

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022407Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY REVIEW

<b>NDA: 22-407</b>	Submission Date(s): 7/12/12
<b>Drug</b>	Telavancin
<b>Trade Name</b>	VIBATIV
<b>OCP Reviewers</b>	Ryan Owen, Ph.D.
<b>OCP Team Leader</b>	Kimberly Bergman, Pharm.D.
<b>OCP Division</b>	DCP4
<b>OND division</b>	DAIP
<b>Sponsor</b>	Theravance
<b>Relevant IND(s)</b>	60,237
<b>Submission Type; Code</b>	Class 2 Resubmission
<b>Formulation; Strength(s)</b>	Single-use vials (for injection) containing either 250 or 750 mg of telavancin
<b>Indication</b>	Nosocomial pneumonia
<b>Dosage and Administration</b>	10 mg/kg infused over 1 hour every 24 hours (for CrCl > 50 mL/min)  For CrCl < 50 and ≥ 30 mL/min: 7.5 mg/kg every 24h  For CrCl < 30 to 10 mL/min: 10 mg/kg every 48h

### BACKGROUND

Telavancin is a lipoglycopeptide antibacterial agent with activity against Gram-positive organisms including *S. aureus*. Telavancin was approved for the treatment of cSSSI on 9/11/09 (under NDA 22-110). The Applicant also conducted a development program for telavancin for the treatment of nosocomial pneumonia (also referred to as HAP/VAP) under NDA 22-407. NDA 22-407 contained the reports for two Phase 3 nosocomial pneumonia trials (referred to as Studies 15 and 19), and cross-referenced NDA 22-110 for all other supportive information.

NDA 22-407 received a complete response letter on 11/23/09 primarily due to studies 15 and 19 being designed to evaluate a clinical response endpoint rather than the Agency's preferred endpoint of 28-day all-cause mortality. The Applicant resubmitted NDA 22-407 on 6/30/10, but received another complete response letter on 12/21/10. NDA 22-407 then went through dispute resolution procedures, and was eventually resubmitted for a third review cycle on 7/12/12.

No additional clinical trials have been conducted since the original submission of NDA 22-407. Both resubmissions and the dispute resolution process have focused on reanalyses from Studies 15 and 19.

From a clinical pharmacology standpoint, most of the supportive information for telavancin was contained in NDA 22-110 and was reviewed by Dr. Jeffrey Tworzyanski (see review in DARRTS on 10/4/07). The clinical pharmacology review for the original

submission of NDA 22-407 was written by Dr. Kevin Krudys (see review dated 9/25/09 in DARRTS). Dr. Krudys' review demonstrated that the proposed dosage adjustments for moderate and severe renal function resulted in comparable telavancin exposures as were observed at the 10 mg/kg once daily dose in patients with normal renal function. Dr. Krudys' review also concluded that there was no relationship between telavancin exposure and clinical cure or death in Studies 15 and 19.

The 6/30/10 resubmission for NDA 22-407 contained no new clinical pharmacology information (as documented in a review by Dr. Aryun Kim in DARRTS on 12/3/10).

#### **EXECUTIVE SUMMARY**

During the current review cycle, the Division examined the possibility of a limited approval for telavancin for the treatment of nosocomial pneumonia above a certain creatinine clearance (CrCl) threshold (see reviews of Dr. Benjamin Lorenz and Dr. Scott Komo for the respective clinical and statistical perspectives). The Applicant's proposed threshold for a CrCl cutoff was 30 mL/min for patients with nosocomial pneumonia. The approved label for telavancin (for the treatment of cSSSI) includes the following statement in the Warnings and Precaution section: "Decreased efficacy among patients treated for skin and skin structure infections with moderate/severe pre-existing renal impairment: Consider these data when selecting antibacterial therapy for patients with baseline CrCl  $\leq$  50 mL/min."

Although no new clinical pharmacology information was submitted in the 7/12/12 NDA resubmission, the medical officer requested assistance from clinical pharmacology in determining an appropriate CrCl cutoff given the differing recommendations between the cSSSI and nosocomial pneumonia indications. The requested analysis was to look at clinical outcome as a function of exposure (in the PK subset) and baseline renal function (see Figure 1).

