

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-110

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	Clinical Pharmacology & Biopharmaceutics (HFD 880) Tracking/Action Sheet for Formal/Informal Consults
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From: Charles R. Bonapace, Pharm.D., HFD-880	To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission
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DATE: 7/23/08	IND No.: Serial No.:	NDA No.: 22-110 Suppl No.: N-000	SUBMISSION DATE: 1/21/08	
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NAME OF DRUG Telavancin for injection	PRIORITY CONSIDERATION:	Date of informal/Formal Consult:
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NAME OF THE SPONSOR: Theravance, Inc., San Diego, CA 94080

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS RELATED ISSUE

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<input type="checkbox"/> ANIMAL to HUMAN SCALING
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<input type="checkbox"/> DOSING REGIMEN CONSULT
<input type="checkbox"/> PK/PD- POPPK ISSUES
<input type="checkbox"/> PHASE IV RELATED | <input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> IN-VIVO WAIVER REQUEST
<input type="checkbox"/> SUPAC RELATED
<input type="checkbox"/> CMC RELATED
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> SCIENTIFIC INVESTIGATIONS
<input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others) | <input type="checkbox"/> FINAL PRINTED LABELING
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<input type="checkbox"/> CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> ANNUAL REPORTS
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Complete response to approvable action letter |
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REVIEW ACTION

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<input checked="" type="checkbox"/> Medical <input type="checkbox"/> Chemistry <input type="checkbox"/> Pharm-Tox
<input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others
(Check as appropriate and attach e-mail) | <input type="checkbox"/> Oral communication with
Name: []
<input type="checkbox"/> Comments communicated in
meeting/Telecon. see meeting minutes dated:
[] | <input type="checkbox"/> Formal Review/Memo (attached)
<input type="checkbox"/> See comments below
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REVIEW COMMENT(S)

NEED TO BE COMMUNICATED TO THE SPONSOR HAVE BEEN COMMUNICATED TO THE SPONSOR

BACKGROUND:
 On December 19, 2006 Theravance, Inc. submitted a New Drug Application for telavancin for injection for the treatment of complicated skin and skin structure infections (cSSSI) caused by *Staphylococcus aureus* (methicillin-resistant and susceptible strains), *Streptococcus pyogenes*, *Enterococcus faecalis* (vancomycin-susceptible isolates only), *Streptococcus agalactiae*, and *Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius* and *S. constellatus*). The proposed dosage regimen is 10 mg/kg infused over 60 min every 24 hrs for 7 to 14 days depending upon the severity of the infection. The sponsor received an approvable action on October 19, 2007 based on the deficiencies stated in the letter. Subheadings d. and f. listed under deficiency #3 ("The benefit to risk ratio of the drug product is in question because of the following:") are relevant to clinical pharmacology and are discussed in this review.

On January 21, 2008 the sponsor provided a Complete Response to the Action Letter Dated 19 October 2007. The pertinent issues of the sponsor's responses are summarized below. The Agency has not responded to the sponsor's submission dated January 21, 2008.

The thorough QT/QTc study demonstrated that the baseline and placebo corrected QTcF interval was lengthened greater than 10 milliseconds

The sponsor acknowledged that telavancin prolongs the QT interval (upper-bound of the 90% CI exceeds 10 msec) although the effect was approximately half that of the commonly used positive control, moxifloxacin. This is supported by the Agency's analysis of the thorough

QT study (Study I6424-104a) in which the $\Delta\Delta QTcF$ maximum mean effect (E14 primary analysis) was 14 msec (90% CI 8 to 20 msec), 17 msec (90% CI 11 to 25 msec), and 24 msec (90% CI 18 to 30 msec) for telavancin 7.5 mg/kg infused over 60 min, telavancin 15 mg/kg infused over 60 min, and moxifloxacin 400 mg IV infused over 60 min, respectively. The expected mean $\Delta\Delta QTcF$ for the 10 mg/kg dose is 12 to 15 msec.

No increased risk for adverse events related to the QT finding has been identified to date. To enable clinicians to accurately assess any risk for their patients, the sponsor proposed that the label should describe the design of the thorough QT study and include cautionary statements consistent with the cautionary QT statements in the labels of other drugs with comparable risk. In addition, they recommend that the statements should reflect the lesser QT prolongation of telavancin relative to the positive control and the observation that clinical efficacy and safety studies have not identified evidence of proarrhythmic events associated with administration of telavancin.

During the Post-Action meeting held on November 19, 2007 the Agency agreed that the results of telavancin as well as the positive control should be stated in the label. However, the Agency stated that identification of the positive control (moxifloxacin) in the labeling is problematic based on the results of a single study. To address that concern, the sponsor proposed labeling that refers to "positive control" rather than moxifloxacin.

3f. There is insufficient information to recommend a dosing regimen for patients with a creatinine clearance of less than 10 mL/min including patients on hemodialysis.

