/A
• OC clearance for approval *(file communication in* Administrative Documents *section)*	N/A
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	X Yes
• Press Office notified of action	X Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	X None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	Included
• Is approval of this application blocked by any type of exclusivity?	
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *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.*	N/A (Not a 505(b)(2) application) N/A
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	N/A
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	N/A
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	N/A
❖ Patent Information (NDAs and NDA supplements only)	
• 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.	X Verified ☐ Not applicable because drug is an old antibiotic.
• 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.	21 CFR 314.50(i)(1)(*i*)(A) 21 CFR 314.50(i)(1) **N/A**
• [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).	☐ No paragraph III certification Date patent will expire **N/A**

• [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). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ **N/A (no paragraph IV certification)** ☐ Verified
• [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 to the next section below (*Summary Reviews*).* *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*	☐ Yes ☐ No ☐ Yes ☐ No ☐ Yes ☐ No ☐ Yes ☐ No

*paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**No**," continue with question (5).* (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? (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). *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*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	☐ Yes ☐ No
Summary Reviews	
Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	October 19, 2007
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	N/A
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	August 27, 2009
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	August 25, 2009
• Original applicant-proposed labeling	December 2006
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	See above
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	See above
• Original applicant-proposed labeling	See above
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	See above
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	July 27, 2008
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	August 18, 2009

• Original applicant-proposed labeling	See above
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	See above
Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	August 27, 2009
• Most recent applicant-proposed labeling	July 28, 2009
❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	X DMEPA 08/06/09 X DRISK 07/15/09 X DDMAC 05/21/09 X SEALD (PLR) 05/09

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	April 17, 2009
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	N/A
❖ Pediatric Page (all actions)	Included
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. *(Include certification.)*	X Verified, statement is acceptable
❖ Postmarketing Commitment Studies	Included
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	See Action Letter dated September 11, 2009
• Incoming submission documenting commitment	N/A
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	Included
❖ Internal memoranda, telecons, email, etc.	Included
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg
• EOP2 meeting *(indicate date)*	☐ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting	
• Date of Meeting	November 19, 2008
• 48-hour alert or minutes, if available	Not available
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	September 5, 2007 November 18, 2008 June 11, 2009
Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	Microsterility – January 14, 2009

❖ BLAs: Product subject to lot release (APs only)	N/A
Environmental Assessment (check one) (original and supplemental applications)	
• ☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	September 5, 2007
• ☐ Review & FONSI *(indicate date of review)*	September 5, 2007
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	September 5, 2007
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	January 14, 2009
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Acceptable

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	N/A
❖ NDAs: Methods Validation	Not needed
Nonclinical Information	
Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	June 18, 2007 (cycle 1) August 12, 2009 (cycles 2 & 3)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	Pregnancy and Maternal Health: June 27, 2007 December 16, 2008 PTCC Subcommittee: August 3, 2007
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ ECAC/CAC report/memo of meeting	N/A
❖ Nonclinical inspection review Summary (DSI)	N/A

Clinical Information	
Clinical review(s) *(indicate date for each review)*	October 18, 2007 December 22, 2008 August 20, 2009
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	N/A
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	Cardio/Renal – June 15, 2007
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	September 26, 2007 March 10, 2009
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	In clinical review(s) – See above
❖ REMS *(indicate location/date if incorporated into another review)*	August 11, 2009
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	
• Clinical Studies	June 21, 2007 September 15, 2008
• Bioequivalence Studies	N/A
• Clin Pharm Studies	N/A
❖ Statistical Review(s) *(indicate date for each review)*	October 10, 2007 December 16, 2008 August 17, 2009
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	August 31, 2007 August 20, 2008

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-110

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 January 21, 2008 of your January 21, 2008 resubmission to your new drug application for Telavancin for Injection.

We consider this a complete, class 2 response to our October 19, 2007 action letter. Therefore, the goal date is July 21, 2008.

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 note that you have not fulfilled the requirement. We are deferring submission of your pediatric studies until December 31, 2013. We acknowledge receipt of your pediatric drug development plan dated June 19, 2007.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of section 2 of the Pediatric Research Equity Act (PREA) within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. Please note that satisfaction of the requirements in section 2 of PREA alone may not qualify you for pediatric exclusivity.

Please cite the NDA number listed above 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

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

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

/s/

Frances LeSane
3/4/2008 01:45:36 PM

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: September 15, 2008

TO: J. Christopher Davi, Regulatory Project Manager
Janice Pohlman, Medical Officer

FROM: John Lee, Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, MD
Branch Chief, Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-110

APPLICANT: Theravance, Inc.

DRUG: Telavancin Powder for Injection (Vibativ)

NME: Yes

THERAPEUTIC CLASSIFICATION: Class II resubmission

INDICATIONS: Treatment of complicated skin and skin structure infections

CONSULTATION REQUEST DATE: March 17, 2008

DIVISION ACTION GOAL DATE: Pending after Advisory Committee meeting (scheduled for November 18, 2008)

PDUFA DATE: July 21, 2008 (date missed due to the inability to hold an Advisory Committee meeting until additional inspections have been completed to further investigate data integrity concerns; Division to take action promptly after the Advisory Committee meeting)

I. BACKGROUND

This NDA is currently under second cycle of review. The inspections performed in support of this NDA consisted of 11 clinical sites, a contract research organization, and the sponsor. This Clinical Inspection Summary describes the results of seven inspections, all clinical sites, performed between March - August 2008. The seven clinical sites were inspected in follow up of the findings at one of the four initial clinical sites, which revealed significant good clinical practice (GCP) non-compliance.

To evaluate the prevalence of the major deficiencies seen at the initial non-compliant clinical site (Schrock) among the nearly 200 clinical sites which participated in the pivotal studies for this NDA, the additional clinical sites were selected based on: (1) large enrollment size, (2) efficacy data favoring the test article (Telavancin) over the active control (vancomycin), and (3) study monitoring by Covance. The sites were selected to include at least one foreign clinical site.

The Product

Telavancin is a new injectable antibiotic drug (new molecular entity) with activity against clinically important Gram-positive pathogens. Its rapid bactericidal activity presumably results from multiple mechanisms of action which include concentration-dependent inhibition of cell wall synthesis and increased bacterial membrane permeability. The sponsor (Theravance, Inc.) proposes that the use of Telavancin to treat complicated skin and skin structure infections (**cSSSI**) will permit briefer duration of intravenous antibiotic therapy and improved clinical as well as socio-economic outcomes: higher rates of infection resolution, lower relapse rates, briefer hospitalizations, and reduced demand on health care resources. The sponsor claims that the results of the phase 3 clinical trials (Studies 0017 and 0018) support clinical and microbiological non-inferiority of Telavancin when compared to Vancomycin in the treatment of cSSSI caused by gram positive microorganisms, including those caused by methicillin-resistant *Staphylococcus aureus*.

Study Protocols

The two phase 3 studies (0017 and 0018) were of identical study design (randomized, double-blind, active-controlled, parallel-group, multicenter, multi-national clinical trials) and compared intravenous Telavancin to the current standard therapy (Vancomycin) for the treatment of cSSSI caused by gram positive bacteria. The primary objective of the studies was to compare the efficacy and safety of Telavancin to Vancomycin in the treatment of adults with complicated gram-positive SSI with an emphasis on patients with infections due to methicillin-resistant *Staphylococcus aureus* (**MRSA**). The primary efficacy endpoint was the clinical response (Cure, Not Cured, or Indeterminate) at the Test-of-Cure visit.

- In randomizing subjects meeting study eligibility criteria, unblinded study personnel were to contact a central randomization service for assignment of a patient number and study medication, Telavancin 10 mg/kg IV Q24 hrs or Vancomycin 1.0 g Q12 hrs.
- Day 1 was considered the calendar day that the first study dose was given. Patients were to be evaluated daily for occurrence of adverse events, assessment of clinical signs and symptoms of the infection, measurement of the primary infection site, blood cultures, documentation of any significant procedures performed, and documentation of all concomitant medications.

- The subjects were to be treated for 7 to 14 days, as determined by the investigator (until resolution of signs and symptoms of the skin infection, or no further therapy deemed necessary). Subjects were to be managed for intercurrent events (e.g., mixed infection with gram negative organisms resistant to aztreonam, coagulation problems).
- An End-of-Therapy (**EOT**) visit was to occur as soon as possible after the last dose of study medication and no later than 3 days following the last dose of study medication; an assessment of the clinical response were to be made during that time.
- Within 7 to 14 days after the last dose of study medication, all subjects are to have a follow-up visit, and only those subjects evaluated as Cure or Indeterminate at the End-of-Therapy visit were to have a Test-of-Cure (**TOC**) evaluation at the follow-up visit.

Initial Inspectional Findings

During the first cycle review (prior to the current class II resubmission), 6 inspections were conducted. Their outcomes are briefly summarized below.

- Hekmat, O'Riordan, Dunbar (clinical investigators) and Theravance (sponsor): **NAI**

  The Hekmat site had 260 subjects who were randomized and received at least one dose of the study medication. The O'Riordan site had 167 subjects who were randomized and received any amount of study medication. These two sites in Study 0017 were the two largest sites in either Study 0017 or Study 0018. The study results showed no efficacy advantage for the investigational drug (Telavancin) over the active control (Vancomycin).

  The Dunbar site had 70 subjects who were randomized and received any amount of study medication. This site was the largest site in Study 0018. The study results showed a significant efficacy advantage for Telavancin.

- Schrock (clinical investigator): **OAI**

  This site had 51 subjects who were randomized and received any amount of study medication. Major violations in good clinical practice (GCP) were noted, which resulted in the inspection of the contract research organization (CRO) responsible for the oversight of this site. See *Covance* below.

- Covance (contract research organization): **VAI**

  This CRO served as the monitor for most of the clinical investigators in Studies 0017 and 0018. In view of the inspectional findings at the Schrock site, DSI had been concerned that inadequate study monitoring by this CRO may have affected many clinical sites. The monitors appeared to have identified many of the GCP violations found at FDA inspection of Dr. Schrock but failed to institute appropriate corrective actions. The GCP violations included: (1) problems with the primary efficacy endpoint; (2) source documents being thrown out; (3) unauthorized pharmacists preparing or dispensing the investigational drug, (4) refrigeration temperatures being lost, and (5) wound measurements and infection assessments made by Schrock personnel being different from those made by contracted health care personnel (home health care nurses).

The inspectional findings at the Schrock site and at Covance raised serious concerns about GCP violations affecting data integrity with this NDA, based on which an FDA Advisory Committee meeting (necessary for the approval of this NDA) scheduled for February 2008 was

cancelled. In follow up of these inspectional findings, additional inspections were conducted to better evaluate the scope and seriousness of GCP violations, particularly those that affect data integrity. As in the first cycle of inspections, the clinical sites selected were among the largest enrolling sites. In the second cycle, however, only those with a large positive efficacy margins (as was the case for the Schrock site) were selected. The 7 additional clinical sites and their inspection results are presented below.

II. INSPECTION RESULTS (Second Cycle)

	Clinical Site	Protocol Site Subjects	Inspection Dates (2008)	Classification	
				Field	Final
1	Christopher Bunce Infectious Disease of Indiana, PSC Indianapolis, IN	protocol 0018 site 38074 26 subjects	3/23 - 4/25	VAI	VAI
2	Rafael Borges Family Medical Clinic Houston, TX	protocol 0018 site 38260 46 subjects	5/12 - 5/21	VAI	VAI
3	Larry Bush South Florida Clinical Research Atlantis, FL	protocol 0017 site 38163 38 subjects	5/19 - 5/30	VAI	VAI
4	Richard Brown Baystate Medical Center Springfield, MA	protocol 0017 site 38024 21 subjects	6/9 - 6/13	VAI	pending
5	David Young San Francisco General Hospital San Francisco, CA	protocol 0018 site 38113 56 subjects	6/9 - 6/27	VAI	VAI
6	Stanley Klein Harbor-UCLA Medical Center Torrance, CA	protocol 0017 site 38016 28 subjects	6/12 - 7/24	VAI	pending
7	Zlatko Fiolic Klinički Bolnički Centar Zagreb Zagreb, Croatia	protocol 0017 site 09002 31 subjects	7/28 - 8/1	NAI	pending

NAI = no action indicated (no deviations from regulations); VAI = voluntary action indicated (no significant deviations from regulations); OAI = official action indicated (significant deviations from regulations); NA = not applicable

Classification:

Field = field investigator's initial recommendation in classifying the inspection result
Final = CDER's final classification of the inspection result

1. **Christopher Bunce (site 38074):**

   Infectious Disease of Indiana, PSC
   10610 North Pennsylvania, Suite A
   Indianapolis, IN 46280

   a. What was inspected:

   - Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, adherence to protocol and applicable regulations.
   - Data verification: primary efficacy endpoint data, adverse events, concomitant medication use, and subject discontinuation
   - Subjects: 38 subjects were screened, 26 were enrolled in study 0018, and 22 completed the study. Complete records were reviewed for 18 subjects.

   b. General observations and commentary:

   The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol.

   The major finding from this site was related to record management practices. Record management practices at this site were deficient in that the procedure for converting paper documents into electronic records (scanning original source documents into electronic hospital medical records) did not include certification of accuracy and completeness prior to shredding approximately 40% of records for each subject (progress notes and physician orders).

   Other Cited deficiencies (Form FDA 483):

   - No record of certification/verification in scanning original source documents into electronic database (hospital medical records) prior to shredding approximately 40% of records for each subject (progress notes and physician orders)

     Review Comment: Although this finding is important, it does not suggest compromised data integrity.

   - Six subjects were reported as "Cure" even though clinical assessment showed continued signs of infection (edema, pain, erythema, and or wound drainage)

     Review Comment: Residual signs and symptoms of inflammation are consistent with Cure as specified in the study protocol.

   - Discrepancies between source documents and Case Report Forms (CRFs) on more than 10 occasions

     Review Comment: The observed discrepancies were limited to minor study observations that did not impact study outcome.

   c. Assessment of data integrity:

   The data from this site appear to be reliable.

2. **Raphael Borges (site 38260):**

   Family Medical Clinic
   2807 Little York Road, Suite 110
   Houston, TX 77093

   a. What was inspected:

   - Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, adherence to protocol and applicable regulations
   - Data verification: primary efficacy endpoint data, adverse events, concomitant medication use, and subject discontinuation
   - Subjects: 46 enrolled in Study 0018, complete records reviewed for 18 subjects.

   b. General observations and commentary:

   The inspectional findings indicate adequate adherence to GCP regulations and the study protocol. Minor deficiencies consisted of inadequate record keeping practices which included the unblinded pharmacist not retaining a copy of the study drug label in the pharmacy and not always indicating the quantity of the study drug used by subjects in drug disposition records. Pharmacy dosing worksheets, however, indicate that appropriate amounts of the study drug were dispensed to the subjects as randomized.

   c. Assessment of data integrity:

   The data from this site appear to be reliable.