**Figure 1: Relationship Between Baseline Renal Function and Telavancin Exposure Stratified by Clinical Outcome**

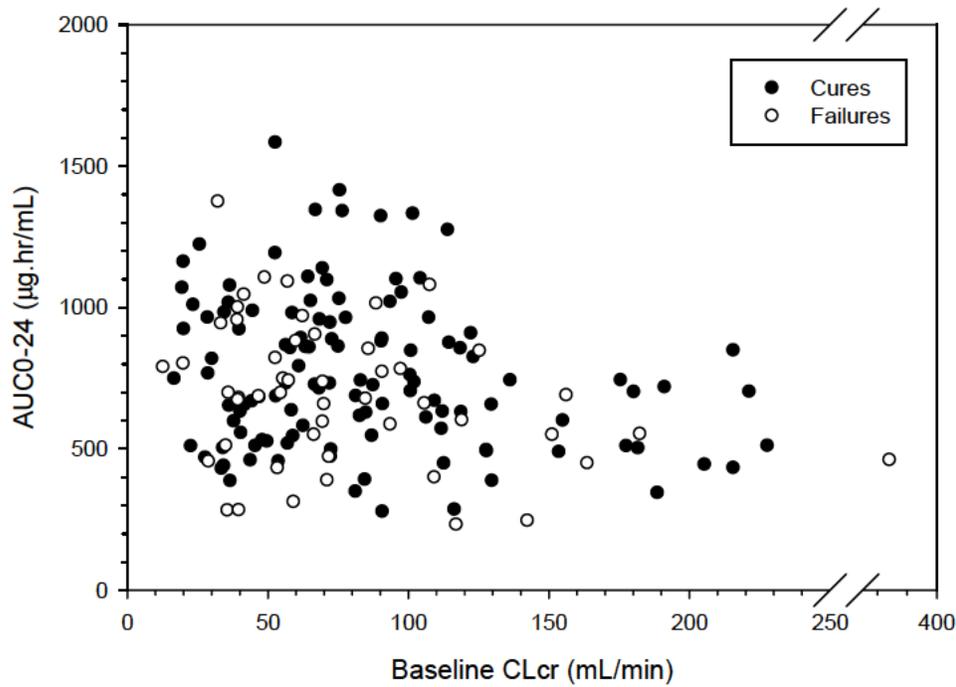


Figure 1 shows pooled PK and outcome data from Study 15 and 19.  $AUC_{0-24}$  is shown on the y-axis and baseline renal function is shown on the x-axis. Clinical cures are indicated with dark circles, and clinical failures are indicated with open circles. For the purposes of this analysis, missing data were assigned as failures. There is no clear trend with respect to the relationship of baseline creatinine clearance, the resulting telavancin exposure, and the ultimate clinical outcome. This assessment supports the Sponsor’s exploratory PK analysis showing no relationship between  $AUC_{0-24}$  and clinical outcome or mortality (see Tables 1 and 2 below).

**Table 1: Telavancin AUC (0 to 24 hours) by Clinical Response at Test of Cure (Studies 15 and 19)**

		Study 0015 ug*hr/mL (N=77)	Study 0019 ug*hr/mL (N=77)	Total ug*hr/mL (N=154)
Clinical Response at TOC				
Cure	Mean±SD	714 ±238.1	793 ±274.0	753 ±258.5
Not Cure	Mean±SD	682 ±234.0	639 ±264.9	661 ±248.5

**Table 2: Telavancin AUC (0 to 24 hours) by All-Cause 28-Day Mortality (Survival, Studies 15 and 19)**

		Study 0015 ug*hr/mL (N=77)	Study 0019 ug*hr/mL (N=77)	Total ug*hr/mL (N=154)
Death within 28 Days				
Died	Mean±SD	742 ±183.3	704 ±301.9	722 ±250.2
Did Not Die	Mean±SD	693 ±246.9	749 ±274.1	720 ±261.1

**RECOMMENDATIONS**

The Office of Clinical Pharmacology Division 4 has reviewed NDA 22-407 and has determined that it is acceptable from a Clinical Pharmacology perspective.

---

Ryan P. Owen, Ph.D.  
Division of Clinical Pharmacology 4  
Office of Clinical Pharmacology

Concurrence:

---

Kimberly L. Bergman, Pharm.D.  
Team Leader  
Division of Clinical Pharmacology 4  
Office of Clinical Pharmacology

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

/s/  
-----

RYAN P OWEN  
12/20/2012

KIMBERLY L BERGMAN  
12/20/2012

## CLINICAL PHARMACOLOGY MEMO

<b>NDA(s):</b> 22-407	Submission Date(s): 30 Jun 2010
<b>Drug</b>	Telavancin for Injection
<b>Trade Name</b>	VIBATIV
<b>OCP Reviewer</b>	Aryun Kim, Pharm.D.
<b>OCP Team Leader</b>	Charles Bonapace, Pharm.D.
<b>OCP Division</b>	DCP4
<b>OND Division</b>	DAIOP (520)
<b>Sponsor</b>	Theravance, Inc., South San Francisco, CA
<b>Submission Type; Code</b>	Class 2 Resubmission
<b>Indication(s)</b>	For the treatment of nosocomial pneumonia caused by susceptible isolates of the following Gram-positive microorganisms: <i>Staphylococcus aureus</i> (including methicillin-susceptible and –resistant strains) or <i>Streptococcus pneumoniae</i> (penicillin-susceptible strains)
<b>Dosage and Administration</b>	10 mg/kg administered over a 60-minute period by intravenous infusion once every 24 hours for 7- <sup>(b)</sup> <sub>(4)</sub> days
<b>Formulation; Strength(s)</b>	Sterile, preservative-free, white to slightly colored lyophilized powder containing 250 mg or 750 mg (free base) in single-use vials

### BACKGROUND

On 11 Sep 2009, telavancin was approved for the treatment of complicated skin and skin structure infections (NDA 22-110). On 23 Jan 2009, NDA 22-407 was submitted (Original Submission) for the proposed indication of the treatment of nosocomial pneumonia, to which a Complete Response letter (dated 23 Nov 2009) was issued. Accordingly, the Sponsor has submitted a Class 2 Resubmission of NDA 22-407 in response.

### RECOMMENDATION

There were no new clinical pharmacology studies provided in this Class 2 Resubmission of NDA 22-407. Thus, no clinical pharmacology issues were identified.