The sponsor acknowledged that the NDA provides limited information regarding the use of telavancin in patients with severe renal impairment (creatinine clearance < 10 mL/min) or those on hemodialysis. However, the sponsor did not discuss plans to further evaluate the pharmacokinetics of telavancin in patients with severe renal impairment.

RECOMMENDATIONS:

Please communicate to the sponsor that the responses to deficiencies 3d. and 3f. in the Complete Response to the Action Letter Dated 19 October 2007, submitted on January 21, 2008 are acceptable from a clinical pharmacology point of view and are considered a complete response.

SIGNATURE OF REVIEWER: _____

Date _____

SIGNATURE OF TEAM LEADER: _____

Date _____

CC.: DCP4 (Lazor, Bonapace); DAIOP MO (Nambiar, Pohlman); DAIOP CSO (Davi)

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**This is a representation of an electronic record that was signed electronically and
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/s/

Charles Bonapace
8/5/2008 11:17:41 AM
BIOPHARMACEUTICS

John Lazor
8/20/2008 03:24:50 PM
BIOPHARMACEUTICS

PHARMACOMETRIC REVIEW

NDA:	22110
Drug name:	Telavancin
Indication:	Complicated skin and skin structure infections
Proposed Regimen (Sponsor):	10mg/kg infused over 60 minutes every 24 hours for 7 to 14 days
Applicant:	Theravance, Inc.
OCP Reviewer	Jeffrey Tworzyanski, Pharm.D.
PM Reviewer:	Hao Zhu, Ph.D.
PM Team Leader:	Joga Gobburu, Ph.D.
Type of Submission:	NDA
Submission Date:	12/19/2006
PDUFA Date:	10/19/2007

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1 EXECUTIVE SUMMARY

The recommendations based on the telavancin exposure-effectiveness and -renal toxicity analyses, in the subgroup with PK measurements, are provided in this review.

Specifically, we found that:

- 10mg/kg dose, as proposed by the sponsor, is acceptable.
 - The clinical cure rate is similar between 7.5 mg/kg and 10 mg/kg groups. The exposures seem to be at the plateau region of the exposure-response curve.
 - Microbiological eradication rate is higher for the 10 mg/kg dose versus 7.5 mg/kg. The expected microbiological response rate for a patient with the exposure of 1239 mg*hr/mL (median exposure at the dose of 7.5 mg/kg) is 72.8%, whereas the response rate increased to 81.6% for a patient with the exposure of 1739 mg*hr/mL (median exposure at the dose of 10 mg/kg) under the treatment duration of 7 days.
 - 10 mg /kg yields only marginally (and numerically) higher risk of renal function reduction (defined as at least 20% reduction in creatinine clearance from baseline at any time during the trial) compared to 7.5 mg/kg (14% vs. 17.6%).
- Treatment duration of 7-14 days is acceptable.
 - The clinical cure and microbiological eradication rates seem to have achieved the maximum between 7-14 days. Patients treated for less than 7 days have lower probability of treatment success.

2 RECOMMENDATIONS

We found that the sponsor proposed telavancin dosing regimen (10 mg/kg administered for 7 -14 days) is acceptable.

3 QUESTION BASED REVIEW

1. Is there any exposure-response relationship for effectiveness?

We investigated the exposure-effectiveness relationship in terms of clinical response rate as well as microbiological response rate from the PK subgroup (344 out of 745 patients) in the two pivotal clinical trials (0017 and 0018).

Our definitions for exposure, clinical response rate, and microbiological response are detailed as following:

1. The telavancin exposure is defined as the steady state AUC over 48 hr (AUC_{ss (0-48)}). This is because 7.5 mg/kg or 10 mg/kg telavancin was administered once every 24 hr in the Study 0017 and Study 0018. In patients with severe renal impairment, 10 mg/kg telavancin was administered once every 48 hr. In order to account for the dosing adjustment in severe renal impaired patients (Creatinine Clearance \leq 30 mL/min), we employed AUC_{ss (0-48)} as the exposure variable. We also explored AUC_{ss (0-48)} over MIC as the exposure variable. MIC data were available only in 233 patients of the 344 with PK data.
2. Clinical response at the test-of-cure (TOC) was determined by the clinical investigator and was used as the primary effectiveness variable. Each patient's response was assigned to one of the four categories: "cured", "not cured", "indeterminate", or "missing". In our exposure-clinical response analysis, we characterized the relationship between AUC_{ss (0-48)} and clinical cure (yes or no). Essentially we performed two types of analyses with respect to handling 'indeterminate' cases. In one analysis, the "indeterminate" responses were not excluded from the analyses; they were designated as "not cured". In the second analysis, the "indeterminate" and "missing" responses were excluded. There were no missing responses in this PK subset.
3. The sponsor determined the microbiological response at the TOC and used it as the secondary effectiveness variable. Based on the protocols of Study 0017 and Study 0018, each patient's microbiological response was assigned to one of the three categories: "eradicated", "not eradicated", or "indeterminate". In our exposure-microbiological response analysis, we characterized the relationship between AUC_{ss (0-48)} and microbiological eradication (yes or no). Essentially we performed two types of analyses with respect to handling 'indeterminate' cases. In one analysis, the "indeterminate" responses were not excluded from the analyses; they were designated as "not eradicated". In the second analysis, the "indeterminate" responses were excluded. There were no missing responses in this PK subset.