3. **Larry Bush (site 38163):**

   South Florida Clinical Research
   5503 South Congress Avenue, Suite 104
   Atlantis, FL 33462

   a. What was inspected:

   - Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, adherence to protocol and applicable regulations
   - Data verification: primary efficacy endpoint data, adverse events, concomitant medication use, and subject discontinuation
   - Subjects: 48 subjects were screened, 44 enrolled in study 0017, and 38 completed the study. Complete records were reviewed for 18 subjects.

   b. General observations and commentary:

   The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. The following deficiencies should be noted:

   - Subject 0791 randomized to Telavancin withdrew from the study and Dr. Bush prescribed a non-study antibiotic on the day of withdrawal. An EOT assessment (Indeterminate) was performed within 3 days of withdrawal. Despite no longer being in the study, a TOC assessment of Indeterminate was made one week after withdrawal, which was later changed to Cure. Regarding this protocol violation, Dr.

Bush commented that he did not have any other choice than to report the subject as Cure since none of the infection symptoms were present at TOC evaluation. The regulatory file contains no records regarding intervention by the study monitor (Covance) for this protocol violation. This was an isolated finding limited to this single subject.

- The protocol states that 3 ECGs are to be performed at 5-10 minute intervals immediately following the active dose on Day 4. If any QTc measurement is > 500 msec in a repeated (15 minute) ECG, the study medication is to be discontinued, an EOT assessment is to be completed, and a follow up visit is to be scheduled. ECG records were reviewed in 18 subjects. In 16 of the 18 subjects, electrocardiograms (ECG) were not performed as specified in the protocol. In 4 of the 16 subjects, the ECGs were performed prior to the active dose. In the remaining 12 of 16 subjects, the ECGs were performed within 0.75 to 4.0 hours after the active dose (and not immediately after the active dose as specified in the study protocol).

  Review Comment: Not performing the ECG within the timeframe specified in the study protocol may or may not be important to the integrity of the cardiac safety (QTc) data obtained at this site.

- For several subjects, the case report forms and source records contained minor discrepancies regarding wound measurements and wound drainage, including purulent drainage.

  Review Comment: These minor discrepancies appear to reflect inaccurate recordkeeping that did not affect critical endpoint assessments.

c. Assessment of data integrity:

Findings regarding TOC assessment were limited to a single subject. The deficiency regarding timing of ECG with study medication dosing was commonly seen, and the significance of this deficiency is unclear. The ECG data from this site should be interpreted in the context of more reliable ECG data from other sites. Overall, the efficacy data from this site appear to be reliable; the review division should consider excluding the ECG-related data from this site in evaluating cardiac safety.

4. **Richard Brown (site 38024):**

Baystate Medical Center
759 Chestnut Street
Springfield, MA 01199

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, adherence to protocol and applicable regulations
- Data verification: primary efficacy endpoint data, adverse events, concomitant medication use, and subject discontinuation
- Subjects: 21 subjects were screened, 21 enrolled in study 0017, and 16 completed the study. Complete records were reviewed for all 21 subjects.

b. General observations and commentary:

The inspectional findings indicate adequate adherence to GCP regulations and the study protocol. The following isolated deficiencies should be noted:

- In one subject who underwent a BKA, the index infection site was removed at amputation. The patient continued in the study on study medication for 5 days following the amputation and the amputation site replaced the index infection site (no longer present) for daily wound assessment.
- In one subject, a complicated abdominal wound with fistulas required surgical excision. Although surgery was permitted in the protocol, the lesion was removed in entirety and the patient should have been discontinued from the study, for receiving a therapy which interferes with the ability to evaluate the efficacy of the study medication. The patient was not discontinued and the surgical site (original lesion no longer present) was assessed as Cure at EOT and TOC.
- In one subject, a prohibited medication (clindamycin) was administered.

c. Assessment of data integrity:

Although the deficiencies described above were significant, they were noted as isolated instances limited to the three subjects described.

Overall, the data from this site appear to be reliable.

5. **David Young (site 38113):**

San Francisco General Hospital
1001 Potrero Avenue, Ward 3A
San Francisco, CA 94110

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, adherence to protocol and applicable regulations
- Data verification: primary efficacy endpoint data, adverse events, concomitant medication use, and subject discontinuation
- Subjects: 139 subjects were screened, 69 enrolled in study 0018, and 54 completed the study. Complete records were reviewed for 35 subjects.

b. General observations and commentary:

The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. The following deficiencies should be noted:

- A subject who did not meet study eligibility criteria (potassium level out of range) was enrolled in study 0018 and the medication was administered for 5 days prior to discontinuing the subject from the study.
- In 5 subjects, the written informed consent used in the study was not approved by the local institutional review board (IRB).

c. Assessment of data integrity:

The data from this site appear to be reliable.

6. **Stanley Klein (site 38016):**

Harbor - UCLA Medical Center
1000 West Carson Street, Box 15
Torrance, CA 90509

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, adherence to protocol and applicable regulations
- Data verification: primary efficacy endpoint data, adverse events, concomitant medication use, and subject discontinuation
- Subjects: 36 subjects were screened, 28 enrolled in study 0017, and 19 completed the study. Complete records were reviewed for all 28 subjects enrolled in the study.

b. General observations and commentary:

The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. Minor protocol violations included the following:

- Blood Cultures: Not obtaining the baseline blood culture prior to infusing the first dose of the study medication (one subject), and in subjects with positive blood cultures at baseline, not obtaining subsequent blood cultures daily until negative (two subjects).
- ECG: Not obtaining baseline serial ECGs prior to starting the study medication (one subject), and not obtaining Day 4 serial ECGs immediately after completing the infusion of the active study medication (12 subjects).

  Review Comment: ECGs were not performed as specified in the protocol in about one-half of all subjects enrolled at this site. This protocol violation may be important to the integrity of the ECG-related (QTc) cardiac safety data obtained at this site.

- Laboratory Tests: Not obtaining all safety laboratory tests (including vancomycin levels) according to the schedule of events as specified in the study protocol.
- In 6 subjects (#0543, 0552, 0614, 0716, 0771, and 0864), a non-study systemic antibiotic was administered inadvertently after (up to a few hours) starting the study medication.

  Review Comments:

  - The study protocol permits the administration of a non-study systemic antibiotic prior to starting the study medication, for up to 24 hours in all subjects and for up to 72 hours in subjects not responding to the non-study antibiotic.
  - These protocol violations were discussed with the review division (8/1/08, 9/10/08) in the context of the study protocol. In all cases, the entire course of the non-study antibiotic appears to be briefer than 24 hours, and the violations do not

appear to have a significant potential to importantly affect the integrity of the efficacy data.

c. Assessment of data integrity:

The data from this site appear to be reliable. However, the final assessment of data integrity is deferred to the review division for the following:

- Efficacy data in 6 subjects who received a non-study systemic antibiotic after starting the study medication.
- ECG-related (QTc) safety data in about one-half of all subjects enrolled at this site. The review division should consider excluding the ECG-related data from this site in evaluating cardiac safety.

7. **Zlatko Fiolic (site 09002):**

Klinički Bolnički Centar Zagreb
Vascular Surgery – IV, II Floor
Kispaticeva 12, Zagreb, 10 000, Croatia

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, adherence to protocol and applicable regulations
- Data verification: primary efficacy endpoint data, adverse events, concomitant medication use, and subject discontinuation
- Subjects: 36 subjects were screened, 31 enrolled in study 0017, and 28 completed the study. Complete records were reviewed for all 31 subjects enrolled in the study.

b. General observations and commentary:

Form FDA 483 was not issued, and the study was noted to be "very clean" including "excellent" study monitoring by Covance.

c. Assessment of data integrity:

The data from this site appear to be reliable.

III. SPONSOR'S TARGETED AUDIT AND FDA'S INFORMATION REQUEST

Sponsor's Targeted Audit

The sponsor conducted an internal audit of the two pivotal studies. In the Targeted Audit (4/21/08 - 6/12/08), the sponsor inspected 31 sites (24% of all sites) and audited the records for 683 subjects (36% of all subjects). The audited sites, selected by the sponsor using prior monitoring reports to identify those suggestive of significant GCP violations, included 5 of the 11 clinical sites inspected by the FDA: Brown, Borges, Bush, Klein, and Young.

The scope and nature of the findings of the Targeted Audit were consistent with FDA's inspectional findings described above in Section II. The sponsor concludes the following:

- The Targeted Audit results support the lack of a systematic pattern or incidence of GCP violations that complicate the interpretation of the reported safety and efficacy data.

- Many GCP deviations and/or data errors were identified in the Targeted Audit, but their occurrence rate appears to be sufficiently low to confidently conclude that the overall study outcomes are not impacted.
- The audit results indicated that study monitoring was adequate in all but two of the sites audited.
  - Site 38020 (Shirin Towfigh, 16 subjects enrolled) and Site 37004 (Mark Nelson, 6 subjects enrolled) had unusually high fractions of subjects (>75%) with significant data errors and/or GCP deviations. As at Site 38091 (Christian Schrock, 51 subjects enrolled), study monitoring by Covance at these two sites may have been ineffective. The two sites were not inspected by the FDA, and Site 38091 (Schrock) was not included in the sponsor's Targeted Audit.
  - The nature of the violations include: (1) study visit assessments performed by personnel who had not been delegated appropriate authority, and (2) source documents not being available to verify EOT and/or TOC assessments.

  Review Comment: As might be expected from the small number of subjects enrolled at these two sites (total of 22), the sponsor's sensitivity analyses which excluded data from these sites did not change the overall study outcome.

FDA's Information Request

The sponsor also provided responses to FDA's information request (May 9, 2008) regarding GCP. The sponsor's responses, based largely on the results of the Targeted Audit, reiterated and provided detailed support for the conclusions (bullets) described above.

The sponsor's summary of the Targeted Audit results and responses to FDA's information request are acceptable from an inspectional point of view. The sponsor's summary, however, raises concerns about the study design and are further discussed below (Section IV, *Observations based on Sponsor's Targeted Audit*).

IV. ADDITIONAL COMMENTS REGARDING DATA INTERPRETATION

Most of the inspectional findings did not have a significant potential to affect data integrity. The few findings that affected data integrity were limited to a few isolated occurrences at any given site. Taken together, however, they suggested trends that were consistent with observations relevant to the interpretation of the study results. These trends and observations, which appear to be review issues rather than inspectional issues, are described below for consideration by the review division.

A. Trends in FDA's Inspectional Observations

1. Study blind potentially not maintained:
   - The study coordinator at the Bunce site reported that the study blind was difficult to maintain because patients receiving Telavancin often reported altered taste sensation. Of the 26 studies enrolled into the study at this site, 16 had been randomized to the Telavancin arm and 10 to the Vancomycin arm. Seven subjects reported altered taste in the study at this site and all 7 had received Telavancin (7 of 16, 44%). Altered taste was not reported in any of the 10 patients treated with Vancomycin.

- The imbalance in the reporting of altered taste was observed at many other sites (Borges, Bush), typically at sites where surgical intervention was less frequently used as adjunctive therapy to antibiotic therapy.

2. Subjective primary endpoint and study blind:

   - Maintaining the study blind is particularly important in this study since the primary endpoint is highly subjective. The assignment of a clinical response at TOC (Cure, Not Cured, or Indeterminate) relies solely on the treating physician's subjective judgment as to whether or not the index skin infection has improved sufficiently to not continue antibiotic therapy.
   - The use of subjective endpoints in unblinded studies may result in biased data collection.

3. Definition of Indeterminate assessment:

   - At the Brown site, the two investigators (Drs. Brown and Lee) differed in their understanding of the term Indeterminate in making EOT and TOC assessments. Dr. Lee interpreted the protocol definition of the tem as meaning "not available for evaluation." If the patient was available for evaluation, he chose between Cure and Not Cured. Dr. Brown interpreted the protocol definition of Indeterminate as meaning "neither Cure nor Not Cured but somewhere in between." Each investigator was clear and confident in his own understanding and use of the tem Indeterminate.
   - Of the 11 sites inspected under this NDA, the definition of Indeterminate to mean or include the meaning of "not available for evaluation" was used at one other site (Schrock). Ambiguous interpretation at 2 of 11 sites suggests that a potentially significant fraction of all primary endpoint determinations (at all sites) may have been affected by different interpretations of Indeterminate.
   - An unclear definition of Indeterminate may be expected to affect not only the choice of Indeterminate at EOT or TOC, but also the choices of Cure and Not Cured; many of the outcome assessments reported as Cure or Not Cured may have in fact been Indeterminate. The ambiguous interpretation of Indeterminate further complicates the interpretation of the subjective primary efficacy endpoint.

4. Methicillin-sensitive Staphylococcus aureas (MSSA):

   - The "appeal" for using Telavancin to treat cSSSI is that it is effective against MRSA, not MSSA. However, a significant fraction of the subjects had wounds infected by MSSA rather than by MRSA, and infection by MSSA contributed significantly to the overall study outcome.
   - A large contribution by MSSA infection (or infection by any other agent against which both the control and the study medications are effective) may be expected to bias the outcome towards supporting non-inferiority.

5. Role of surgery in evaluating antibiotic efficacy:

   - In one subject at the Brown site, a complicated abdominal wound with fistulas required surgical excision. Although this surgery resembled in appearance the incision and drainage procedure permitted in the protocol, it removed the lesion in entirety and was closer in concept to limb amputation, for which the patient should be discontinued from

the study for receiving a therapy which interferes with the ability to evaluate the efficacy of the study medication. The patient was not discontinued and the surgical site (original lesion no longer present) was assessed as Cure at EOT and TOC.

- The role of surgery in evaluating antibiotic efficacy was less clear in the overwhelming majority of cases that involved surgical intervention. In cases that required relatively extensive surgery, the index lesion may be expected to improve with either the control or the test medication. In relatively uncomplicated cases that did not require surgical intervention, the index lesion may again be expected to improve with either agent. Both extremes of seriousness (surgical intervention) may be expected to favor the outcome of non-inferiority.

B. Observations Based on Sponsor's Targeted Audit

From a study design perspective, the following results of the sponsor's Targeted Audit suggest potential bias in study conduct that may have resulted from the study design. Inadequate safeguards against bias during study conduct may have favored Telavancin over vancomycin in obtaining efficacy outcome; such bias would be difficult to identify at inspection.