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

/s/  
-----

ARYUN KIM  
12/01/2010

CHARLES R BONAPACE  
12/03/2010

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

<b>NDA</b>	22-407
<b>Submission Date</b>	January 26, 2009
<b>Brand Name</b>	VIBATIV <sup>®</sup>
<b>Drug Name</b>	TELAVANCIN HYDROCHLORIDE
<b>OCP Division</b>	Division of Clinical Pharmacology 4
<b>OND Division</b>	Division of Anti-Infective and Ophthalmology Products (DAIOP)
<b>Sponsor</b>	Theravance Inc.
<b>Formulation; Strength</b>	Sterile lyophilized powder for injection, 250 mg and 750 mg vials
<b>Indication</b>	Treatment of patients with nosocomial pneumonia caused by susceptible isolates of the following Gram-positive microorganisms: <i>Staphylococcus aureus</i> (including methicillin-susceptible and – resistant strains) or <i>Streptococcus pneumoniae</i>
<b>Dosing Regimen</b>	10 mg/kg administered over a 60-minute period by intravenous infusion once every 24 hours for 7 to (b) (4) days
<b>Submission Type</b>	Original NDA
<b>Reviewer</b>	Kevin Krudys, Ph.D.
<b>Pharmacometrics Team Leader</b>	Pravin Jadhav, Ph.D.
<b>Clinical Pharmacology Team Leader</b>	Charles R. Bonapace, Pharm. D.

<b>1 EXECUTIVE SUMMARY .....</b>	<b>2</b>
1.1 RECOMMENDATION .....	2
1.2 PHASE IV COMMITMENTS .....	3
1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS .....	3
<b>2 QUESTION BASED REVIEW (QBR).....</b>	<b>3</b>
2.1 GENERAL ATTRIBUTES OF THE DRUG.....	4
2.1.1 What is the proposed mechanism of action and therapeutic indication? .....	4
2.1.2 What is the proposed dosage and route of administration? .....	4
2.2 GENERAL CLINICAL PHARMACOLOGY .....	4
2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims? .....	4
2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD) and how are they measured in clinical pharmacology and clinical studies? .....	5
2.2.3 Exposure-Response.....	5
2.2.4 Is the population pharmacokinetic model used by the sponsor appropriate? .....	7
2.3 INTRINSIC FACTORS .....	8

2.3.1	Is there a difference in telavancin PK between VAP and non-ventilator-associated hospital acquired pneumonia (NVAHAP) patients?.....	8
2.3.2	Is there a difference in telavancin PK between cSSSI and HAP patients? .....	9
2.3.3	Can dosing recommendations be proposed for patients with creatinine clearance < 10 mL/min, including patients receiving hemodialysis?.....	9
2.3.4	Does the proposed dosage adjustment in patients with renal impairment provide telavancin exposure in this population that is comparable to patients with normal renal function?.....	10
2.4	EXTRINSIC FACTORS .....	11
2.5	GENERAL BIOPHARMACEUTICALS.....	11
2.6	ANALYTICAL SECTION.....	11
<b>3</b>	<b>DETAILED LABELING RECOMMENDATIONS.....</b>	<b>11</b>

## 1 EXECUTIVE SUMMARY

Telavancin, a semisynthetic lipoglycopeptide antibiotic with *in vitro* activity against a broad range of Gram-positive pathogens, was approved on September 11, 2009 for the treatment of complicated skin and skin structure infections (cSSSI). The current application makes reference to the clinical pharmacology studies included in NDA 22-110 which were previously reviewed in Dr. Tworzanski’s Clinical Pharmacology Review, dated October 4, 2007. The applicant is seeking a new indication for the treatment of patients with nosocomial pneumonia caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and –resistant strains) or *Streptococcus pneumoniae*. The proposed dosing regimen for telavancin is 10 mg/kg administered over a 60-minute period by intravenous infusion once every 24 hours for 7 to <sup>(b)</sup><sub>(4)</sub> days.

Two Phase 3 studies were submitted to support the safety and efficacy of telavancin for the treatment of nosocomial pneumonia. Sparse pharmacokinetic data was collected in these studies and used to compare the pharmacokinetics of telavancin in patients with hospital-acquired pneumonia (HAP) to healthy subjects and to identify sources of inter-individual variability in telavancin pharmacokinetics. The following are the major findings:

- The pharmacokinetics of telavancin in HAP patients are comparable to patients with cSSSI.
- Ventilator status does not influence telavancin pharmacokinetics in HAP patients.
- The linear relationship between creatinine clearance and telavancin clearance supports the telavancin dosing regimen based on creatinine clearance.
- Telavancin AUC<sub>SS(0-48h)</sub> in HAP patients with renal impairment receiving the adjusted dose is comparable to patients with normal renal function receiving the 10 mg/kg dose.
- No relationship between telavancin exposure and clinical cure or death was observed in Studies 0015 and 0019.

### 1.1 Recommendation

The Clinical Pharmacology information provided by the applicant is acceptable.

### 1.2 Phase IV Commitments

No Phase IV commitments are recommended.

### 1.3 Summary of Important Clinical Pharmacology Findings

Telavancin is approved for the treatment of complicated skin and skin structure infections. The applicant is seeking to extend the indication to the treatment of patients with nosocomial pneumonia with this original NDA. The proposed dose is 10 mg/kg administered over a 60-minute period by intravenous infusion once every 24 hours for 7 to (b) (4) days. Dose adjustment is required for patients with creatinine clearance less than 50 mL/min. This NDA is based on the efficacy and safety data from Studies 0015 and 0019 in adult patients with hospital acquired pneumonia (HAP).