We found that clinical effectiveness response rates in PK subgroup are similar with the overall response rates from studies 0017 and 0018.

- Clinical cure rates in PK subgroup are slightly higher than the overall rates.

- There are 346 and 399 clinically evaluable patients receiving 10 mg/kg telavancin from Study 0017 and Study 0018. The overall clinical cure rates are 87.9% (Study 0017) and 88.7% (Study 0018).
- In the PK subgroup dataset, there are 211 (61%) and 133 (33%) subjects from Studies 0017 and 0018 respectively. The clinical cure rates are 97.2% (Study 0017) and 90.9% (Study 0018).
- Microbiological eradication rates in PK subgroup were similar to the overall rates.
 - There are 290 and 237 microbiologically evaluable patients receiving 10 mg/kg from Studies 0017 and 0018. The overall microbiological eradication rates are 88.6% (Study 0017) and 88.6% (Study 0018).
 - In the PK subgroup dataset, there are 163 (56%) and 103 (43%) subjects from Study 0017 and Study 0018. The microbiological eradication rates are 88.3% (Study 0017) and 91.3% (Study 0018).

We explored exposure-effectiveness relationship for telavancin by using logistic regression. Our exposure-effectiveness analyses indicate that:

1. From exposure-clinical cure rate relationship:

- Within the exposure range tested, the clinical cure rate does not appear to be exposure dependent, as shown in Figure 1. From our analysis, logistic regression demonstrated no statistical significant exposure effect ($P = 0.61$, odds ratio for exposure is 1.33 with 95% CI from 0.45 to 3.95).
- 10 mg/kg dose does not appear to provide additional benefit in terms of clinical cure rate comparing to 7.5 mg/kg. Following our analysis (Figure 1), the fitted curve sufficiently describes the observed data. The 10th, 50th, and 90th percentile of telavancin exposure following 7.5 mg/kg and 10 mg/kg (tested dose) telavancin administration was illustrated respectively as boxes in the plot. The clinical cure rate is 94.5% at the exposure of 1235 $\mu\text{g/mL}\cdot\text{h}$ (equivalent to the median exposure at the dose of 7.5 mg/kg), whereas the clinical cure rate is 95.1% when the exposure is increased to 1736 $\mu\text{g/mL}\cdot\text{h}$ (equivalent to the median exposure at the dose of 10 mg/kg). No superior clinical cure rate can be shown for the dose at 10 mg/kg as compared to 7.5 mg/kg.
- The clinical cure rate is driven by treatment duration, regardless of the telavancin exposure (Figure 2). Our analyses demonstrated statistical significant treatment duration effect ($P=0.0001$, odds ratio for treatment duration is 1.56 with 95% CI from 1.25 to 1.95). Longer treatment duration time yields higher clinical cure rate – the cure rate is 71.2% at the treatment duration of 5 days, whereas it is increased to 86% when the treatment duration is increased to 7 days.

2. Exposure-microbiological eradication rate relationship:

- Microbiological eradication rate is driven by both telavancin exposure and treatment duration. Our multivariate logistic regression demonstrated significant exposure effect ($P = 0.035$ on Log_2 AUCss (0-48), odds ratio is 2.83 with 95% CI of 1.08 to 7.44) and treatment duration effect ($P = 0.0007$, odds ratio is 1.26 with 95% CI of 1.10 to 1.43). As illustrated in

Figure 3, in general a patient with higher exposure and longer treatment duration yields higher microbiological response rate. Following the same treatment duration, 10 mg/kg leads to higher microbiological eradication rate than 7.5 mg/kg. For example, under the treatment duration of 7 days, the expected microbiological response rate for a patient with the exposure of 1239 mg*hr/mL (median exposure at the dose of 7.5 mg/kg) is 72.8%, whereas the response rate increased to 81.6% for a patient with the exposure of 1739 mg*hr/mL (median exposure at the dose of 10 mg/kg).

3. In summary, based on our exposure-effectiveness analysis, we found:
- Sufficient treatment duration (7-14 days) is important to ensure both clinical cure rate and microbiological eradication rate. The results are supported by the sponsor's summary table (Table 1 and Table 2). However, this study is not designed to test the treatment duration effect on telavancin efficacy, therefore confounding factors such as the demographic and disease status exist.
 - The 10 mg/kg dose does not appear to provide additional benefit compared to 7.5 mg/kg in terms clinical cure rate.
 - The microbiological eradication rate is driven by both exposure and treatment duration. Thereby, following the same treatment duration, 10 mg/kg leads to higher microbiological eradication rate than 7.5 mg/kg.
 - As part of our exploratory analysis, we investigated the AUC/MIC versus clinical cure rate (with or without indeterminate) and microbiological eradication rate relationships (with or without indeterminate). MIC distribution in the analysis dataset derived from Study 0017 and Study 0018 is presented in Table 3. The modeling results are presented from Figure 4, to Figure 7. AUC_{SS (0-48)} over MIC as the exposure measure did not explain any more unexplained variability in the exposure-response relationships, compared to AUC_{SS (0-48)} alone. This result is expected given the rather high response rates.