1. Attachment 11 of the Targeted Audit Summary lists all subjects with one or more deviations and/or data errors that potentially affected the efficacy outcome. Of the 155 subjects identified, 91 were in the Telavancin arm and 64 were in the vancomycin arm. Since the study protocols specified 1:1 randomization ratio using permuted blocks, this approximately 3:2 ratio (91 vs 64) in favor of Telavancin observed in this particular audit suggests that the deviations and/or data errors occurred more often in the Telavancin arm than in the vancomycin arm. The reason for this apparently significant deviation from the expected 1:1 ratio is unclear, but the unexpected 3:2 ratio suggests bias in study conduct, possibly from a study blind that is difficult to maintain.
2. Further, of the 155 deviations and/or data errors listed in Attachment 11, 65 were in favor of Telavancin (or against vancomycin) and 48 were in favor of vancomycin (or against Telavancin), for a net of 17 (65 minus 48) that favored Telavancin over vancomycin. This net 17 (out of a total of 155, or 11%) also represented a nearly 3:2 ratio (65 vs 48) in favor of Telavancin over vancomycin. The reason for this apparently significant deviation from the expected (net of 0, 1:1 ratio) is unclear, but the unexpected result further suggests systematic bias in study conduct; not only did the deviations occur more frequently in the Telavancin arm, but the deviations also resulted in an efficacy outcome that favored Telavancin over vancomycin.
3. Attachment 14 of the Targeted Audit Summary lists all subjects who did not receive the study medication as intended. Of the 16 subjects identified, 4 received the study medication after the EOT visit, 5 received an unintended dose of the study medication, and 7 received the study medication on a schedule not specified in the protocol. All but two of the 16 subjects were in the Telavancin arm. In the vancomycin arm, one subject received an unintended dose and one subject received a dose on a schedule not specified in the protocol. The 7:1 ratio (14 vs 2) in favor of Telavancin appears to be significant. The reason for this deviation from the expected (1:1 ratio) is unclear, but the unexpected 7:1 ratio for study medication

dosing errors again suggests systematic bias in study conduct.

V. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for the second cycle review of this NDA consisted of six US clinical sites and one foreign site (Croatia). The second cycle of inspections was initiated to further investigate the concerns identified at one of four initial clinical sites (Schrock) and at inspection of the study monitor (Covance). The major concerns identified at first cycle of inspections included:

1. Incorrect interpretation of the term Indeterminate,
2. Protocol violations that directly affect primary efficacy endpoint assessment,
3. Inadequate data management and pharmacy procedures,
4. Retrospective data alteration,
5. Violations that uniformly favored Telavancin, suggestive of unblinding,
6. Lack of study monitoring by the sponsor, either directly or through Covance.

At second cycle of inspections, these deficiencies were either not seen (items 5 and 6 above) or found only as isolated instances (items 1 - 4 above). No new concerns were observed and study monitoring by Covance was adequate at all sites including the foreign (Croatia) site.

A. Overall, the inspectional findings support acceptable adherence to GCP for the two pivotal studies. The results of the sponsor's own audit (Targeted Audit) are consistent with FDA's inspectional findings. The sponsor's response to FDA's request for information (May 9. 2008) regarding GCP, largely based on the results of the targeted audit, is acceptable.

B. The concerns identified (at second cycle of inspections) appear to be protocol-related and typically not site-specific. These concerns are summarized below.

   - The studies rely on subjective investigator discretion (need for further antibiotic therapy) in making the endpoint assessment critical to the success of the study. The validity of the subjective endpoint is also complicated by an unclear definition of the term Indeterminate (important to endpoint assessment), as evidenced by the use of an inappropriate definition at two of the 12 clinical sites inspected to date under this NDA.

   - The unbalanced (5:1) reporting of altered taste between the two treatment groups had the potential to unblind the study. This concern was supported at inspection: the research coordinator at one inspected clinical site (Bunce) acknowledged that dysgusia was unblinding. The potential for unblinding make it difficult to interpret the results of these two pivotal studies (0017 and 0018) intended to be conducted under a double-blinded non-inferiority design using a subjective primary efficacy endpoint (investigator judgment regarding the need for continued antibiotic therapy).

Based solely on inspectional findings at the 7 additional sites that were inspected, the data appear acceptable in support of the indication. However, the review division will need to consider the additional issues raised above in their determination of safety and efficacy of telavancin in support of the proposed indication.

Note: The final inspection reports for Sites 4, 6, and 7 (Brown, Klein, and Fiolic, respectively) are pending; upon receipt and review of the final inspection reports, an addendum to this clinical inspection summary will be provided if additional observations of clinical or regulatory significance are discovered.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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

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/s/

John Lee
9/15/2008 01:15:20 PM
MEDICAL OFFICER

Tejashri Purohit-Sheth
9/15/2008 04:37:43 PM
MEDICAL OFFICER

Leslie Ball
9/15/2008 09:47:52 PM
MEDICAL OFFICER

Dr. Coleman,

With regard to the questions presented in your meeting request, dated September 3, 2008, for NDA 22-110, the Division of Anti-Infective and Ophthalmology Products (DAIOP) has the following replies *(italics)*:

SECTION 8.1 – DATA INTEGRITY:

Division Response: *The Division is awaiting final recommendations from the Division of Scientific Investigations (DSI). A response to the questions pertaining to data integrity will be provided once the DSI review is complete and the Division has made a determination regarding acceptability of the data.*

1. Can Theravance answer any questions or provide additional information about the Targeted Audit data that we submitted to the Agency on August 6, 2008?

   Division Response: *Response to be provided at a later date.*

2. What is the status of the Division of Scientific Investigations data integrity review of NDA 22-110? We would like to discuss any findings from their review.

   Division Response: *Response to provided at a later date.*

3. Have the Division of Scientific Investigations and the Division of Anti-infective Drugs reached a conclusion regarding the integrity of the clinical data submitted in NDA 22-110?

   Division Response: *Response to be provided at a later date.*

SECTION 8.2 – ADVISORY COMMITTEE:

1. Are there potential implications of the data integrity review for the development of Briefing Documents and other AC preparations? Does the Division plan to revise the Briefing Document that was previously provided?

   Division Response: *If additional data integrity issues are identified by DSI, data from such sites will need to be excluded from the briefing document and from the Advisory Committee presentations. Efficacy and safety data from Dr. Schrock's site will need to be excluded from the briefing document and from the Advisory Committee presentations. The Division plans to revise the briefing document that was previously provided with respect to the following:*

   - *Discussion of the non-inferiority margin*
   - *Summary of the safety update*
   - *Additional analyses if needed based on DSI review*

2. To aid in preparation of our presentation, please share with us the nature and objective of the NIM discussion planned for the morning of November 18?

   Division Response: *The objective of the non-inferiority (NI) margin discussion is to determine if NI trials are acceptable for the indication of cSSSI and if so, what an appropriate margin would be. The details of the presentation are still being worked on and will include review of pertinent historical information that was used to determine placebo cure rates and the methodology used to determine a treatment effect and the NI margin.*

3. Please advise us as to the currently planned timeline for the Federal Register notification of the Advisory Committee meeting.

   Division Response: *The Division is not aware of the exact date of publication of the FR notice. It will likely be in the first half of October, 2008.*

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
9/5/2008 03:09:21 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-110

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 Televancin (TD 6424, AMI 6424).

We also refer to the teleconference between representatives of your firm and the FDA on March 19, 2007. The purpose of the teleconference was for the Agency to provide a 90-day status update on the review of NDA 22-110.

The official minutes of that teleconference 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, Regulatory Project Manager, at (301) 827-2217.

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

Enclosure: Minutes from Teleconference

MEMORANDUM OF TELECONFERENCE

TELECONFERENCE DATE:	February 25, 2008
TIME:	10:30 to 11:30 AM, EST
APPLICATION (DRUG):	Telavancin (NDA 22-110)
SPONSOR:	Theravance, Inc.

TYPE OF MEETING:	Teleconference (advisory committee cancellation)
MEETING CHAIR:	John Jenkins, MD, Office Director, OND
MEETING RECORDER:	J. Christopher Davi, MS, Regulatory Project Manager

FDA PARTICIPANTS:
John Jenkins, MD, Office Director, OND
Edward M. Cox, MD, MPH, Office Director, OAP
Wiley A. Chambers, MD, Acting Division Director, DAIOP
J. Christopher Davi, MS, Regulatory Project Manager

INDUSTRY PARTICIPANTS (Hogan and Hartson, LLP, legal council for Theravance, Inc):
David M. Fox, Attorney
Nancy Parsons

MEETING OBJECTIVE:

- To discuss the Agency's cancellation of the advisory committee meeting for NDA 22-110 scheduled for February 27, 2008

SUMMARY OF DISCUSSION:

- Dr. Jenkins informed Mr. Fox that it would be necessary for the Agency to verify that Hogan and Hartson, LLP were authorized representatives of Theravance before any substantive information could be exchanged during the teleconference. Mr. Fox provided an authorization letter via facsimile dated November 1, 2007, signed by David L. Brinkley, Senior Vice President of Theravance.

- Mr. Fox indicated that he had been involved as legal council for Theravance since approximately 1 week prior to the original PDUFA date for the marketing application (NDA 22-110). Mr. Fox queried the Agency as to why the advisory committee had been cancelled just a few days before the February 27, 2008, date.

- Dr. Cox indicated that Theravance was informed of the cancellation as soon as it was determined by the Agency that there were unresolved issues from an inspectional standpoint (i.e., monitoring and conduct of studies). Dr. Cox added that had the issues been elucidated earlier, more advance notice would have been provided.

- Dr Jenkins discussed the Agency's commitment to Congress that in situations where data integrity issues arise, any public vetting of information (i.e., in the form of an advisory committee) should ordinarily not proceed.

- Mr. Fox indicated that he had been following the issues surrounding the Ketek matter, and that he understood the position of the Agency as a result. Mr. Fox asked the Agency how the data integrity issues with the Telavancin NDA compared to data integrity issues with the Ketek application.

- Dr. Jenkins stated that it is difficult to say whether or not issues with the Telavancin application rose to the level of severity identified in the Ketek scenario. Dr. Jenkins also indicated however, that inspections of Covance (CRO) have lead to significant Division of Scientific Investigation (DSI) questions surrounding deficiencies at a study site (i.e., Schrock; #38901). These deficiencies had not been corrected by the CRO. As Covance was also the contracted CRO for many of the study sites supporting the application, the Agency had a need to determine if there was a more systemic problem with data integrity.

- Mr. Fox indicted that he was aware of the 483 issued to Schrock's site in April of 2007. He added that the issue was not raised to a high level of importance during the initial review cycle, but that it had become more of an issue in recent weeks, leading up to the scheduled advisory committee meeting. Mr. Fox acknowledged that the company (Theravance) had been instructed to eliminate data from the Schrock site from the briefing materials for the advisory committee during a January 30, 2008, teleconference with the Agency. He stated that it was Theravance's understanding at the time that data issues were confined to study site 38901 and involved 51 patients.

- Dr. Chambers noted that the issuance of a 483 and a full study report from DSI are two separate activities that take place on different timeframes. Dr. Chambers added that it was the CRO inspection in December of 2007 that actually lead to the DSI report (which became available in preliminary form the week of February 18, 2008).

- Dr. Jenkins indicated that Covance's degree of involvement as CRO raises concern that the problem may be more systemic, and that one could not just eliminate the Schrock data and assume that there are not problems at other sites.

- Mr. Fox agreed that the Agency had a difficult judgement call to make regarding the scope of the issue. However, Mr. Fox stated that he had been informed that the Covance inspection was very detailed, and that only one (1) observation was found that paralleled the Schrock issue. Mr. Fox acknowledged that the observation made was not favourable, but that it seemed like a limited event. Mr. Fox asked the Agency if the cancellation of the advisory committee meeting was an appropriate remedy, given the facts.

- Dr. Jenkins indicated that more time would be necessary to assess the findings. Dr. Jenkins indicated that the application will still require an advisory committee meeting to address other issues (i.e., risk/benefit, teratogenicity, etc.)

- Dr. Cox stated that the advisory committee members had been told about the cancellation, and that the Agency has not yet determined what additional information regarding the cancellation will be disseminated to the committee at this time.

- Mr. Fox expressed concern over "tainting" the view of the advisory committee panel. He added that Theravance had suffered a disproportionate impact as a result of the advisory committee cancellation, and that the company would have complicated disclosure issues to deal with as a result.

- Mr. Fox made reference to the fact that there was only one 483 at this time involving one site. Mr. Fox asked that if further DSI investigation did not reveal any systemic issues, would the application still have to go to an advisory committee.

- Dr. Jenkins again confirmed that the application would still have to go to an advisory committee. Dr. Jenkins stated that this would normally be the case with new molecular entities (NME). Further, Dr. Jenkins indicated that if the DSI concern is valid (i.e., systemic data integrity problems) additional studies may be necessary before it can be taken back to an advisory committee.

- Mr. Fox asked if the Agency would indulge the company in a face to face meeting on Wednesday February 27, 2008. Mr. Fox suggested that DSI representatives be involved in the face to face meeting and also requested attendance by Dr. Jenkins.

- Dr. Jenkins stated that he would leave the logistics of planning a meeting up to the Division.

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, MD
Acting Division Director

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/s/

Christopher Davi
5/9/2008 04:25:55 PM
CSO

Wiley Chambers
5/30/2008 09:53:45 AM
MEDICAL OFFICER

Questions from DSI

NDA 22-110

Request to Sponsor
Telavancin Protocols 0017 and 0018

Quality Assurance:

1. In conducting your Telavancin Studies 0017 and 0018, we are aware that you audited selected clinical sites under your own quality assurance (QA) program, independent of monitoring by contract research organizations (CROs). We are also aware that Covance provided monitoring of the Schrock site and that you also directly audited the Schrock site under your QA program. Please provide the following information regarding your QA audit program:
   a. A report of your QA audit plan, including your plan for securing compliance from non-compliant clinical investigators.
   b. A report of your audit findings, including any corrective actions taken and final outcome, for the Schrock site and for all other sites you audited under your QA program.
   c. Were any clinical investigators terminated for non-compliance? If so, please provide a list of the clinical investigators, their sites, the specific violations, and whether the data were included in the NDA submission.
   d. For any reported non-compliant site, what steps did you take as the sponsor of the studies to ensure compliance? Were these investigators reported to the FDA?
2. Did your QA program include oversight of contract research organizations (CROs) that you hired to monitor the clinical sites? Please describe the procedures you implemented to make sure that your CROs adequately monitored the clinical sites. In your response, include the following information:
   a. How were you kept apprised by your CROs concerning monitoring of the clinical sites during the course of the study? Specifically, what information did the CROs provide? Please provide a list of non-compliant clinical study sites reported by the CROs.
   b. As the sponsor, how did you review the information obtained from the CROs, during the course of the study and at the end of the study? What monitoring information did you keep at the end of the study?
   c. Regarding monitoring of the Schrock site by Covance, we note that the monitoring plan that Covance provided to FDA is dated 21 November 2005 (Version 2), which is after your site visits on 17 April 2005. Please provide a copy of the monitoring plan that Covance actually used to monitor Schrock's site.

3. We are aware that many home health care service (HHCS) organizations were involved in delivering care under your Telavancin Studies 0017 and 0018. Please provide the following information regarding HHCS:

   a. A list of all clinical sites that used HHCS in support of the two Telavancin studies. Within this list, describe which sites were monitored by CROs and/or audited by your QA group, and provide the monitoring reports and/or quality audit reports, including the corrective action plan associated with non-compliant sites.

   b. In providing training to HHCS, what training did you provide, how was the training provided, and how was the delivery of training documented?