Population pharmacokinetic analysis was conducted with sparse telavancin concentrations from a subset of 197 patients enrolled in Studies 0015 and 0019. The results indicate:

- The pharmacokinetics of telavancin in HAP patients are comparable to patients with cSSSI. The median[range] of telavancin clearance was 1.07[0.26 – 2.42] L/h in patients with HAP from Studies 0015 and 0019 and 1.23[0.27 – 2.48] L/h in patients with cSSSI from Studies 0017 and 0018 from NDA 22-110.
- Ventilator status does not influence telavancin pharmacokinetics in HAP patients. The median[range] of telavancin clearance was 1.15[0.5 - 2.37] L/h in ventilator-associated pneumonia(VAP) patients and 1.05[0.26 – 2.42] L/h in non-ventilator-associated hospital-acquired pneumonia (NVAHAP) patients from Studies 0015 and 0019.
- There is a positive linear relationship between creatinine clearance and body weight and telavancin clearance, given by the following equation:  
$$CL = 0.524 + 0.00238 \cdot CrCL + 0.00317 \cdot WT$$
where CrCL is creatinine clearance (mL/min) calculated by the Cockcroft-Gault equation and WT is body weight in kg.
- Telavancin AUC<sub>SS(0-48h)</sub> in HAP patients with renal impairment receiving the adjusted dose is comparable to patients with normal renal function receiving the 10 mg/kg dose. Median[range] values in patients with severe, moderate, mild and normal renal function were 1166[371 – 2272], 1235[568 – 1903], 1497[619 – 2795] and 1264[553 – 3237] µg\*hr/mL, respectively.
- No relationship between telavancin exposure and clinical cure or death was observed in Studies 0015 and 0019. The overall clinical cure rate was 45% and overall death rate was 17% in the 197 patients in Studies 0015 and 0019 who had pharmacokinetic and outcome data. Logistic regression analysis indicated a flat relationship between AUC<sub>SS(0-48h)</sub> and clinical cure and death.

## 2 Question Based Review (QBR)

An abbreviated version of the QBR is used for this clinical pharmacology review because key QBR elements have been addressed previously in NDA 22-110.

## 2.1 General attributes of the drug

Telavancin was submitted to the FDA previously (December 6, 2006) under NDA 22-110 for the treatment of complicated skin and skin structure infections (cSSSI). A complete response letter was issued on February 20, 2009 for NDA 22-110 and approval was granted on September 11, 2009. The current NDA makes reference to the clinical pharmacology studies included in NDA 22-110 and also includes data from two Phase 3 studies to support the use of telavancin for the treatment of nosocomial pneumonia.

### 2.1.1 What is the proposed mechanism of action and therapeutic indication?

Telavancin has a multifunctional mechanism of action which includes the inhibition of bacterial cell wall synthesis and the disruption of the functional integrity of the bacterial plasma membrane. Telavancin inhibits cell wall biosynthesis by binding to late stage peptidoglycan precursors which prevents the polymerization of precursor into peptidoglycan and subsequent cross-linking events. It also binds to bacterial membranes and causes depolarization of membrane potential and an increase in membrane permeability. The proposed therapeutic indication is the treatment of nosocomial pneumonia caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and –resistant strains) or *Streptococcus pneumoniae*.

### 2.1.2 What is the proposed dosage and route of administration?

The recommended dose for telavancin is 10 mg/kg administered over a 60-minute period by intravenous infusion once every 24 hours for 7 to <sup>(b)</sup><sub>(4)</sub> days. A dosage adjustment is required for patients with creatinine clearance  $\leq 50$  mL/min according to the following table:

Creatinine Clearance* (mL/min)	Telavancin Dosage Regimen
> 50	10 mg/kg every 24 hours
>30 -50	7.5 mg/kg every 24 hours
10 - 30	10 mg/kg every 48 hours

\*As calculated using the Cockcroft-Gault formula

## 2.2 General clinical pharmacology

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor conducted two Phase 3, randomized, double-blind, parallel, multinational clinical trials (Study 0015 and Study 0019) of identical design to compare the safety and efficacy of telavancin (10 mg/kg once every 24 hours) and vancomycin (1 g every 12 hours) for the treatment of adult patients with hospital acquired pneumonia (HAP). The studies were designed to enroll male and female patients  $\geq 18$  years of age with Gram-positive HAP, and at least one risk factor for methicillin-resistant *Staphylococcus aureus* (MRSA). The use of concomitant Gram-negative therapy was left to the investigator's decision. The minimum duration of study therapy was to be 7 days and the maximum allowable duration was to be 21 days.

Pharmacokinetic samples were collected from a subset of patients from Studies 0015 and 0019 who participated in the pharmacokinetic portion of the studies. Four blood samples were obtained per patient on Day 4 of study treatment ( $\pm 1$  day) at the following time points: 0 – 30 minutes before the start of the IV infusion, 0 – 15 minutes before the end of the IV infusion, 15 – 45 minutes after the end of the infusion, 6 – 12 hours after the start of the IV infusion and prior to the second dose that day. A total of 101 patients in Study 0015 and 97 patients in Study 0019 had sufficient data for pharmacokinetic analysis.