2. Is there any exposure-response relationship for renal toxicity?

We investigated the exposure-renal function reduction relationship from the PK subgroup in the two pivotal clinical trials (0017 and 0018).

Our definitions for exposure and renal toxicity are detailed as following:

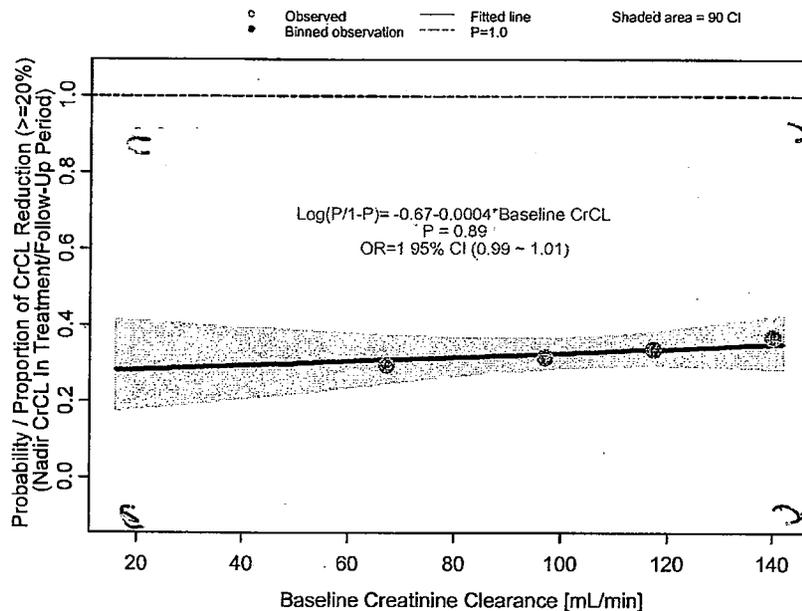
1. The renal toxicity is described by renal function reduction rate, which is defined as the percentage of subjects who experienced at least 20% creatinine clearance (CrCL) reduction comparing to baseline. The CrCL values higher than 140 mL/min are physiologically implausible. Any CrCL values greater than 140 mL/min were treated as 140 mL/min. The percentage reduction from baseline (P.CHG) was calculated by the following method. Patients with P.CHG > (-)20% were designated as 'yes' (reduced renal function), else 'no'.

$$P.CHG = \frac{TBCLCR - TCLCR}{TBCLCR} \times 100\%$$

Where P.CHG represents the CrCL percentage reduction from baseline, TBCLCR baseline creatinine clearance and TCLCR is the CrCL at any visit.

In order to sufficiently characterize the drug related renal toxicity, we choose to perform exposure-renal function reduction analyses under two scenarios. In the first scenario, we performed the analysis using the lowest CrCL value observed during the treatment and follow-up periods (worst CrCL scenario). In the second scenario, we performed similar analysis using the last CrCL value observed during the treatment period (last CrCL scenario). Our findings are the following:

The incidence of renal function reduction does not appear to be treatment duration dependent under both worst CrCL (P = 0.996, odds ratio =1 with 95% CI of 0.93 to 1.07) (Figure 8) and last CrCL scenarios (P=0.17, OR = 0.94 with 95% CI (0.87 ~ 1.03)) (Figure 12 Univariate logistic regression model fitting for worst renal reduction rate versus baseline CrCL



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-).
- Under both worst CrCL and last CrCL scenarios, higher telavancin exposure yields only a slightly numerically higher incidence of renal function reduction (14% for 7.5 mg/kg vs. 17.6% for 10 mg/kg). However, this increased trend is not statistically significant (under worst CrCL scenario: Figure 10, $P = 0.19$, $\text{OR} = 1.39$ with 95% CI (0.85 ~ 2.28); under last CrCL scenario: Figure 11, $P = 0.07$, $\text{OR} = 1.76$, 95% CI (0.96 ~ 3.26)).
- Under both worst and last CrCL scenarios, baseline CrCL does not appear to influence the renal function reduction (worst CrCL scenario: Figure 12, $P = 0.89$, $\text{OR} = 1$ with 95% CI (0.99 ~ 1.01); last CrCL scenario: Figure 13, $P = 0.09$, $\text{OR} = 0.99$ with 95% CI (0.99 ~ 1.00)).