Targeted Audit:

At the recent meeting with the FDA (CDER/DAIOP) on 16 April 2008, you indicated that you intend to perform a targeted audit of clinical sites involved in your Telavancin Studies 0017 and 0018.

4. Please provide a report of your targeted audit plan, and describe the following information regarding your intended targeted audit plan:

   a. How many clinical sites will be audited, how many subject records will be examined, and how the clinical sites will be selected for your targeted audit.

   b. If not all subject records at a given clinical site will be audited, describe how subject records will be sampled and how extensive your sampling will be.

5. Please describe the timeline for completing your targeted audit. When available, please provide a report of your audit results, and include the following information in your report for all sites included in your targeted audit:

   a. In evaluating treatment response at end of therapy (EOT) and at test of cure (TOC), Dr. Schrock interpreted the term "Indeterminate" to mean any condition or situation that does not permit an assessment of either "Cure" or "Not Cured," including the situation of a subject not being available for evaluation.

      1) Please clarify the meaning of "Indeterminate" as you intended in the protocols.

      2) In addition to Dr. Schrock, how many clinical investigators involved in your Telavancin Studies 0017 and 0018 interpreted the term "Indeterminate" in this way, to include any situation that does not permit an assessment of the wound?

      3) Did your QA audit or CRO monitoring identify this as a problem? As the sponsor, what instructions did you provide to clinical sites and/or CROs regarding this potential problem?

b. At each clinical site audited, how many protocol violations involved each of the following specific protocol violations? For each specific violation, list the clinical sites involved and provide a breakdown by treatment group for each site and overall for the two Telavancin studies.

   1) Performing the EOT or TOC assessment outside the protocol-specified time window.

   2) At either EOT or at TOC, an assessment of treatment response (Cure, Indeterminate, Not Cured) as recorded on the case report form (CRF) that is inconsistent with or not clearly supported by source documents (SD).

   3) Performing a TOC assessment: without performing an EOT assessment, in follow up of an assessment of Not Cured at EOT, or in follow up of an incorrect Indeterminate assessment at EOT.

   4) Performing the EOT or TOC assessment in a manner not designated in the study protocol and not optimal for study evaluation, such as: over the phone, without removing wound dressing, by untrained or unauthorized personnel, or at locations other than the designated clinical site.

   5) Retrospectively revising an EOT or TOC assessment, either on CRF or on SD, without adequate explanation and documentation.

   6) Discrepant wound measurements among those recorded on CRF or SD without documentation of an adequate explanation and resolution of the discrepancy.

   7) Incomplete wound assessment at EOT or TOC because the wound was covered with a dressing or wound vacuum dressing. Examples of incomplete wound assessment include: not measuring wound size, not evaluating or incompletely evaluating for the presence/degree of inflammation/infection, and not obtaining gram stain/culture when indicated per protocol.

   8) Not reporting or not promptly reporting adverse events to your local institutional review board (IRB), data safety monitoring board (DSMB), or FDA as specified in your protocols and applicable regulations.

c. Identify the clinical sites where the following specific violative pharmacy procedures are identified.

   1) Unauthorized personnel dispensing the study drug.

   2) Not being able to account for the disposition of all study drug delivered to the clinical site.

   3) Using remnants from partially used vials of the study drug to produce additional "batches" of the study drug for other subjects.

   4) Subjects receiving unintended dose of the study drug or not receiving the study drug as intended.

d. List all clinical sites where CRO monitoring was ineffective, either in identifying significant violations or in taking actions towards securing compliance (such as notifying the sponsor).

6 Our analysis of the violations observed at the Schrock site indicates that the violations occurred more frequently in patients randomized to the Telavancin arm than in those randomized to the vancomycin arm (8:2 ratio). This imbalance was disproportionate to the randomization ratio at this site (3:2 favoring Telavancin). In 8 of 10 patients affected by the violations, the violation supported efficacy of Telavancin. In your targeted audit, for each of the 8 specific violations listed in item 5b above, please provide the following information:

a. Indicate the treatment arm to which the affected patient was randomized

b. Determine whether the violation increased or decreased the apparent efficacy of Telavancin or vancomycin

c. Summarize the results to compare the two treatment arms as impacted by the violations

-End

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/s/

Christopher Davi
5/9/2008 04:56:39 PM
CSO

DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGY PRODUCTS

Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue,
Silver Spring, MD 20993

FACSIMILE TRANSMISSION

DATE: 3/5/08 NUMBER OF PAGES (including cover sheet): 2

TO: Rebecca Coleman, Pharm D

COMPANY: Theravance, Inc. (NDA 22-110)

FAX NUMBER: (650) 808-3786

MESSAGE: Becky,
Please see the attached labeling comments from the product quality microsterility reviewer. Let me know if you have questions.

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the content of this transmission.

FROM: Chris Davis

TITLE: Regulatory Project Manager

TELEPHONE: (301) 796-0702 FAX NUMBER: 301-796-9881

Thank You

Dr. Coleman,

With regard to Section 2.3 of your proposed label, the microsterility review team has the following comments and information requests (NDA 22-110):

- Microbiological studies in support of the post-constitution storage time (( )-hours at room temperature or 72 hours under refrigeration, as stated in the proposed labeling) have not been provided. Please provide a risk assessment summarizing studies that show adventitious microbial contamination does not grow under the storage conditions. Reference is made to *Guidance for Industry: ICH Q8 Pharmaceutical Development*, Section II.E and *Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products*, Section 2.2.7. b(4)

- The report should describe test methods and results that employ a minimum countable inoculum to simulate potential microbial contamination that may occur during product constitution. It is generally accepted that growth is evident when the population increases more than 0.5 Log_{10}. The test should be run at the label's recommended storage conditions and be conducted for 2 to 3-times the label's recommended storage period and using the label-recommended fluids. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should recommend that the post-constitution storage period is not more than 4 hours at room temperature.

- Findings from these studies may also be useful for developing manufacturing controls, such as bulk solution holding periods, as part of your Quality by Design program.

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
3/5/2008 11:49:30 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-110

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

Dear Dr. Coleman:

Please refer to Theravance's New Drug Application (NDA) for Telavancin. We also refer to the meeting between representatives of Theravance and the FDA on August 21, 2007.

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}

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

Enclosures: Minutes from meeting

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 21, 2007
MEETING TIME: 3:00 to 4:00 PM, EST

APPLICATION (DRUG): NDA 22-110
Telavancin for Injection

SPONSOR: Theravance, Inc.

TYPE OF MEETING: Type-C, Pregnancy Labeling Category Discussion

MEETING CHAIR: Wiley A. Chambers, MD, Acting Division Director

MEETING RECORDER: J. Christopher Davi, MS, Regulatory Project Manager

FDA PARTICIPANTS:
Edward M. Cox, MD, MPH, Office Director, 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
Wendelyn Schmidt, PhD, Acting Team Leader, Preclinical Pharmacology
Zhou Chen, PhD, Preclinical Pharmacology Reviewer
Lynnda Reid, PhD, Chair, CDER Reproductive Toxicology Committee
Lisa Mathis, MD, Associate Director, Pediatric and Maternal Health Staff
Frederic Marsik, PhD, Clinical Microbiology Team Leader
Kerry Snow, MS, Clinical Microbiology Reviewer
Dave Roeder, MS, Associate Director of Regulatory Affairs, OAP
J. Christopher Davi, MS, Regulatory Project Manager

INDUSTRY PARTICIPANTS:
Kenjie Amemiya, PhD, Sr. Director, Safety Assessment, Theravance
Rebecca Coleman, PharmD – Sr. Director, Regulatory Affairs, Theravance
Michael Conner, DVM, PhD – Vice President, Safety Assessment, Theravance
Michael Kitt, MD – Senior VP, Development, Theravance
Rochelle Maher, Director, Project Management, Astellas
Robert Reed, Director, Regulatory Affairs, Astellas
Anthony Scialli, MD, Consultant

MEETING OBJECTIVE:

- To provide the Sponsor an opportunity to present their rationale for the proposed Pregnancy Labeling Category "C" for telavancin.

SUMMARY OF DISCUSSION:

The Sponsor opened the meeting with a presentation of preclinical findings, which they believe supports a pregnancy labeling category "C" designation for telavancin. Following the presentation, a question and answer session was held. Salient points from the question and answer session are recorded as follows:

- The Sponsor indicated that category C best described telavancin based on the preclinical data and potential clinical benefit. The Sponsor discussed the data from rat, rabbit and mini-pig studies, and noted that both the rat and rabbit were positive for developmental toxicity.

- The Sponsor indicated that category X was inappropriate for telavancin, because it did not allow for the physician and patient to make the decision on whether or not to use the drug, based on a risk/benefit profile.

- The Sponsor noted that the mini-pig is prone to skeletal malformations and that these abnormalities have been observed in control groups as described in the literature (i.e., malformations may not necessarily be due to a treatment effect).

- The Sponsor indicated that the use of the mini-pig was requested by the Agency. The Sponsor agreed that reproductive toxicity was seen, based on the rat and rabbit studies, and added that they would have come to the same conclusion on the pregnancy category irrespective of the mini-pig data.

- The Division maintained that there were teratogenic findings in 3 animal species.

- The Sponsor suggested that if the use of telavancin confers clinical benefit, it would be reasonable to describe the teratogenic effects in the label, with a pregnancy category C designation.

- The Division indicated that the ultimate decision on a C versus X pregnancy category designation by the Agency would be based on a benefit/risk profile for the drug.

- The Division suggested that the Sponsor further justify their position on a category "C" designation by focusing on the situations where telavancin would provide a benefit over existing therapies. Such information could include cases seen in the compassionate use program or hypothetical situations, though real examples would be preferred.

- The Sponsor offered to provide a case report of a young woman (not pregnant) who required the use of telavancin. The Division stated that while this case would be interesting, it alone would not be sufficient to support the fact that telavancin offered an additional benefit over drugs that are already approved for cSSSI.

ACTION ITEMS:

1. The Sponsor will consider providing an amendment to the NDA describing situations where telavancin would provide a benefit over existing therapies, as described in the final bullet point, above.

2. The Division will consider the Sponsor's supplemental submission in the determination of a "C" versus "X" pregnancy category determination.

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.
Deputy Division Director

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/s/

Frances LeSane
11/27/2007 03:26:45 PM

Davi, Christopher

From: Davi, Christopher
Sent: Tuesday, October 09, 2007 10:07 AM
To: 'Coleman, Becky'
Cc: Pohlman, Janice; Nambiar, Sumathi
Subject: FW: financial disclosure (Form 3454)

Dr. Coleman,

Please see the following comment and information request from the medical officer:

The financial certification for investigators for the clinical studies for telavancin is incomplete.

In module 1, under administrative section 1.3.4 financial certification, Theravance noted that they were unable to obtain financial information on a small set of subinvestigators and they stated they thought they would be able to submit full financial disclosure data by the 120 day safety update. I have reviewed the submissions and can not locate their update. Please inquire with Theravance and see if it the information has been appended, or if we may be overlooking it somewhere else in the submission.

Please let me know if you can provide any information, or if you have questions.

Regards,

Chris Davi

J. Christopher Davi, MS
Regulatory Project Manager
Food and Drug Administration (FDA)
Division of Anti-Infective and Ophthalmology Products
christopher.davi@fda.hhs.gov
(301) 796-0702

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/s/

Christopher Davi
10/9/2007 10:13:55 AM
CSO

DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGY PRODUCTS

Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue,
Silver Spring, MD 20993

FACSIMILE TRANSMISSION

DATE: 9/24/07 NUMBER OF PAGES (including cover sheet): 2

TO: Rebecca Coleman, Pharm D

COMPANY: Theravance, Inc (NDA 22-110)

FAX NUMBER: (650) 808-3786

MESSAGE: Dr. Coleman
Please see attached comments and information request. Let me know if you have questions

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the content of this transmission.

FROM: Chris Davis

TITLE: Regulatory Project Manager

TELEPHONE: (301)-796-0702 FAX NUMBER: 301-796-9881

Thank You

Dr. Coleman,

Please see the following information request from the clinical reviewer for NDA 22-110:

> In the Integrated Summary of Safety (ISS - Module 5.3.5.3), there are several Supporting Tables pertaining to safety laboratory results (mean change from baseline to worst value through EOT) that have a footnote that seems to be an incomplete statement.
>
> Specifically, Section 6.2.2.1 Hematology, Supporting Tables 122, 123, and 124, and Section 6.2.2.2 Serum Chemistry, Supporting Tables 128, 129, and 130, have the following footnote:
>
> > "The total number of patients for each parameter should represent the number of patients for the treatment group who (1) had that parameter assessed at baseline and at least one follow up time and (2) for whom the baseline assessment"
>
> Should the statement following (2) be "for whom the baseline assessment is normal", as it reads in the potentially clinically significant (PCS) abnormality tables (e.g., Table 6-3 of the ISS)?

Please let me know if you have any questions.

J. Christopher Davi, MS
Regulatory Project Manager
(301) 796-0702

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/s/

Christopher Davi
9/24/2007 01:18:24 PM
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Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue,
Silver Spring, MD 20993

FACSIMILE TRANSMISSION

DATE: 9/5/07 NUMBER OF PAGES (including cover sheet): 2

TO: Rebecca Coleman, Pharm D

COMPANY: Theravance, Inc. (NDA 22-110)

FAX NUMBER: (650) 808-3786

MESSAGE: Dr. Coleman,
Please see the attached comments and information requests from the clinical review team. Let me know if you have questions

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the content of this transmission.

FROM: Chris Davi

TITLE: Regulatory Project Manager

TELEPHONE: (301) 796-0707 FAX NUMBER: 301-796-9881

Thank You

Dr. Coleman,

As we continue our review of your application (NDA 22-110) we have the following comments and information requests to convey:

> Section 6.4.5 (Selection and Timing of Dose for Each Patient) of the Clinical Study Reports for Study 0017 and 0018 state that an Independent Dosing Regimen Adjudicator (IDRA) was responsible for evaluating the appropriateness of initial and subsequent dosage regimens of telavancin and vancomycin in individual patients. Theravance's primary charge to the IDRA was to assess whether or not individual patient's dosage regimen of study medication at the outset and during the course of treatment was appropriate based upon protocol-specified dosage adjustments for both medications.
>
> There is a link reportedly to the charter for the IDRA (Appendix 11) which actually leads to a section labeled "Documentation of Statistical Methods" that contains the statistical analysis plan (SAP) for the study.
>
> Section 3 (Administrative Structure) of the Clinical Study Reports states that one function of Omnicare (contract research organization) was to support the IDRA with independent unblinded personnel.
>
> 1. Please provide the location of the IDRA charter document for Study 0017 and 0018.
>
> 2. Outline the procedure which the IDRA used to communicate the requirement for dose regimen adjustments to the investigative sites.
>
> 3. Was an analysis performed that looked at the time interval between detection of a change in a patient's creatinine clearance (i.e., date on which serum Cr was measured) necessitating dose adjustment and implementation of that adjustment? Please provide a list of patients with a change in renal function requiring dose adjustment and time interval required to institute the appropriate change.