### **2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD) and how are they measured in clinical pharmacology and clinical studies?**

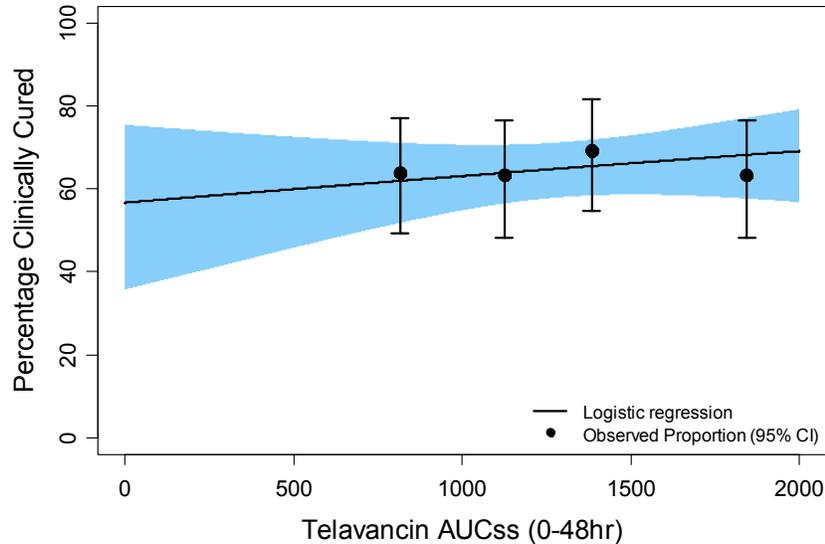
The primary efficacy variable in the two Phase 3 trials was the clinical response at the test-of-cure (TOC) as determined by the investigator 7 to 14 days after the last dose of antibiotic therapy. Clinical response was defined as failure for relapsed pneumonia with the same Gram-positive organism after termination of study medication or death after the end of study medication therapy attributable to primary infection. Cure was defined as resolution of signs and symptoms of pneumonia or improvement or no progress of baseline radiographic findings. These endpoints were based on FDA guidelines for developing antimicrobial drugs for treatment of nosocomial pneumonia.

### **2.2.3 Exposure-Response**

#### **2.2.3.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?**

No relationship between exposure and response for efficacy was observed in Studies 0015 and 0019. Telavancin  $AUC_{SS(0-48h)}$  values did not differ significantly between patients with HAP who were cured at TOC and patients with HAP who were not cured at TOC. Logistic regression was performed to assess the exposure-response relationship for effectiveness based on clinical cure in 197 patients from Studies 0015 and 0019 who had exposure and outcome data. Lack of a relationship is observed by a flat mean logistic prediction in Figure 1.

**Figure 1: The probability of patients in Studies 0015 and 0019 with cure vs. telavancin AUC<sub>ss(0-48h)</sub>.** Solid black symbols represent the observed percentage of patients responding to treatment in each AUC<sub>ss(0-48h)</sub> quartile and vertical bars represent the 95% confidence interval. The solid line is the mean logistic prediction and the shaded area is the 95% confidence interval of the prediction.



Furthermore, there was no relationship between MIC and clinical cure as seen in the Table below. The lack of an observed relationship between telavancin exposure and clinical cure may be due to the fact that only one dose was studied in the Phase 3 trials. Also, observed MICs were generally well below the susceptible breakpoint of 1 mcg/mL for *Staphylococcus aureus*.

Table 43: Telavancin MIC versus Clinical Cure in Telavancin Treatment Groups – ME Population, Studies 0015 and 0019

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

<sup>a</sup> Data not available

Source: Module 2, Section 2.7.3, Figure 43, Page 133.

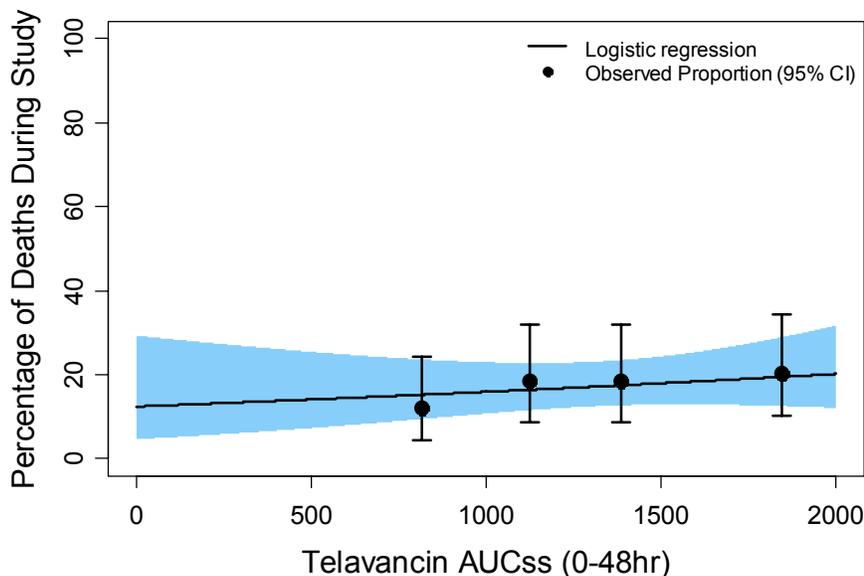
### 2.2.3.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

The dose-response relationship for safety was explored in 58 patients in Studies 0015 and 0019 who received doses of telavancin in excess of that specified by the protocol. A higher incidence of death was observed in patients who received a higher than protocol-specified dose of telavancin (28%) compared to patients who received the protocol-specified or lower dose (19%). In addition, patients who received the higher than protocol-specified dose of telavancin had a higher rate of serious adverse events (36%)

than patients who received the protocol-specified or lower dose (31%). These results may be confounded by the fact that errors resulting in a higher dose were more frequent in patients with baseline renal impairment who are predicted to have higher mortality and more frequent adverse events.

Logistic regression was performed to assess the exposure-response relationship for safety based on death during study in 197 patients from Studies 0015 and 0019 who had exposure and outcome data. Lack of a relationship is observed by a flat mean logistic prediction in Figure 2.