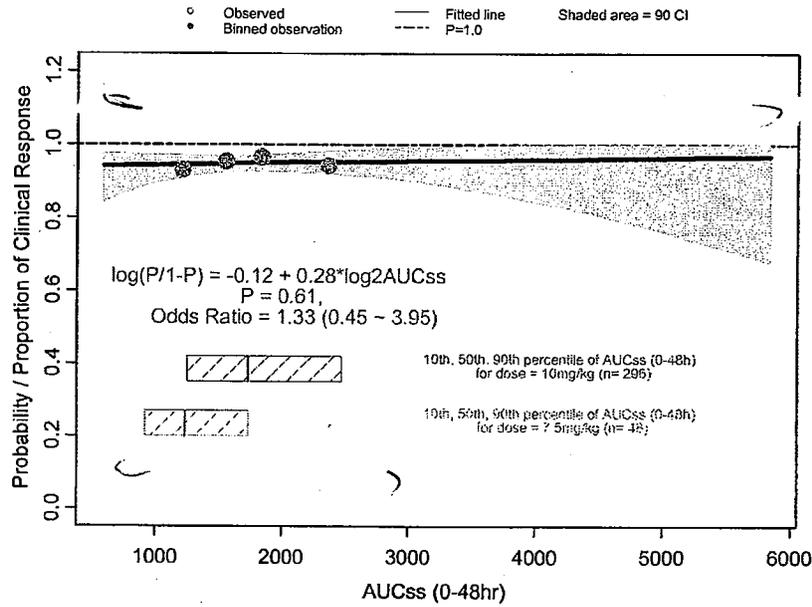
3. Is the mean $\Delta\Delta\text{QTcF}$ observed in the Moxifloxacin group in the Study I6424-104a (Safety and Pharmacokinetics of Intravenous Telavancin in Healthy Subjects) within the expected normal range?

Study I6424-104a is a thorough QT study, in which Moxifloxacin is used as positive control. Typically Moxifloxacin is administered as a single oral dose of 400 mg. In order to keep the patient blinded in this study, 400mg Moxifloxacin is administered as 60 minute i.v. infusion once daily for 3 days before the ECG was measured. The observed mean $\Delta\Delta\text{QTcF}$ value is 24 msec in the Moxifloxacin group. The mean $\Delta\Delta\text{QTcF}$ interval change is usually about 10-16 msec, following 400mg single oral dose of Moxifloxacin. Question arises whether the observed mean $\Delta\Delta\text{QTcF}$ value of 24 msec is higher than the expected normal range.

Our estimation indicates that the expected normal range of mean $\Delta\Delta\text{QTcF}$ is 18-30 msec following 60 minute i.v. infusion of 400mg Moxifloxacin once daily for 3 days. The observed 24 msec is within the expected normal range. The result is derived based on the following reasoning:

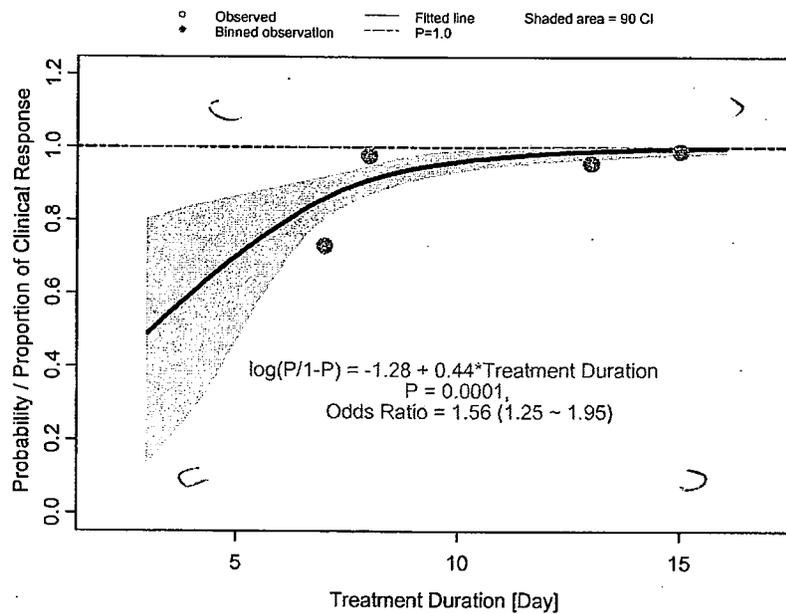
1. From historical data (NDA 21277, Study report 0139), the observed mean maximum concentration (C_{max}) is 3.62 mg/L following the 60 min IV infusion and 2.5 mg/L following the 400mg single dose of Moxifloxacin. Thereby the mean C_{max} is about 1.4 fold higher for i.v. infusion as compared to oral dose.
2. Given the 12 hr half life of Moxifloxacin, once daily dose for 3 days results in a 1.3-fold accumulation relative to single dose.
3. The C_{max} of 400mg Moxifloxacin under i.v. infusion once daily for 3 days is about 1.8 fold higher than the C_{max} of 400 mg Moxifloxacin single oral dose.
4. Taking into consideration the IV route of administration and accumulation by Day 3, the estimated $\Delta\Delta\text{QTc}$ interval change is 18 – 30 msec (1.8 times 10-16 msec). The observed change is 24 msec, well within the expected range.