Please let me know if you have any questions, and when you anticipate being able to provide a response to our information requests.

J. Christopher Davi, MS
Regulatory Project Manager, DAIOP
(301) 796-0702

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/s/

Christopher Davi
9/5/2007 08:34:00 AM
CSO

Davi, Christopher

From: Davi, Christopher
Sent: Friday, August 10, 2007 10:40 AM
To: 'Coleman, Becky'
Cc: Nambiar, Sumathi; Bonapace, Charles
Subject: Telavancin request (PK) NDA 22-110

Dr. Coleman,

Please see the following information request from the clinical pharmacology review team. A reply to this inquiry is requested no later than **Wednesday, August 15, 2007:**

> **We request an analysis be conducted on the patient database for Phase 3 clinical trials 0017 and 0018 combined to determine the clinical cure rate in the clinically evaluable population and the microbiological cure rate in the microbiologically evaluable population by treatment day (i.e., day 7, day 8, etc.) for patients treated with telavancin for 7-14 days. In addition, we request that you provide a subgroup analysis of the clinical cure rate in the clinically evaluable population and the microbiological cure rate in the microbiologically evaluable population by treatment day stratified by the nature of the cSSSI infection (e.g., ulcer, abscess, cellulitis, etc.), infecting organism (i.e., MRSA, MSSA), and patient age (i.e., <50 years of age, >50 years of age).**
>
> **If such analyses have already been performed and are included in the study reports, please indicate which sections of the study reports contain this information.**

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

Regards,

Chris Davi

J. Christopher Davi, MS
Regulatory Project Manager
Food and Drug Administration (FDA)
Division of Anti-Infective and Ophthalmology Products
christopher.davi@fda.hhs.gov
(301) 796-0702

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/s/

Christopher Davi
8/10/2007 10:44:57 AM
CSO

Davi, Christopher

From: Davi, Christopher
Sent: Wednesday, August 08, 2007 2:08 PM
To: 'Coleman, Becky'
Cc: Komo, Scott; Pohlman, Janice
Subject: Clinical/Statistical Information Request (NDA 22-110)

Dr. Coleman,

The Clinical and Statistics group have the following information request:

Please specify the dataset(s) and population flags needed to recreate the following tables:

- **CSR Tables 8-10: Pathogens Isolated from Primary Infection Site at Pre-Treatment – MAT Population Only for the "Number (%) of Patients with Any Primary Infection Site Pathogen" section**
- **CSR Table 8-12: Presence or Absence of PVL in Patients with S. aureus at Baseline – MAT Population**
- **CSR Table 8-28: Clinical Response at Test-of-Cure by Pathogen – ME Population.**

If you have any questions, please contact me.

Regards,

Chris Davi

J. Christopher Davi, MS
Regulatory Project Manager
Food and Drug Administration (FDA)
Division of Anti-Infective and Ophthalmology Products
christopher.davi@fda.hhs.gov
(301) 796-0702

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/s/

Christopher Davi
8/8/2007 02:15:38 PM
CSO

Davi, Christopher

From: Davi, Christopher
Sent: Tuesday, August 07, 2007 10:09 AM
To: 'Coleman, Becky'
Cc: Bonapace, Charles; Tworzyanski, Jeffrey
Subject: Clinical Pharmacology Information Request (NDA 22-110)

Dr. Coleman,

The Clinical Pharmacology review team has the following information request at this time:

Please provide the data from the animal model(s) of infection demonstrating the AUC/MIC ratio of 219 (1-log net reduction of the initial inoculum) used in the Monte Carlo simulations to support the dose selection of 10 mg/kg for the Phase 2 and 3 clinical trials.

Please let me know when you will be able to provide the requested information, and if you have any questions.

Thank you,

Chris Davi

J. Christopher Davi, MS
Regulatory Project Manager
Food and Drug Administration (FDA)
Division of Anti-Infective and Ophthalmology Products
christopher.davi@fda.hhs.gov
(301) 796-0702

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/s/

Christopher Davi
8/7/2007 10:42:18 AM
CSO

Davi, Christopher

From: Davi, Christopher
Sent: Monday, July 30, 2007 11:44 AM
To: 'Coleman, Becky'
Cc: Komo, Scott; Pohlman, Janice; Nambiar, Sumathi
Subject: Question for telavancin (NDA 22-110)

Dr. Coleman,

Please see the information request below from the statistics review team for NDA 22-110. Let men know if you have any questions.

Thank you,

Chris Davi

Please specify the location of variables in the datasets provided that will enable us to recreate the Analyses in "APPENDIX 26: ALTERNATE ANALYSES – FDA EVALUABILITY CRITERIA."

J. Christopher Davi, MS
Regulatory Project Manager
Food and Drug Administration (FDA)
Division of Anti-Infective and Ophthalmology Products
christopher.davi@fda.hhs.gov
(301) 796-0702

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/s/

Christopher Davi
7/30/2007 01:33:41 PM
CSO

Davi, Christopher

From: Davi, Christopher
Sent: Monday, July 23, 2007 11:47 AM
To: 'O'Beirne, Michael'
Cc: 'Coleman, Becky'; Shanmugam, Balajee
Subject: NDA22-110/CMC IR

Importance: High

Dr. Coleman,

Please see the attached request below. Let me know when we can expect a reply.

Thanks very much,

Chris Davi

From: Shanmugam, Balajee
Sent: Monday, July 23, 2007 11:44 AM
To: 'bcoleman@theravance.com'
Cc: Davi, Christopher; Schmuff, Norman R; Shanmugam, Balajee
Subject: NDA22-110/CMC IR
Importance: High

Dear Ms. Coleman:

I am the Chemistry reviewer for the above NDA and I have a Chemistry information request. Could you kindly provide me with the report, "Nonconformance report No. NC06-002, Unexpected Results for Solution Appearance for TD-6424 Hydrochloride Drug Substance Registration Stability, Covance Study No. 7057-336" at the earliest possible?

To expedite, you could either email or fax (301) 796-9850 the report.

Thank you,

Balajee Shanmugam

****

Balajee Shanmugam, Ph.D.
Chemistry Reviewer
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph: (301) 796-1457
Fax: (301) 796-9850
Balajee.Shanmugam@fda.hhs.gov

****

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/s/

Christopher Davi
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Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue,
Silver Spring, MD 20993

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DATE: 7/16/07 NUMBER OF PAGES (including cover sheet): 2

TO: Rebecca Coleman, Pharm D

COMPANY: Theravance, Inc (NDA 22-110)

FAX NUMBER: (650) 808-3786

MESSAGE: Dr. Coleman
Please find attached an additional information request from the PK reviewers. Please let me know if you have questions.

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the content of this transmission.

FROM: Chris Davi

TITLE: Regulatory Project Manager

TELEPHONE: (301) 796-0702 FAX NUMBER: 301-796-9881

Thank You

Please submit the pooled safety data in the control group (such as: Vancomycin group), from the major clinical studies (Study 0017, Study 0018, Study 16424-202a, and Study 16424-202b), in order for us to perform safety analysis. All datasets should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a separate Define.pdf file.

Population CrCL Analysis Dataset (Control group) :

SUBJECT (patient unique ID number), STUDY (study number), AT(subject belongs to all treated group=1, otherwise=0), MAT (subject belongs to modified all treated group=1, otherwise=0), CE(subject belongs to clinical evaluable group=1, otherwise=0), DOSE (actual dose), WT (body weight with the unit of [kg]), ATAFD (actual time after the 1st dose with the unit of [day]), PHASE (phase of the treatment, baseline evaluation=0, treatment phase=1, end of therapy phase=3, follow-up phase=4), AUCSS1 (steady state AUC for 0-24hr, if a subject had no PK samples, using missing value), AUCSS2 (steady state AUC for 0-48hr, if a subject had no PK samples, using missing value), AUCACC (accumulative AUC from the 1st dose, if a subject had no PK samples, using missing value). PK (a subject belongs to a PK sub group=1, otherwise=0), BCLCR (baseline creatinine clearance), CLCR (creatinine clearance at different time points during study), DUR (duration of the treatment, e.g. if a patient was on therapeutic drug for 14 days, then put 14 here).

SUBJECT	STUDY	AT	MAT	CE	ME	DOSE	TRT	WT	ATAFD	PHASE	AUCSS1	AUCSS2	AUCACC	PK	BCLCR	CLCR
123	Study0017	1	1	1	1	250 mg	Vancomycin	75	0	1	123	246	0	1	100	100
123	Study0017	1	1	1	1	250 mg	Vancomycin	75	4	2	123	246	80	1	100	100
123	Study0017	1	1	1	1	250 mg	Vancomycin	75	7	2	123	246	190	1	100	90
123	Study0017	1	1	1	1	250 mg	Vancomycin	75	10	2	123	246	300	1	100	85
123	Study0017	1	1	1	1	250 mg	Vancomycin	75	13	2	123	246	423	1	100	50
123	Study0017	1	1	1	1	250 mg	Vancomycin	75	16	3	123	246	546	1	100	50
123	Study0017	1	1	1	1	250 mg	Vancomycin	75	17	3	123	246	669	1	100	50
123	Study0017	1	1	1	1	250 mg	Vancomycin	75	20	4	123	246	792	1	100	80
123	Study0017	1	1	1	1	250 mg	Vancomycin	75	22	4	123	246	915	1	100	90

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/s/

Christopher Davi
7/16/2007 03:02:13 PM
CSO

Comments on NDA 22-110 telavancin HCl
From A. Jacobs 7/13/07

1. Approvability

Approvability would be based on the clinical determination of the risk-benefit ratio for patients. Although the primary reviewer/TL concluded that the P/T findings did not support approval of this product (see review in DFS), the decision regarding product approval would be based on clinical data. There are no approvability issues with this NDA from a pharm/tox perspective.

2. Pregnancy category:

I would recommend Pregnancy Category C as appropriate for telavancin, rather than the Category X recommended by the reviewer. Category X is unprecedented for an antimicrobial and indicates that the risk benefit ratio would never be appropriate for a pregnant woman. Findings from the animal studies may be described in the labeling.

3. Perhaps an addendum could be written to the pharm/tox review, if the reviewer agrees.

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/s/

Abby Jacobs
7/13/2007 11:39:42 AM
PHARMACOLOGIST

DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGY PRODUCTS

Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue,
Silver Spring, MD 20993

FACSIMILE TRANSMISSION

DATE: 7/13/07 NUMBER OF PAGES (including cover sheet): 2

TO: Rebecca Coleman, PharmD

COMPANY: Theravance, Inc

FAX NUMBER: (650) 808-3786

MESSAGE: Dr Coleman,

Please find attached some additional information requests from the CMC reviewer. Let me know if you have questions

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the content of this transmission.

FROM: Chris Davi

TITLE: Regulatory Project Manager

TELEPHONE: (301) 796-0702 FAX NUMBER: 301-796-9881

Thank You

NDA #: 22-110 – Telavancin Hydrochloride

Dr. Coleman,

We are in the process of reviewing the Chemistry, Manufacturing, Controls section of telavancin hydrochloride and have the following request.

Questions to the sponsor:

1. The proposed acceptance criteria of (for degradant B seem to be high given the batch analysis data. Please consider revising the acceptance criteria to reflect a lower value for this degradant and accordingly for total degradants. b(4)

2. Report DVP089 on "Stability of TD-6424 for injection of bulk solution" provides for the levels of a degradant ( ) of ( ). Please explain the reasons for choosing this degradant as an indicator of stability since ( ) (Section 3.2.P.5.5). In addition, please indicate if degradant A or B were monitored in this study and provide data if available or justification if they were not monitored. b(4)

3. Please clarify if the levels of degradant A or B were tracked in the study in "In-use stability dosing solutions of TD-6424 for injection, 250 mg/ml", Report DVP086.

4. Please revise the post-approval stability commitment to place a single production batch of both 250 mg and 750 mg on long-term stability annually. Also, please fulfill the stability data requirement for commercial batches per ICH Q1A (R2) requirement.

Please contact me at (301) 796-0702 if you have any questions.

J. Christopher Davi, MS
Regulatory Project Manager

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/s/

Christopher Davi
7/13/2007 10:23:23 AM
CSO

Davi, Christopher

From: Davi, Christopher
Sent: Thursday, July 12, 2007 2:05 PM
To: 'Coleman, Becky'
Cc: Shanmugam, Balajee
Subject: Outstanding CMC Information Requests (NDA 22-110)

Dr. Coleman,

The CMC reviewer has informed me that the following information requests (i.e., from the April 20, 2007 facsimile) are outstanding:

5. Please provide data to show that ( ) and its impurities are not carried over in the drug substance. Also, provide details on how you plan to control the carry over, if any. b(4)

6. Please indicate if the drug substance is tested for the presence of ( ) which is ( ) ( ) telavancin hydrochloride. Please provide details on the levels, if any present and the plan to remove/ control the same. b(4)

Please let me know when you anticipate being able to provide information on the above items.

Thank you,

Chris Davi

J. Christopher Davi, MS
Regulatory Project Manager
Food and Drug Administration (FDA)
Division of Anti-Infective and Ophthalmology Products
christopher.davi@fda.hhs.gov
(301) 796-0702

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/s/

Christopher Davi
7/12/2007 02:10:58 PM
CSO

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: June 14, 2007

TO: J. Christopher Davi, MS, Regulatory Health Project Manager
Janice Pohlman, MD, MPH, Medical Reviewer
Division of Anti-Infective and Ophthalmologic Products

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Dan-My T. Chu, PhD
Regulatory Review Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-110

NME: Yes

APPLICANT: Theravance

DRUG: Telavancin

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of Complicated Gram Positive Skin and Skin Structure Infections

CONSULTATION REQUEST DATE: January 22, 2007

DIVISION ACTION GOAL DATE: June 29, 2007

PDUFA DATE: October 19, 2007

I. BACKGROUND:

Theravance Inc submitted a New Drug Application (NDA 22-110) for Telavancin (previously known as TD-6424, AMI-6424, ARBELIC™) for the treatment of complicated gram positive skin and skin structure infections. The sponsor claims that the results of the clinical trials conducted under this NDA show that Telavancin is clinically and microbiologically non-inferior to Vancomycin in the treatment of complicated skin and skin structure infections caused by gram positive microorganisms, including those caused by methicillin-resistant *Staphylococcus aureus*.