**Figure 2: The probability of patients in Studies 0015 and 0019 with death during study vs. telavancin AUC<sub>ss(0-48h)</sub>.** Solid black symbols represent the observed percentage of patients with death during study in each AUC<sub>ss(0-48h)</sub> quartile and vertical bars represent the 95% confidence interval. The solid line is the mean logistic prediction and the shaded area is the 95% confidence interval of the prediction.



#### 2.2.4 Is the use of creatinine clearance and body weight, as predictors of telavancin clearance, supported by the population pharmacokinetic model?

The sponsor's pharmacokinetic model provides an adequate description of telavancin concentrations. Data for the population pharmacokinetic analysis was obtained from 236 adult subjects in seven Phase 1 trials and 197 HAP patients from Studies 0015 and 0019. The structural model for telavancin pharmacokinetics was previously developed with the Phase 1 data and reviewed in Dr. Hao Zhu's Pharmacometrics Review for NDA 22-110. A two-compartment model with first-order elimination adequately described telavancin concentrations in the Phase 1 and Phase 3 studies. Telavancin clearance was found to be significantly correlated with markers of renal function and body weight. The final clearance model is described below:

$$CL = 0.524 + 0.00238 \cdot CrCL + 0.00317 \cdot WT$$

where CrCL is creatinine clearance (mL/min) calculated by the Cockcroft-Gault equation and WT is body weight in kg. The parameter estimates of the final model are provided in the table below:

Table 10: Final Model Estimated Pharmacokinetic Parameters

Pharmacokinetic Parameter	Population Estimate (% RSE)	Inter-individual %CV (%RSE)
CL	0.524 (29.2)	30.822 (11.3)
Slope for CrCL	0.00238 (28.7)	
Slope for WT	0.00317 (66.2)	
V <sub>1</sub>	4.28 (32.7)	46.690 (24.6)
Slope for CrCL	-0.031 (17.4)	
Slope for WT	0.0569 (32.7)	
Q	5.16 (8.7)	43.128 (35.5)
V <sub>2</sub>	1.35 (74.8)	31.401 (34.7)
Slope for WT	0.0752 (19.0)	
Slope for CrCL	-0.0129 (37.3)	
Factor for Age Above 75 yrs	1.41 (7.8)	
Residual Error Parameters	Estimate (RSE)	Intra-individual Error
Additive	0.240 (39.6)	0.490 µg/mL
Proportional	0.023 (11.4)	15.3 (%CV)

Method FOCE was used.

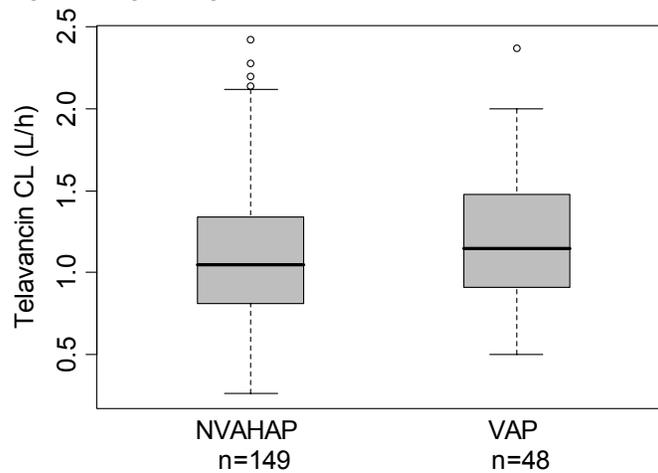
Source: Population Pharmacokinetic Report, Table 10, Page 41.

### 2.3 Intrinsic Factors

#### 2.3.1 Is there a difference in telavancin PK between VAP and non-ventilator-associated hospital acquired pneumonia (NVAHAP) patients?

There is no difference in telavancin PK between patients with VAP and NVHAP. The median[range] of telavancin clearance was 1.15[0.5 - 2.37] L/h in VAP patients and 1.05[0.26 – 2.42] L/h in NVAHAP patients from Studies 0015 and 0019 (Figure 3). Therefore there is no need to adjust the dose based on ventilator status.

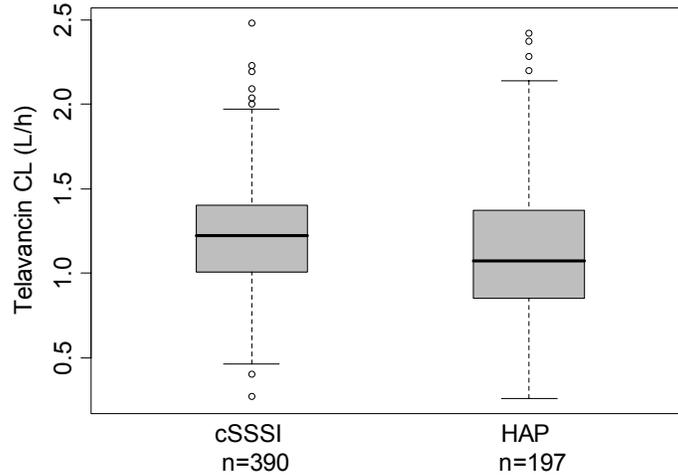
Figure 3: Telavancin Clearance in Patients with ventilator- and non-ventilator associated hospital acquired pneumonia in Studies 0015 and 0019.