Figure 1 Logistic regression for clinical cure rate versus telavancin exposure



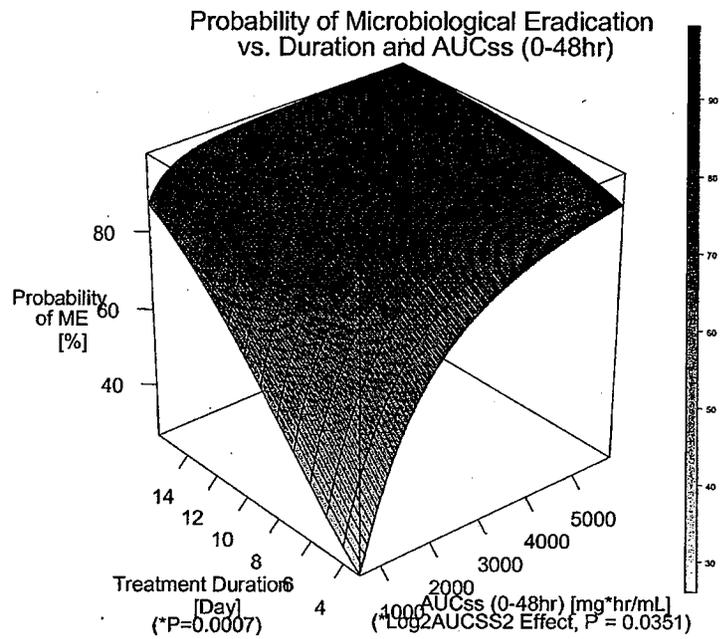
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Figure 2 Logistic regression for clinical cure rate versus telavancin treatment duration



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Figure 3 Multivariate logistic regression model fitting for microbiological response and treatment duration and telavancin exposure



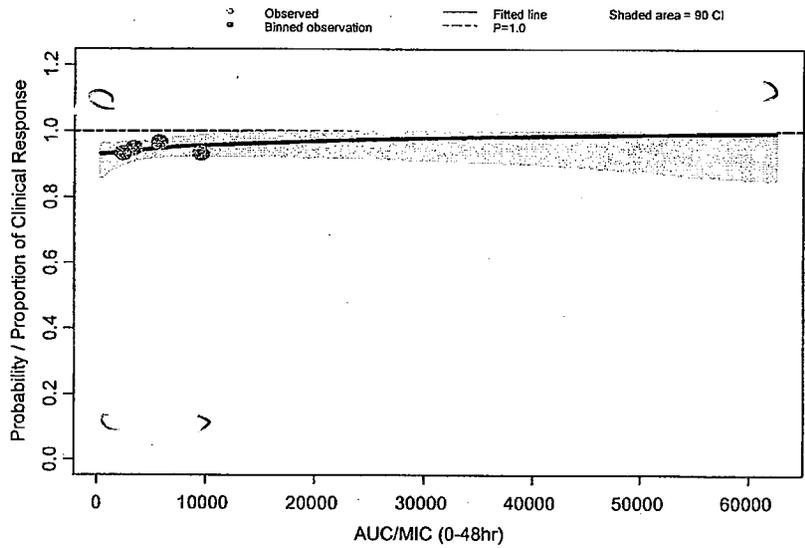
Note: the fitted model is:

$$\text{Log}(P/1-P) = -11.29 + 1.04 \times \text{Log}_2\text{AUCSS}_{(0-48)} + 0.23 \times \text{duration}$$

For Log₂AUCSS₍₀₋₄₈₎ effect: P = 0.035, Odds ratio = 2.83 with 95% CI (1.08 ~ 7.44)

For duration effect: P = 0.0007, Odds ratio = 1.26 with 95% CI (1.1 ~ 1.43)

Figure 4 AUC/MIC versus Clinical Cure rate relationship (With indeterminate)



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Figure 5 AUC/MIC versus Microbiological eradication rate (with indeterminate)