Telavancin is a new molecular entity and its mechanism of action is proposed to occur via multiple mechanisms which include the inhibition of cell wall syntheses and increased bacterial membrane permeability. Telavancin has been proposed to be a concentration-dependent, rapidly bactericidal, injectable antibiotic with activity against clinically important Gram-positive pathogens. The rapid bactericidal activity is proposed to lead to a reduction in the duration of therapy, improved outcomes such as higher and/or faster rates of resolution of the infectious process, lower rates of relapse, and decreased duration of hospitalization and reduced use of health care resources.

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State	Protocol #	Insp. Date	EIR Received Date	Final Classification
Site # 38101 Razi Hekmat, MD	Site: National City, CA Records at: San Diego, CA	17	3/6-21/2007	4/4/2007	VAI
Site # 38271 William O'Riordan, MD	Site: Chula Vista, CA Records at: San Diego, CA	17	3/12/2007 – 4/3/2007	04/26/2007	NAI
Site # 38091 Christian Schrock, MD	Minneapolis, MN	18	3/14/2007- 4/10/2007	5/1/2007	OAI
Site # 38112 Lala Mathers Dunbar, MD, PhD	New Orleans, LA	18	3/20-26/ 2007	04/17/2007	NAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

Protocol 17 and 18 are of identical design.

These studies were a phase III, randomized, double-blind, active-controlled, parallel-group, multicenter, multinational trial comparing intravenous Telavancin to the current standard therapy, Vancomycin, for treatment of complicated gram positive skin and skin structure infections. The primary objective of the studies was to compare the efficacy and safety of Telavancin to Vancomycin in the treatment of adults with complicated gram-positive skin and skin structure infections with an emphasis on patients with infections due to methicillin-resistant *Staphylococcus aureus* (MRSA). The primary efficacy endpoint was the clinical response (ie cure, not cured, indeterminate) at the Test-of-Cure visit (Section 7.2.7.1).

After written consent was obtained, subjects were examined for eligibility into the study (Sections 5.1, 5.2, 7.2.1). If the patient qualified for the study, unblinded study personnel were to contact a central randomization service for assignment of a patient number and study medication [Telavancin (10 mg/kg) IV q 24 hrs or Vancomycin 1 g q 12 hrs]. Day 1 was considered the calendar day that the first study dose was given. Patients were to be evaluated daily for occurrence of adverse events, assessment of clinical signs and symptoms of the infection, measurement of the primary infection site, blood cultures if baseline blood cultures were positive or if there was a suspected bloodstream infection, documentation of any significant procedures performed, and documentation of all concomitant medications (Section 7.2.3). On study days 4, 7, 10 and 13 additional protocol required procedures were to be conducted (Section 7.2.4-7.2.5). An End-of-Therapy visit was required to occur as soon as possible after the last dose of study medication and no later than 3 days following the last dose of study medication (Section 7.2.6). An assessment of the clinical response was to be made during that time (Section 7.2.6.1). Within 7 to 14 days after the last dose of study medication, all subjects were to have a follow-up visit (Section 7.2.7). In addition, only those subjects that were evaluated as a clinical "cure" or "indeterminate" at the End-of-Therapy visit were to have a Test-of-Cure evaluation at the follow-up visit (Section 7.2.7).

The duration of the study was between 7 and 15 days and was determined by the investigator as clinically indicated until there was a resolution of signs and symptoms of the skin infection or until improvement to such an extent that no further therapy was deemed necessary to a maximum of 14 days.

During the study, subjects were to be managed for intercurrent events (eg mixed infection with gram negative organisms that are resistant to aztreonam, coagulation problems, etc) that may occur during the subjects enrollment in the study (Section 8). Subjects were to be discontinued if they meet any indications described in Section 9.

A. Protocol 17

1. Site # 38101
   Razi Hekmat, MD
   Paradise Valley Hospital
   2400 East Fourth Street
   National City, CA 91950
   (619) 470-4321

( ) b(4)

   a. At this site, 387 subjects were randomized (123 under the original protocol and 264 under protocol amendment #1) and 358 subjects completed the study. An audit of 65 subject records was conducted.

   b. Limitations of inspection: None

   c. The following deviations were noted during the inspection:

      1. The clinical investigator did not adhere to the signed investigator statement and investigational plan [21 CFR 312.60]. Specifically subject 199 was randomized to vancomycin and should have received 1 g of vancomycin during the study; however the subject only received 750 mg.

2. The investigator failed to prepare and maintain adequate and accurate case histories [21 CFR 312.62(b)]. Specifically, discrepancies were noted in the investigational drug dosing start time in the source document and the case report form for several subjects (0035, 0135, 0141, 0142, 0147, 0189, 0206, 0208 and 0243); Local and Central Laboratory Adverse Events form was not completely filled out for subjects 0252, 0773, 0933, 0963, and 0998; and discrepancies were noted in the records concerning concomitant medications for subjects 0269, 0525, and 0998

d. Assessment of data integrity: The data generated as this site appear acceptable in support of the respective indication.

2. Site # 38271
William O'Riordan, MD
3450 Bonita Road Suite 201
Chula Vista, CA 31310

b(4)

a. At this site, 202 subjects were screened and randomized to the study, 22 subjects withdrew from the study due to personal reason, withdrawal of consent, SAE, infectiveness of the study drug, or were lost to follow up, and 180 subjects completed the study. An audit of 50 subject records was conducted.

b. Limitations of inspection: None

c. No significant deviations were noted during the inspection.

d. Assessment of data integrity: The data generated as this site appear acceptable in support of the respective indication.

B. Protocol # 18

1. Site # 38091
Christian Schrock, MD
Infectious Disease-Minneapolis-LTD
3366 Oakdale Avenue, North
Suite 520
Minneapolis, MN 55422

a. At this site, 51 subjects were enrolled into the study. An audit of 51 subject records was conducted.

b. Limitations of inspection: None

c. The following deviations were noted during the inspection:

1. The clinical investigator did not adhere to the investigational plan [21 CFR 312.60]. Specifically, problems with the primary efficacy endpoint data for 6 subjects (2220, 2469, 2847, 2833, 2287, 2177) were identified; two pharmacists prepared or dispensed investigational drug without receiving authorization; and the investigational product could not be confirmed to be stored at appropriate temperatures for two time periods during the study.

2. The clinical investigator did not maintain adequate control of the drug [21 CFR 312.60]. Specifically subject #2584 received study drug from a different study that was examining the same investigational agent for a different indication.

3. The clinical investigator did not maintain adequate records of the disposition of the drug [21 CFR 312.62(a)]. Specifically, it could not be determined which lot of investigational agent a subject was given on which day, how outpatients received their medication from the pharmacy and which lot(s) were being delivered to them, how the investigational product was stored at the outpatients homes, and how the medication was returned to the pharmacy and/or discarded for days in which the subject did not receive medication.

4. The clinical investigator did not maintain adequate and accurate case histories that record all observations and data pertinent to the investigation [21 CFR 312.62(b)]. Specifically, (a) source documents were thrown out for 13 subjects (2042, 2056, 2122, 2132, 2177, 2192, 2221, 2297, 2427, 2634, 2910, 2997, 3067) and (b) infection measurements and clinical signs and symptoms of disease were discrepant between the CRF, daily signs and symptoms log, and source records.

5. The clinical investigator did not retain records as required by 21 CFR 312 for a period of 2 years [21 CFR 312.62(c)]. Specifically source documents were thrown out for 13 subjects (2042, 2056, 2122, 2132, 2177, 2192, 2221, 2297, 2427, 2634, 2910, 2997, 3067).

6. The clinical investigator did not promptly report to the IRB all unanticipated problems involving risk to human subjects or others [21 CFR 312.66]. Specifically, delayed SAE reporting to the IRB was noted for subjects 2087, 2132, 2189 and 2192.

d. Assessment of data integrity: The data generated as this site does not appear acceptable in support of the respective indication. In reference to the primary efficacy endpoint, DSI recommends that the 6 subjects (2220, 2469, 2847, 2833, 2287, 2177) whose primary efficacy endpoint data were noted to have been discrepant, be excluded from the safety and efficacy analysis for this NDA. In addition, DSI recommends that the 13 subjects (2042, 2056, 2122, 2132, 2177, 2192, 2221, 2297, 2427, 2634, 2910, 2997, 3067) whose source data were confirmed to have been thrown out by the site, should also be excluded from the safety and efficacy analysis for this NDA.

2. Site # 38112
Lala Mathers Dunbar, MD, PhD
Louisiana State University Health Sciences Center
Dept. of Medicine/Emergency Medicine
1542 Tulane Avenue
New Orleans, LA 70118

a. At this site, 220 patients were screened for the study, 75 subjects entered the study (1 under the original protocol and 74 under protocol amendment #1), 1 subject had an SAE, 9 subjects discontinued from the study due to drug allergy, being hospitalized elsewhere or noncompliance, 5 subjects voluntarily withdrew from the study, 9 patients were lost to follow-up due to Hurricane Katrina, and 23 subjects had adverse events. An audit of 75 subjects' records was conducted to examine (1) informed consent and (2) the primary efficacy endpoint. In addition, the FDA field investigator examined all 75 research subject files for hospital medical records (ie charts), labs, EKGs, and progress reports and found that available records were organized and legible.

b. Limitations of inspection:

1. The inspection was conducted over a span of only 6 days. It appears that the FDA field investigator therefore only examined all of the subject records to ensure that adequate documentation (whether on paper on in the electronic computer system) existed within each of the subject records in order to assess the impact of the Hurricane on research related records. In addition, it appears that the FDA field investigator only spot checked various records for inclusion/exclusion criteria and protocol requirements. It does not appear that an in depth review of records to ensure adequate and accurate case histories or drug accountability (ie detailed accounting of vials) was done at this site due to inspection time constraints.

2. The site was impacted by Hurricane Katrina, thus not all research related records were available for review during the inspection.

c. No significant deviations were noted during the inspection.

d. Assessment of data integrity: The data generated as this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

In general Dr. Hekmat, O'Riordan, and Dr. Dunbar's sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigation. The data at these sites appear acceptable in support of this NDA.

The data obtained from Dr. Schrock's site is questionable. As noted above, DSI would recommend that certain data not be used in support of the NDA.

DSI would recommend that the review division consider the following items that were identified during the course of the above inspections, as these may impact the NDA:

1. At Dr. Hekmat and Dr. O'Riordan's sites, it was noticed that a high number of subjects had increased liver enzymes during the study. These increased liver enzymes were not reported on the CRF as AEs or SAEs but instead on the sponsor's laboratory AE form. Section 10 of the approved protocol noted that laboratory abnormalities (eg clinical chemistry, hematology, urinalysis) or other abnormal assessments (eg electrocardiogram, X-rays, vital signs) were not to be recorded as AEs or SAEs unless they are associated with signs and/or symptoms and meet the protocol definition of an AE or SAE. Thus DSI recommends that the review division examine how the sponsor is reporting the cumulative findings of abnormal laboratory results that are not associated with clinical signs and symptoms of disease and did not meet the definition of an AE or SAE, as these abnormal laboratory findings may impact the overall safety profile of the investigational product.

2. At Dr. Dunbar's site, a subject experienced an SAE after the Test of Cure visit and subsequently died. Subject 2079's wound infection was listed as a "Cure" at the "Test of Cure" visit ( ). 45 days after the last dose of study medication and 38 days after the Test of Cure visit, the subject died due to bilateral pneumonia confirmed to be caused by MRSA. Dr. Dunbar's site properly notified the CRO about the SAE; however, the CRO noted that it was not necessary to notify the sponsor as the approved protocol noted that SAEs were only to be reported until resolution or stabilization or until the study is completed. DSI notes that any SAEs reported after the study has been completed would therefore not be required to be reported to the sponsor for follow up based on the current approved protocol. Thus DSI recommends that the review division

b(6)

examine whether this lack of reporting of SAEs that occur after the study has been completed, could affect the overall long term safety and efficacy profile of the drug.

3. In the investigation of Dr. Schrock, a possible problem was identified in the way in which the primary efficacy endpoint could be interpreted by clinical investigators and subsequently reported to the sponsor and to the agency. There appears to be a grey area between the definitions of "Not Cured" and "Indeterminate" within the protocol. Specifically, the protocol does not tell investigators how to handle the clinical response at the Test of Cure evaluation when a situation arises where a subject is discontinued from the study and is subsequently treated with different antibiotics, prior to the Follow-up visit and Test of Cure evaluation.

In the case of Dr. Schrock, he felt that the use of the term "Indeterminate" was justified in this type of situation because the subjects were discontinued early in the study and it would be premature to determine if the investigational agent "Cured" or did "Not Cure" the subject. Thus he used the term "Indeterminate" for the clinical response of these types of subjects at the End of Therapy visit. The protocol specified that all subjects were to have a Follow-up visit and those who were listed as "Cure" or "Indeterminate" at the End of Therapy visit, would thus also receive a Test of Cure evaluation. In the case of Dr. Schrock, if a subject was discontinued prematurely and treated with additional non-study antibiotics, and listed as "Indeterminate" at the End of Therapy visit, at the Test of Cure evaluation, there would still be a question as to whether the investigational agent had an effect on the infection; thus the use of the term "Indeterminate" could be used for the clinical response at the Test of Cure. DSI would therefore recommend the review division examine the protocol definition and possible use of the term "Indeterminate" in its evaluation of how this term could be interpreted by investigators and subsequently how the frequent use of this term vs the use of the term "Not Cure" could impact the overall statistical value of primary efficacy endpoint for the investigational product being studied in this NDA.

{See appended electronic signature page}

Dan-My T. Chu, PhD
Regulatory Review Officer

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Dan-My Chu
6/18/2007 08:24:25 AM
UNKNOWN

Leslie Ball
6/21/2007 03:19:34 PM
MEDICAL OFFICER

DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGY PRODUCTS

Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue,
Silver Spring, MD 20993

FACSIMILE TRANSMISSION

DATE: 5/11/07 NUMBER OF PAGES (including cover sheet): 2

TO: Rebecca Coleman, Pharm D

COMPANY: Theravance, Inc (NDA 22-110)

FAX NUMBER: (650) 808-3786

MESSAGE: Dr Coleman,
Please see the attached information request from the Maternal Health Team.
Let me know if you have questions

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the content of this transmission.

FROM: Chris Davis

TITLE: Regulatory Project Manager

TELEPHONE: (301) 796-0702 FAX NUMBER: 301-796-9881

Thank You

Dear Dr. Coleman,

The Pregnancy and Maternal Health Team is providing a consultation for the Division of Anti-Infective and Ophthalmology Products (DAIOP) for NDA 22-110. If possible, they have requested that Theravance provide details on the following:

1. Do you have any information about the presence or absence of telavancin in human semen? Have any studies been conducted that provide information on telavancin concentrations in semen in men treated with the drug, and how long does it take to clear?

2. Can you provide information on the rationale for choosing three months as the period for contraceptive use following telavancin treatment in a male, and one month for females treated with telavancin?