### 2.3.2 Is there a difference in telavancin PK between cSSSI and HAP patients?

The pharmacokinetics of telavancin in HAP patients were comparable to patients with cSSSI. The median[range] of telavancin clearance was 1.07[0.26 – 2.42] L/h in patients with HAP from Studies 0015 and 0019 and 1.23[0.27 – 2.48] L/h in patients with cSSSI from Studies 0017 and 0018 from NDA 22-110 (Figure 4).

**Figure 4: Comparison of Telavancin PK in HAP and cSSSI patients**



### 2.3.3 Can dosing recommendations be proposed for patients with creatinine clearance < 10 mL/min, including patients receiving hemodialysis?

Dosing recommendations can not be proposed for patients with creatinine clearance <10 mL/min, including patients receiving hemodialysis. Pharmacokinetic data was available in only 4 patients from Studies 0015 and 0019 who were receiving hemodialysis and/or had creatinine clearance <10 mL/min (Table 1). However, it is unclear whether subject #4007 was actually receiving hemodialysis based on a creatinine clearance of 90 mL/min and telavancin clearance of 1.52 L/h. The individual estimates of clearance in this population were variable and similar to the overall population median[range] of 1.07[0.26 – 2.42] L/h. Given the lack of a consistent, significant effect on telavancin in this small subpopulation, dosing recommendations can not be derived.

**Table 1: Patients in Studies 0015 and 0019 with pharmacokinetic data and creatinine clearance <10 mL/min and/or receiving hemodialysis**

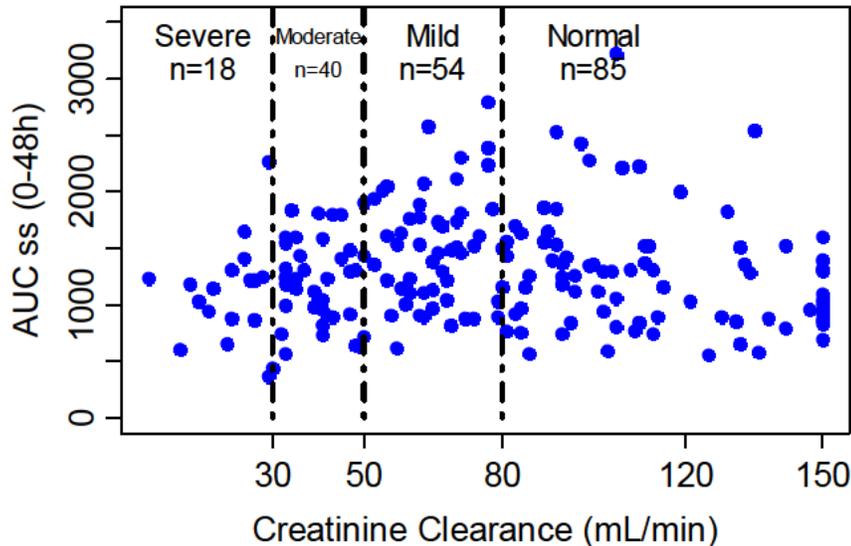
Subject ID	Study	Telavancin Clearance (L/h)	Creatinine Clearance (mL/min)	Receiving Hemodialysis (Y/N)
4007	0015	1.52	90	Y
4188	0015	0.73	14	Y
4721	0015	0.57	3	Y
6239	0019	0.82	10	N

**2.3.4 Does the proposed dosage adjustment in patients with renal impairment provide telavancin exposure in this population that is comparable to patients with normal renal function?**

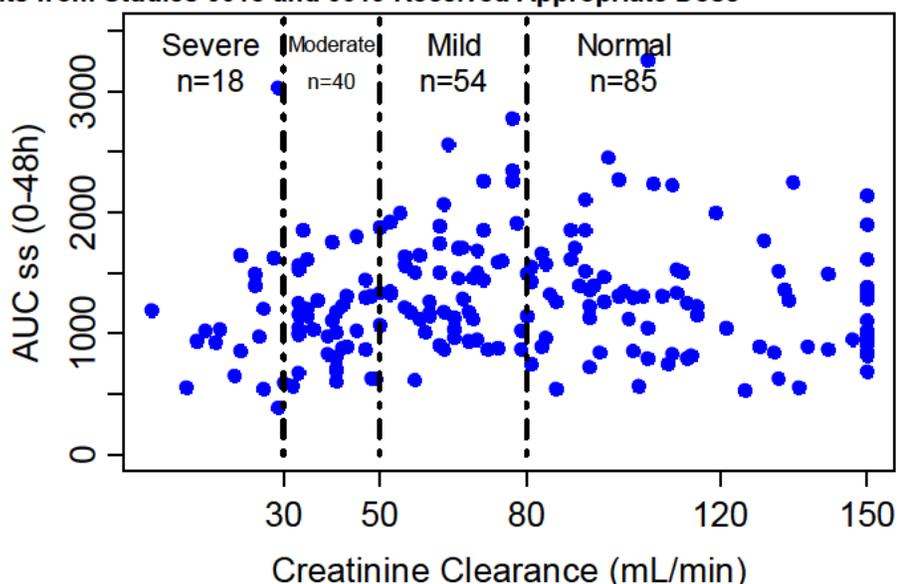
Telavancin exposure, measured as  $AUC_{SS(0-48h)}$ , was similar across the range of renal function observed in Studies 0015 and 0019 as illustrated in Figure 5. As mentioned previously, 58 patients in Studies 0015 and 0019 received doses of telavancin in excess of that specified by the protocol. Of these 58 patients, 21 had creatinine clearance at or near the cut-offs for dose adjustment. Therefore, the reviewer used individual clearance estimates to predict the telavancin  $AUC_{SS(0-48h)}$  in each patient if that patient had received the correct dose specified in the protocol. The results are presented in Figure 6 and are very similar to the observed values presented in Figure 5. The results are also presented in