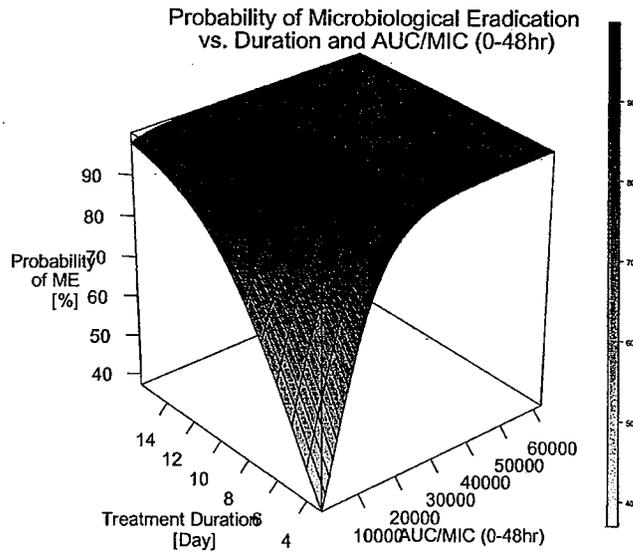
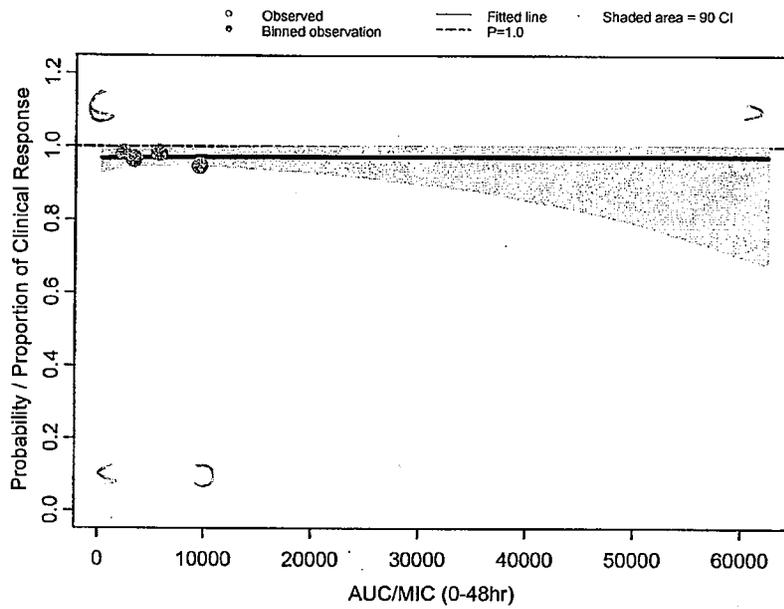


Figure 6 AUC/MIC versus clinical cure rate (without indeterminate)



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Figure 7 AUC/MIC versus microbiological eradication rate (without indeterminate)

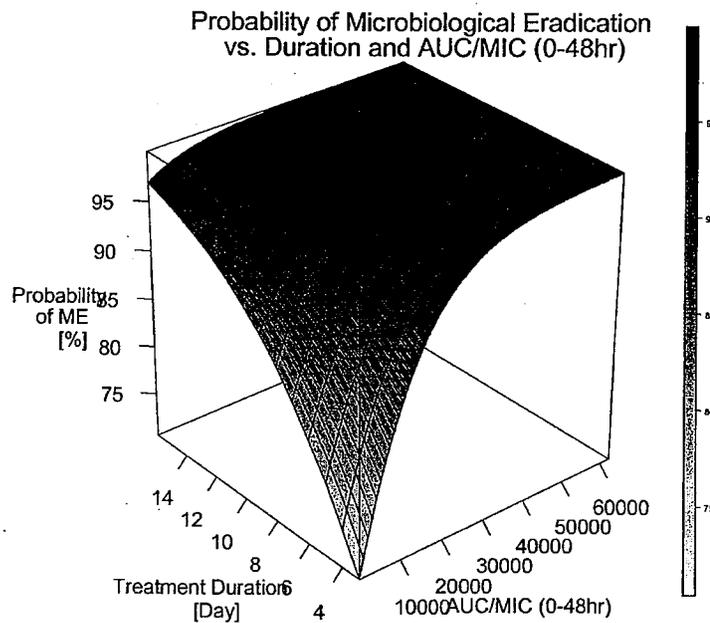
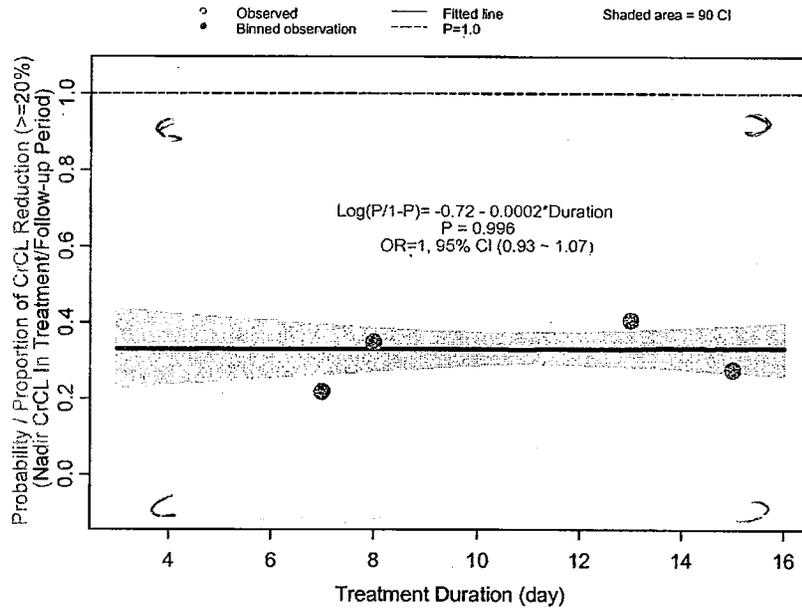
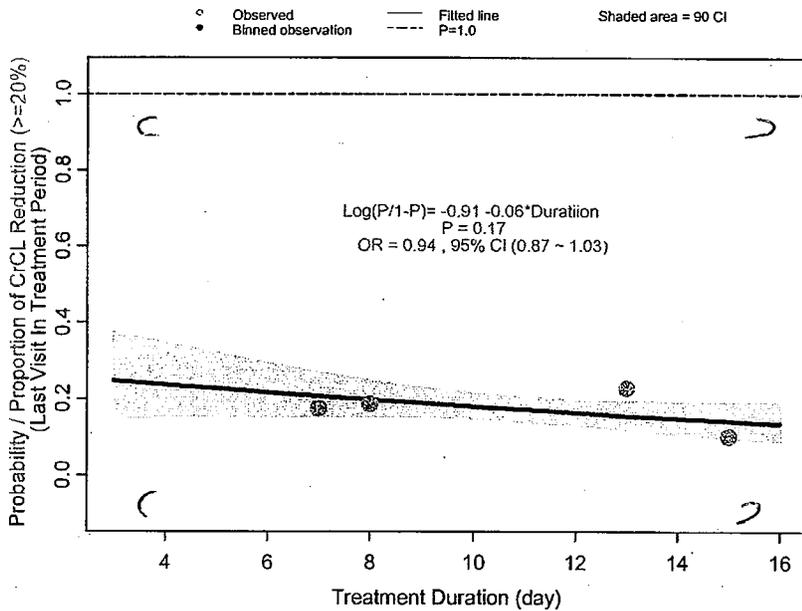