3. How many men treated with telavancin in the studies had partners who became pregnant within three months of telavancin therapy? If this information is available, can you provide additional information on these pregnancies, including:

    a) Therapeutic abortions
    b) Spontaneous abortions (gestational age, any noted abnormalities on pathology)
    c) Stillbirths (gestational age and any anomalies)
    d) Live births (gestational age and any anomalies)

Please contact me at (301) 796-0702 if you have any questions.

Best regards,

J. Christopher Davi, MS
Regulatory Project Manager, DAIOP

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/s/

Christopher Davi
5/14/2007 08:55:02 AM
CSO

DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGY PRODUCTS

Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue,
Silver Spring, MD 20993

FACSIMILE TRANSMISSION

DATE: 5/1/07 NUMBER OF PAGES (including cover sheet): 2

TO: Rebecca Coleman, Pharm D

COMPANY: Theravance, Inc NDA 22-110

FAX NUMBER: (650) 808-3786

MESSAGE: Dr. Coleman,
Please see the attached information request from the Maternal Health Team.
Let me know if you have questions

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the content of this transmission.

FROM: Chris Davi

TITLE: Regulatory Project Manager

TELEPHONE: (301)796-0707 FAX NUMBER: 301-796-9881

Thank You

Dr. Coleman,

The Maternal Health Team has been consulted in the review of NDA 22-110 and has made the following information request:

> According to the Clinical Safety Summary for NDA 22-110, Televancin, one pregnancy occurred in a woman who conceived six days after a 15 day course of treatment with televancin. This woman should have delivered in mid-December of 2006. The sponsor is requested to report on the outcome of that pregnancy. They should have followed her until after delivery.

Please let me know if you can provide any information pertinent to the Maternal Health team's request. If you have questions, I can be reached at (301) 796-0702.

J. Christopher Davi
Regulatory Project Manager

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/s/

Christopher Davi
5/1/2007 10:36:20 AM
CSO

Davi, Christopher

From: Davi, Christopher
Sent: Tuesday, April 10, 2007 10:40 AM
To: 'Coleman, Becky'
Subject: Additional PK dataset request (NDA 22-110)

Dear Dr. Coleman,

The PK and pharmacometrics group has an additional information request. Please provide information for the 202A, 202B, 0017 and 0018 studies in a SAS transport file format (.XPT) as follows:

Microbiological dataset:

SUBJECT (patient unique ID number), MICRO_NAME (microorganism name), MIC (measured MIC values from the isolated microorganism), UNIT (unit of MIC), SOURCE (source of the sampling).

SUBJECT	SUTDY	MICRO_NAME	MIC	UNIT	SOURCE
123	Study0017	XYZ	0.2	ng/mL	SKIN

Please let me know if you have any questions. A copy of this information request will be placed in the division file for NDA 22-110.

Regards,

Chris Davi

J. Christopher Davi, MS
Regulatory Project Manager
Food and Drug Administration (FDA)
Division of Anti-Infective and Ophthalmology Products
christopher.davi@fda.hhs.gov
(301) 796-0702

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/s/

Christopher Davi
4/10/2007 10:46:24 AM
CSO

DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGY PRODUCTS

Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue,
Silver Spring, MD 20993

FACSIMILE TRANSMISSION

DATE: 4/6/07 NUMBER OF PAGES (including cover sheet): 4

TO: Rebecca Coleman Pharm D

COMPANY: Theravance, Inc (NDA 22-110)

FAX NUMBER: (650) 808-3786

MESSAGE: Dr. Coleman
Please see the attached information request from the PK group. Let me know if you have any questions

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the content of this transmission.

FROM: Chris Davi

TITLE: Regulatory Project Manager

TELEPHONE: (301) 796-0702 FAX NUMBER: 301-796-9881

Thank You

Dr. Coleman,

Please see the attached information request presented in landscape format on the following 2 pages for NDA 22-110. The PK group has requested a reply by April 20, 2007. If you have questions, please contact me at (301) 796-0702.

Regards,

J. Christopher Davi, MS

Population PK analysis datasets:

Please submit the following datasets to support the population PK analysis for report 06-6424-pop-PK-01 (A Population Pharmacokinetic Analysis of Phase I data of Telavancin) and report 06-6424-pop-PK-02 (A Population Pharmacokinetic Analysis of Telavancin Phase1, 2, 3 Data):

All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). Please add one more column named SUBJECT in each of the datasets to represent the subject unique ID that is correspondent to the ID number in the safety and efficacy datasets. A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.

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).

A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports, we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Please submit the pooled effectiveness and safety datasets from the major clinical studies (Study 0017, Study 0018, Study 16424-202a, and Study 16424-202b), in order to perform exposure-response modeling. All datasets should be submitted as a SAS transport files (*.xpt)

Population exposure-effectiveness analysis dataset:

SUBJECT (patient unique ID number), STUDY (study number), AT (subject belongs to all treated group=1, otherwise=0), MAT (subject belongs to modified all treated group=1, otherwise=0), CE (subject belongs to clinical evaluable group=1, otherwise=0), ME (subject belongs to the microbiological evaluable group=1, otherwise=0), DOSE, (actual dose with the unit of [mg/kg]), TRT (protocol dose group with the unit of [mg/kg]), WT (body weight with the unit of [kg]), AUCSS1 (steady state daily AUC for 0-24hr, please note if a subject has no PK information, please leave as missing value), AUCSS2 (steady state AUC for 0-48hr, please not if a subject has no PK information, use missing value. Also please not for a patient with severe renal impairment, the AUCSS2 ≠ 2*AUCSS1 after dose adjustment), PK (if a subject belongs to PK subgroup=1, otherwise=0), TOC1 (test of cure, where not cured=0, intermediate =2, cured=3), TOC2, (test of cure, where not cured=0, intermediate or cured =1). ME (Microbiological eradication=1, otherwise=0), DUR (duration of the treatment, if a subject was given telavancin for 14 days, use 14 here in the column)

SUBJECT	STUDY	AT	MAT	CE	ME	DOSE	TRT	WT	AUCSS1	AUCSS2	PK	TOC1	TOC2	ME	DUR
123	STUDY0017	1	1	1	1	10	10	75	123	246	1	2	1	1	14

Population exposure-CLcr analysis dataset:

SUBJECT (patient unique ID number), STUDY (study number), AT(subject belongs to all treated group=1, otherwise=0), MAT (subject belongs to modified all treated group=1, otherwise=0), CE(subject belongs to clinical evaluable group=1, otherwise=0), DOSE (actual dose with the unit of [mg/kg]), TRT(protocol dose group with the unit of [mg/kg]), WT (body weight with the unit of [kg]), ATAFD (actual time after the 1st dose with the unit of [day]), PHASE (phase of the treatment, baseline evaluation=0, treatment phase=1, end of therapy phase=3, follow-up phase=4), AUCSS1 (steady state AUC for 0-24hr, if a subject was not in a PK subgroup, using missing value), AUCSS2 (steady state AUC for 0-48hr, if a subject was not in a PK subgroup, using missing value, please note for the severe renal impaired patient, the AUCSS2 ≠ 2*AUCSS1 after dose adjustment), AUCACC (accumulative AUC from the 1st dose, if a subject was not in a PK subgroup, using missing value). PK (a subject belongs to a PK sub group=1, otherwise=0), BCLCR (baseline creatinine clearance), CLCR (creatinine clearance at different time points during study), DUR (duration of the treatment, e.g. if a patient was on telavancin for 14 days, then put 14 here).

SUBJECT	STUDY	AT	MAT	CE	ME	DOSE	TRT	WT	ATAFD	PHASE	AUCSS1	AUCSS2	AUCACC	PK	BCLCR	CLCR	DUR
123	Study0017	1	1	1	1	10	10	75	0	1	123	246	0	1	100	100	14
123	Study0017	1	1	1	1	10	10	75	4	2	123	246	80	1	100	100	14
123	Study0017	1	1	1	1	10	10	75	7	2	123	246	190	1	100	90	14
123	Study0017	1	1	1	1	10	10	75	10	2	123	246	300	1	100	85	14
123	Study0017	1	1	1	1	10	10	75	13	2	123	246	423	1	100	50	14
123	Study0017	1	1	1	1	10	10	75	16	3	123	246	546	1	100	50	14
123	Study0017	1	1	1	1	10	10	75	17	3	123	246	669	1	100	50	14
123	Study0017	1	1	1	1	10	10	75	20	4	123	246	792	1	100	80	14
123	Study0017	1	1	1	1	10	10	75	22	4	123	246	915	1	100	90	14

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/s/

Christopher Davi
4/6/2007 01:28:58 PM
CSO

DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGY PRODUCTS

Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue,
Silver Spring, MD 20993

FACSIMILE TRANSMISSION

DATE: 4/2/07 NUMBER OF PAGES (including cover sheet): 2

TO: Rebecca Coleman, Pharm D

COMPANY: Theravance, Inc

FAX NUMBER: (650) 808-3786

MESSAGE: R. Coleman

Please see the attached information requests from the clinical microbiology review team for NDA 22-110. Let me know if you have questions.

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the content of this transmission.

FROM: Chris Davi

TITLE: Regulatory Project Manager

TELEPHONE: (301) 796-0702 FAX NUMBER: 301-796-9881

Dr. Coleman,

Please see the following information requests from the clinical microbiology review team (in reference to NDA 22-110):

1. Please provide information on the activity of telavancin against *Staphylococcus aureus* that have been shown to demonstrate vancomycin hetero-resistance. This information is being requested because of the increasing occurrence of vancomycin heteroresistant *S. aureus* infections, the difficulty in detecting these organisms, and the difficulty in treating infections due to these organisms.

2. Please provide information on whether telavancin heteroresistance occurs in *S. aureus*. Because telavancin is similar chemically in some aspects to vancomycin it is felt that such information would be beneficial in order to determine the full spectrum of activity of telavancin. It is suggested that such determinations be done using isolates of *S. aureus* that do and do not demonstrate vancomycin heteroresistance. It is recognized by the Agency that there are a variety of methods that can be used to detect heteroresistance. One such method that might be used is one described in the reference below.

Reference

Pfeltz, R, JL Schmidt, and BJ Wilkinson. 2001. A microdilution plating method for population analysis of antibiotic-resistant staphylococci. Microbial Drug Resistance 7:289-295.

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
4/2/2007 11:20:42 AM
CSO

MEMORANDUM OF TELECONFERENCE

DATE:	March 19, 2007
TIME:	11:25 to 11:50 AM, EST
APPLICATION:	NDA 22-110
DRUG NAME:	Telavancin
TYPE OF MEETING:	90-Day NDA Status Update

MEETING CHAIR: Sumathi Nambiar, MD, MPH, Medical Team Leader

MEETING RECORDER: J. Christopher Davi, MS, Regulatory Project Manager

FDA ATTENDEES (Division of Anti-Infective and Ophthalmology Products):
Edward M. Cox, MD, MPH, Office Director, OAP
Janice M. Soreth, MD, Director, DAIOP
Sumathi Nambiar, MD, MPH, Medical Team Leader
Janice K. Pohlman, MD, MPH, Medical Reviewer
Kerry Snow, MS, Clinical Microbiology Reviewer
Scott Komo, PhD, Statistical Reviewer
Jeff Tworyzyanski, PhD, Clinical Pharmacology Reviewer
Hao Zhu, PhD, Clinical Pharmacology Reviewer
Rapti Madurawe, PhD, Pharmaceutical Assessment Leader, CMC
Balajee Shanmugam, PhD, Chemistry Reviewer
J. Christopher Davi, MS, Regulatory Project Manager
Fatima Stimpson, Consultant, Booze Allen Hamilton

EXTERNAL CONSTITUENT PARTICIPANTS (Theravance, Inc.):

Kenjie Amemiya (Safety Assessment)
Bret Benton, PhD (Molecular and Cellular Biology)
David Brinkley (Commercial Development)
Rebecca Coleman, PharmD (Regulatory Affairs)
Michael Conner, DVM (Safety Assessment)
Alan Hopkins, PhD (Biometrics)
Michael Kitt, MD (Development)
John Kent, PhD (Pharmaceutical Sciences)
Kipp Kreutzberg (Commercial Development)
Steve Pomerantz (Commercial Development) Astellas
Rochelle Maher (Project Management)
Robert Reed (Regulatory Affairs)
Nkechi Azie, MD (Clinical Research)

BACKGROUND:

The Sponsor submitted marketing application NDA 22-110 for the Agency's review on December 19, 2006. As provided for under 21 CFR 314.102(c), the Sponsor requested a brief report on the status of the review from the Division of Anti-Infective and Ophthalmology Products (DAIOP). The Division granted this request, and a teleconference was held on March 19, 2007. Minutes from the teleconference are provided herein.

MEETING OBJECTIVES:

- To provide a brief status on the progress of the review for application NDA 22-110.

DISCUSSION POINTS:

The Division opened the discussion, and provided the Sponsor a brief update from the following review disciplines:

1. Clinical Pharmacology
2. Chemistry Manufacturing and Controls
3. Pre-Clinical Pharmacology
4. Clinical Microbiology
5. Biostatistics & Clinical

For review disciplines numbered 1 through 4, above, DAIOP informed the Sponsor that reviews were in progress, and that there were no review issues (or additional information requests) to report at the time of the teleconference. With respect to item #5 above, the Division informed the Sponsor that additional information would be needed to justify the proposed 10% non-inferiority margin. Possible sources of data for the Sponsor to consider recommended by the Division were discussed as follows:

- Literature describing the natural history of cSSSI in the preantibiotic era.

- Treatment effect of non-antibiotic treatment such as incision and drainage compared to treatment effect of antimicrobials with or without adjunctive surgical procedures for the treatment of abscesses.

- Natural history studies or placebo-controlled/local wound care only trials for uncomplicated SSSI with clinically meaningful extrapolation of results from uncomplicated infections to complicated SSSI infections.

The Division asked the Sponsor to take into consideration the severity of the underlying infections, types of infections, and extent of surgical interventions.

The Sponsor acknowledged the Divisions points, and indicated that they had been working diligently on the justification of the 10% non-inferiority margin. The Sponsor added that they hoped to provide additional information to justify the non-inferiority margin sometime in the next several weeks.

The Division asked the Sponsor to provide an update on submission of an alternate trade name for consideration by the Division of Drug Marketing, Advertising and Compliance (DDMAC). The Sponsor informed the Division that they would be providing an alternate trade name for review in the first week of April, 2007.

DECISIONS (AGREEMENTS) REACHED:

1. The Sponsor will provide additional justification for the 10% non-inferiority margin as soon as possible (i.e., within the next several weeks).

2. The Sponsor will submit an alternate trade name for review in the first week of April, 2007.

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/s/

Frances LeSane
3/23/2007 01:28:38 PM

DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGY PRODUCTS

Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue,
Silver Spring, MD 20993

FACSIMILE TRANSMISSION

DATE: 3/19/07 NUMBER OF PAGES (including cover sheet): 2

TO: Rebecca Coleman, Pharm D

COMPANY: Theravance, Inc NDA 22-110

FAX NUMBER: (650) 808-3786

MESSAGE: Dr. Coleman,
As a follow-up to today's teleconference please see the attached comments from Drs. Nambiar and Pohlman. Let me know if you have questions

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the content of this transmission.