Table 2. Although the group with the lowest creatinine clearance is predicted to have the lowest telavancin  $AUC_{SS(0-48h)}$ , the minimum  $AUC_{SS(0-48h)}$  values were similar across creatinine clearance categories. Given the flat exposure response relationships for efficacy and safety this difference is not expected to be clinically relevant. Furthermore, in a neutropenic mouse thigh infection model, an  $AUC_{0-24}/MIC$  of 219 was required for a one  $\log_{10}$  reduction in colony-forming units. Assuming a MIC value of 1 mcg/mL, this corresponds to an  $AUC_{SS(0-48h)}$  of 438  $\mu\text{g}\cdot\text{hr}/\text{mL}$  in patients receiving telavancin. Only one subject who participated in the PK portion of Studies 0015 and 0019 had an  $AUC_{SS(0-48h)}$  value less than 438  $\mu\text{g}\cdot\text{hr}/\text{mL}$ . However, the actual  $AUC_{0-24}/MIC$  value for that subject is unknown and may have exceeded the  $AUC_{0-24}/MIC$  target of 219 if the MIC value was  $\leq 0.5$  mcg/mL. Thus, these findings suggest the sponsor's proposed dose adjustment in patients with renal impairment is appropriate.

**Figure 5: Observed Telavancin  $AUC_{SS(0-48h)}$  by Creatinine Clearance Categories from Studies 0015 and 0019**



**Figure 6: Predicted Telavancin AUC<sub>ss(0-48h)</sub> by Creatinine Clearance Categories if All Patients from Studies 0015 and 0019 Received Appropriate Dose**



**Table 2: Observed (Studies 0015 and 0019) and Predicted (Assuming Each Patient Received Protocol Defined Dose) Telavancin AUC<sub>ss(0-48h)</sub> by Creatinine Clearance Category**

<b>Creatinine Clearance Category</b>	<b>Observed AUC<sub>ss(0-48h)</sub> (µg.hr.mL) (Median[Range])</b>	<b>Predicted AUC<sub>ss(0-48h)</sub> (µg.hr.mL) (Median[Range])</b>
> 80 mL/min	1264 [553 – 3237]	1271 [529 – 3261]
> 50 – 80 mL/min	1497 [619 – 2795]	1452 [616 – 2778]
> 30 – 50 mL/min	1235 [568 – 1903]	1089 [570 – 1875]
≤ 30 mL/min	1166 [371 – 2272]	1006 [393 – 3035]

#### **2.4 Extrinsic Factors**

See Clinical Pharmacology Review for NDA 22-110.

#### **2.5 General Biopharmaceuticals**

See Clinical Pharmacology Review for NDA 22-110.

#### **2.6 Analytical section**

See Clinical Pharmacology Review for NDA 22-110.

### **3 Detailed Labeling Recommendations**

None.

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

---

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

---

/s/

---

KEVIN M KRUDYS  
09/25/2009

PRAVIN R JADHAV  
09/25/2009

CHARLES R BONAPACE  
09/25/2009

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

**Office of Clinical Pharmacology**

*New Drug Application Filing and Review Form*

*General Information About the Submission*

	Information		Information
NDA/BLA Number	22-407	Brand Name	VIBATIV
OCP Division (I, II, III, IV, V)	IV	Generic Name	Telavancin
Medical Division	DAIOP	Drug Class	Lipoglycopeptide (first in class)
OCP Reviewer	Ryan Owen, PhD	Indication(s)	Nosocomial pneumonia
OCP Team Leader	Charles Bonapace, PharmD	Dosage Form	Lyophilized powder
Pharmacometrics Reviewer	Kevin Krudys, PhD	Dosing Regimen	10 mg/kg QD for 7- <sup>(b) (4)</sup> days
Date of Submission	23JAN2009	Route of Administration	Intravenous infusion
Estimated Due Date of OCP Review		Sponsor	Theravance
Medical Division Due Date		Priority Classification	Standard
PDUFA Due Date			

*Clin. Pharm. and Biopharm. Information*

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary				Referenced NDA 22-110
Labeling	x			
Reference Bioanalytical and Analytical Methods				
<b>I. Clinical Pharmacology</b>				Referenced previous NDA (22-110) for all clinical pharmacology studies
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<b>Healthy Volunteers-</b>				
single dose:				
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD -</b>				
Phase 2:				
Phase 3:				
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:	x	1		One new population PK study (06-6424-pop-PK-03) was submitted based on sparse sampling from the two Phase 3 trials.
<b>II. Biopharmaceutics</b>				Refer to NDA 22-110
<b>Absolute bioavailability</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>				
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	Used to-be-marketed form
2	Has the applicant provided metabolism and drug-drug interaction information?			x	Refer to NDA 22-110
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	Refer to NDA 22-110
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 090808

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		x		
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		x		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			x	Refer to NDA 22-110
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

### IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

\_\_\_\_\_

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

The application is fileable from a Clinical Pharmacology perspective.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 090808

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Ryan Owen, PhD

12MAR2009

---

Reviewing Clinical Pharmacologist

Date

---

Team Leader/Supervisor

Date

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

/s/

-----  
Ryan P Owen  
3/24/2009 03:44:07 PM  
PHARMACOLOGIST

Charles Bonapace  
3/30/2009 06:24:22 AM  
BIOPHARMACEUTICS