FROM: Chris Davi

TITLE: Regulatory Project Manager

TELEPHONE: (301) 796-0702 FAX NUMBER: 301-796-9881

Thank You

Dr. Coleman,

Per our teleconference this morning, additional information is requested for justification of the 10% non-inferiority margin for NDA 22-110. Possible sources of data to consider include:

- Literature describing the natural history of cSSSI in the pre-antibiotic era. In addition to mortality data, information on the clinical course and resolution of infection (i.e., time to defervescence, time to resolution of inflammation, etc.) and rates of complications such as bacteremia, osteomyelitis, or amputation may be helpful. Historical reports on the change in the course of the disease following the introduction of antimicrobial agents (e.g., sulfonamides, penicillins) may also be helpful.

- Treatment effect of non-antibiotic treatment such as incision and drainage compared to treatment effect of antimicrobials with or without adjunctive surgical procedures for the treatment of abscesses.

- Natural history studies or placebo-controlled/local wound care only trials for uncomplicated SSSI with clinically meaningful extrapolation of results from uncomplicated infections to complicated SSSI infections.

In addition to submission of information from the literature, it would be helpful to provide a rationale for how that information may be extrapolated and applied to the efficacy analysis of the ATLAS trial study population(s). Please take into consideration severity of the underlying infections, types of infections, and extent of surgical interventions.

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

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

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/s/

Christopher Davi
3/19/2007 03:26:27 PM
CSO

Davi, Christopher

From: Davi, Christopher
Sent: Monday, March 12, 2007 10:51 AM
To: 'Coleman, Becky'
Cc: Kozeli, Devi; Nambiar, Sumathi
Subject: FW: NDA 22110 - QT consult / Additional data request

Dr. Coleman,

Please see the information request below from the cardio/renal group, and let me know when you might be able to provide the information requested.

Thank-you,

Chris
J. Christopher Davi, MS
Regulatory Project Manager
Food and Drug Administration (FDA)
Division of Anti-Infective and Ophthalmology Products
christopher.davi@fda.hhs.gov
(301) 796-0702

From: Kozeli, Devi
Sent: Monday, March 12, 2007 9:02 AM
To: Davi, Christopher
Cc: Hinton, Denise; Li, Mike
Subject: NDA 22110 - QT consult / Additional data request

Good morning Christopher,

For the above mentioned consult request we have received only the ECG.xpt for study I6424-104a. Please ask the sponsor to submit the whole datasets for this clinical trial, including the PK concentration data and definition sheet.

Please let me know if you have any questions.

Thank you,

Devi Kozeli
Project Specialist &
Assistant to the Division Director
QT Interdisciplinary Review Team
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Office of New Drugs
Center of Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue, Building 22, Room 4179
Silver Spring, MD 20993-0002

Phone: (301) 796-1128
Fax: (301) 796-9841

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/s/

Christopher Davi
3/12/2007 11:47:29 AM
CSO

Davi, Christopher

From: Davi, Christopher
Sent: Thursday, January 11, 2007 5:31 PM
To: 'Coleman, Becky'
Cc: Nambiar, Sumathi; Pohlman, Janice; Komo, Scott; Valappil, Thamban
Subject: Non-Inferiority Margin Justification (NDA 22-110)

Dr. Coleman,

The Medical Team Leader and Statistician have the following comment and information request regarding the non-inferiority margin for NDA 22-110:

> The Division requests that you provide justification for the use of the 10% non-inferiority margin in the Phase 3 complicated skin and skin structure infection studies as requested in the written statistical comments for Serial Submission 201 (facsimile on September 19, 2006). Citing use of the 10% non-inferiority margin in prior approvals is not sufficient. The justification should include the rationale used to estimate the benefit of active drug treatment versus placebo and that the use of a 10% non-inferiority margin preserves at least 50% of this benefit. The strategy used to search the literature and pertinent references should be submitted to the NDA.

Please let me know if you have any questions. A copy of this request will be archived in the Division file.

Regards,

Chris Davi

J. Christopher Davi, MS
Regulatory Project Manager
Food and Drug Administration (FDA)
Division of Anti-Infective and Ophthalmology Products
christopher.davi@fda.hhs.gov
(301) 796-0702

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/s/

Christopher Davi
1/11/2007 05:36:27 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 60,237

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

Dear Dr. Coleman:

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

We also refer to the meeting between representatives of your firm and the FDA on December 15, 2005. The purpose of the meeting was to discuss the efficacy, safety and microbiology aspects of a future NDA submission for Telavancin.

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, Regulatory Project Manager, at (301) 827-2217.

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

Enclosure: Minutes from Meeting

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	December 15, 2005
TIME:	10:00 to 11:30 AM
LOCATION:	10903 New Hampshire Boulevard Silver Spring, MD, 20993 Buildg. #22, Conference room #1309
APPLICATION:	IND 60,237
DRUG NAME:	Telavancin for Injection
TYPE OF MEETING:	Pre-NDA
MEETING CHAIR:	Janice M. Soreth, MD, Director, Division of Anti-Infective and Ophthalmology Products (DAIOP)
MEETING RECORDER:	J. Christopher Davi, MS, Regulatory Project Manager

FDA ATTENDEES:

Edward M. Cox, MD, Deputy Director, Office of Antimicrobial Products (OAP)
Janice M. Soreth, MD, Director, DAIOP
Sumathi Nambiar, MD, MPH, Medical Team Leader, DAIOP
Janice K. Pohlman, MD, Medical Reviewer, DAIOP
Venkateswar Jarugula, PhD, Clinical Pharmacology Team Leader, DAIOP
Jeffery Tworzyanski, PhD, Clinical Pharmacology Reviewer, DAIOP
Thamban Valappil, PhD, Biostatistics Team Leader, DAIOP
Scott Komo, PhD, Biostatistics Reviewer, DAIOP
Terry Peters, DVM, Pharmacology and Toxicology Reviewer, DAIOP
David L. Roeder, MS, Associate Director of Regulatory Affairs, OAP
J. Christopher Davi, MS, Regulatory Project Manager, DAIOP

EXTERNAL CONSTITUENT ATTENDEES (Theravance:

Steve Barriere, PharmD, Senior Director of Clinical Research
Gary Koch, PhD, Professor of Biostatistics, Univ. of North Carolina
Alan Hopkins, PhD, Senior Director of Biometrics
Ralph Corey, MD, Professor, Duke University
Michael Kitt, MD, Senior Vice President of Clinical Development
David Friedland, MD, Senior Director of Clinical Research
Fred Genter, PhD, Director of Biostatistics
Rebecca Coleman, PharmD, Senior Director of Regulatory Affairs
Kenjie Ameniya, PhD, Director of Nonclinical Drug Safety
Robert Reed, PhD, Director of Regulatory Affairs, Astellas US
Michael Goldberg, MD, PhD, Vice President of Clinical Pharmacology
Elizabeth Spencer, Senior Manager of Clinical Operations
Joanne DiGorgio, Senior Clinical Research Manager
Rochelle Maher, Director of Drug Development, Astellas US

b(4)

BACKGROUND:

Theravance, Inc., (Sponsor) requested a Type-B meeting with the Division of Anti-Infective and Ophthalmology Products to discuss a targeted NDA submission in mid-2006. The Division granted the meeting request, and provided preliminary comments to the Sponsor on December 8, 2005. Minutes from the December 15, 2005 meeting are recorded herein.

MEETING OBJECTIVES:

The Sponsor stated the following objectives for the meeting in their November 16, 2005 briefing package:

- To confirm that the clinical information proposed for submission will result in a fileable NDA for the use of telavancin at the proposed dosage for the proposed indication.
- To verify that the planned analysis of the soon to be completed Phase 3 studies in complicated skin and skin structure infections (cSSSI) will, if results are positive, support the proposed labeling.
- To discuss the table of contents and format for the presentation of the NDA, along with the timeline for submission.

DISCUSSION POINTS/QUESTIONS FROM BRIEFING DOCUMENT:

1. *Is the clinical program adequate to support a fileable NDA for the use of telavancin at the proposed dosage (10 mg/kg) for the proposed indication (cSSSI)?*

   The Division informed the Sponsor that in general, the clinical program is sufficient to support a fileable NDA. The Division noted that the current enrollment of 750 to 800 patients is more than sufficient to determine adverse events at the 1% level. The Division asked the Sponsor what the size of enrollment in the pneumonia study would be at the time of NDA submission for the cSSSI study. The Sponsor anticipated enrollment of approximately 500 in the pneumonia study with a total targeted enrolment of 1,500.

2. *Are the planned analyses of Studies 017 and 018 acceptable?*

   The Division indicated that the statistical analysis plan is generally acceptable, however, there are specific comments related to the plan, which will be communicated to the Sponsor at a later date. These comments are primarily related to Section 3.4, Sponsor's Determinations While Blinded, as well as Section 3.3.3, the Clinically Evaluable population definition criteria. The Division noted that these determinations will need to be pre-specified with algorithms before the statistical analysis begins. The Sponsor acknowledged this point and indicated that they had already prepared a draft statistical analysis plan (SAP) for the Division's review. In the draft plan they have specified exactly what they intend to do in terms of blinding. The Division agreed to review the draft SAP and will forward specific comments to the Sponsor in the near future.

3. *If the results of the analyses of Studies 017 and 018 are positive, do these two Phase 3, adequate and well-controlled studies, when considered together with the results of the completed adequate and well-controlled Study I6424-202b, have the potential to provide the substantial evidence of effectiveness necessary to support the use of telavancin at the proposed dosage (10 mg/kg) for the proposed indication (cSSSI)?*

   The Division indicated that absent a safety signal, these studies may be adequate to support use of telavancin in the proposed indication. However, product labeling may reflect preclinical toxicities, such as teratogenicity in rodents and rabbits. The Division asked the Sponsor when they planned to provide an audited draft on the minipig study, which was being performed to allay concerns surrounding teratogenicity. The Sponsor indicated that the study will be available for review mid-first quarter of 2006.

4. *Does the planned pooled analysis of Studies 017 and 018, when considered with the results of completed Study I6424-202b, have the potential to support the proposed labeling regarding superiority of telavancin 10 mg/kg to vancomycin for the treatment of cSSSI due to MRSA?*

   The Division asked the Sponsor to elaborate on how they planned to demonstrate the comparability of telavancin and vancomycin with respect to efficacy in the MRSA complement as indicated in the flow chart on pages 7 and 15 in Appendix 5. Also, the Division recommended that the Sponsor assess the difference in success rates in the MRSA subgroup between the two arms in the two studies prior to pooling. The Division added that to allow for pooling of results, the treatment difference between the two groups should be similar in the two studies. The Division asked the Sponsor how they planned to pool for MRSA.

   The Sponsor indicated that they will be evaluating confidence intervals for the two studies, and depending upon overlap, they will determine how they should be pooled. They will prepare event rates and stratification-adjusted confidence intervals for the studies. This will allow the statistical reviewer to assess the overlap of confidence intervals for both pooled and combined studies.

5. *Is the proposed clinical safety database adequate for filing an NDA for the use of telavancin at the proposed dosage (10 mg/kg) for the proposed indication (cSSSI)?*

   The Division indicated that absent a safety signal, the safety database outlined in Appendix 7 of the meeting package is sufficient (estimated exposure of 760 patients to 10 mg/kg dose for 7-14 days). However, the Division expressed concern that there has yet to be a study report submitted on the 10.0 mg/kg dose, and cited nephrotoxicity as a particular concern. The Division recommended that the Sponsor collect as much information on nephrotoxicity as possible via consultation or any other means. The Sponsor acknowledged this point, and agreed to take the Division's recommendation under advisement. The Sponsor stated that toxicity information on the liver would be collected, and that they would make every effort to characterize nephrotoxicity as requested.

6. *Is it acceptable to submit examples of the analysis datasets for the controlled studies in cSSSI for Agency review prior to the submission?*

   The Division informed the Sponsor that this would be acceptable.

7. *Theravance intends to submit the NDA in CTD format. Is this acceptable?*

   The Division informed the Sponsor that this would be acceptable.

8. *Does the Division have a preference for format of the electronic submission (eNDA vs. eCTD)?*

   The Division informed the Sponsor that the Agency's preference is for the NDA to use the eCTD format according to the latest guidance. However, the Division informed the Sponsor that either the eCTD or the old PDF TOC eNDA are acceptable formats according to the 1997 guidance. The Sponsor indicated that they had spent a significant amount of time developing the CDISC format, and asked if it would be acceptable to submit the NDA in this format. The Division stated that this would also be acceptable but cautioned the Sponsor regarding the size of the impact file used for CDISC, stating that it should be large for ease of navigation. The Division also informed the Sponsor that they would need to submit a sample data set prior to submission if they have never submitted before. The Sponsor agreed to do so.

9. *Is the plan proposed below for selection of CRFs for submission with the NDA acceptable?*

   The Division stated that the plan for CRF submission is acceptable with the addition of case report forms form all serious adverse events (not limited to treatment emergent SAEs). The Sponsor indicated that they intend to submit all SAE's.

   The Sponsor asked if the Division would be interested in reviewing patient profiles. The Division stated that though patient profiles are helpful, often the reviewer needs to refer to the CRF for additional information. The Division recommended that sample patient profiles be submitted prior to the NDA submission for the Division's review.

10. *Are the timelines proposed for presubmission of the Safety (nonclinical) section of the NDA, the remaining sections of the NDA for cSSSI and the Clinical Safety Update acceptable?*

    The Division informed the Sponsor that this would be acceptable.

11. *Is the Agency in agreement that the original NDA will seek approval for the use of telavancin in the treatment of cSSSI and that an application for approval for use for the treatment of hospital acquired pneumonia (HAP) will take the form of a sNDA?*

    The Division indicated that given the apparent toxicity noted in preclinical testing, such as nephrotoxicity, elevation in transaminases, macrophage hypertrophy and hyperplasia of uncertain clinical significance, testicular toxicity, effects on sperm, and teratogencity in rodent and rabbits species, (b(4)

3

12. Will the sNDA for HAP be eligible for a priority review?

Priority review status is determined at the time of filing, and is dependent upon the indication, population studied, and trial results as outlined in CDER MAPP 6020.3.

DECISIONS (AGREEMENTS) REACHED:

1. The Division will review the Sponsor's SAP and provide comments.

2. The Sponsor will provide a draft report on the minipig study in the mid-first quarter of 2006.

3. The Sponsor will compile as much information as possible on the potential nephrotoxicity of telavancin and include this information in the NDA submission.

4. The Sponsor will include information on liver toxicity in the NDA submission.

5. The Sponsor understands that they will need to submit a sample dataset prior to the official NDA submission.

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/s/

Janice Soreth
1/13/2006 03:14:19 PM