Figure 8 Univariate logistic regression model fitting for worst renal reduction rate versus telavancin treatment duration



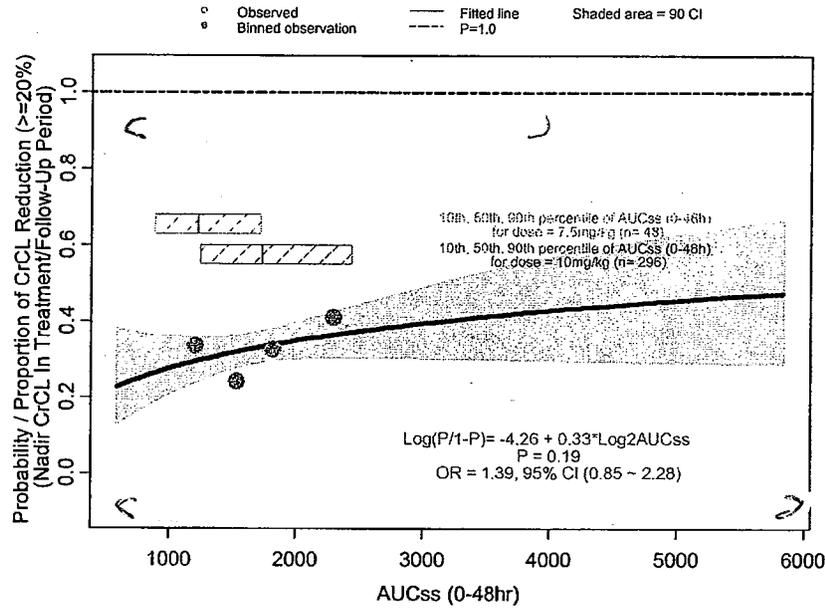
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Figure 9 Univariate logistic regression model fitting for last renal function reduction rate versus telavancin treatment duration



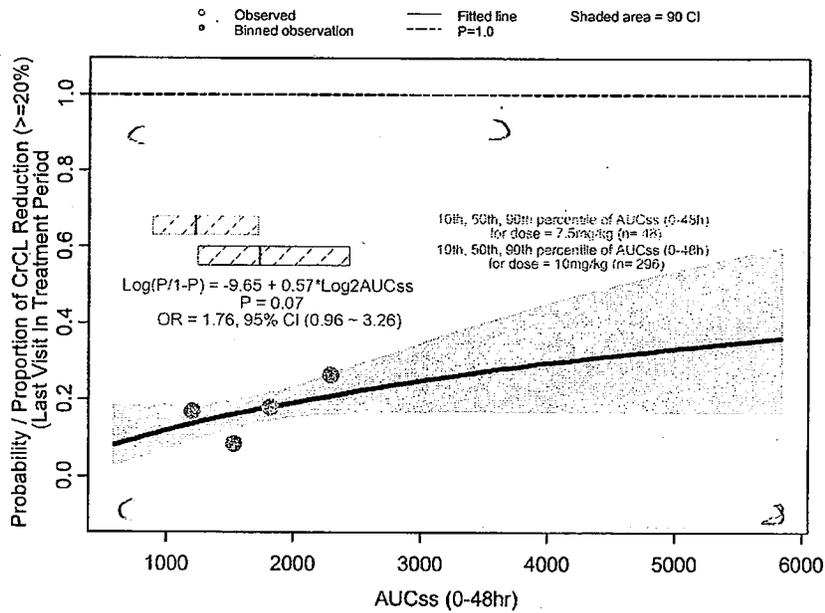
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Figure 10 Univariate logistic regression model fitting for worst renal reduction rate versus telavancin exposure (AUC_{0-48hr})



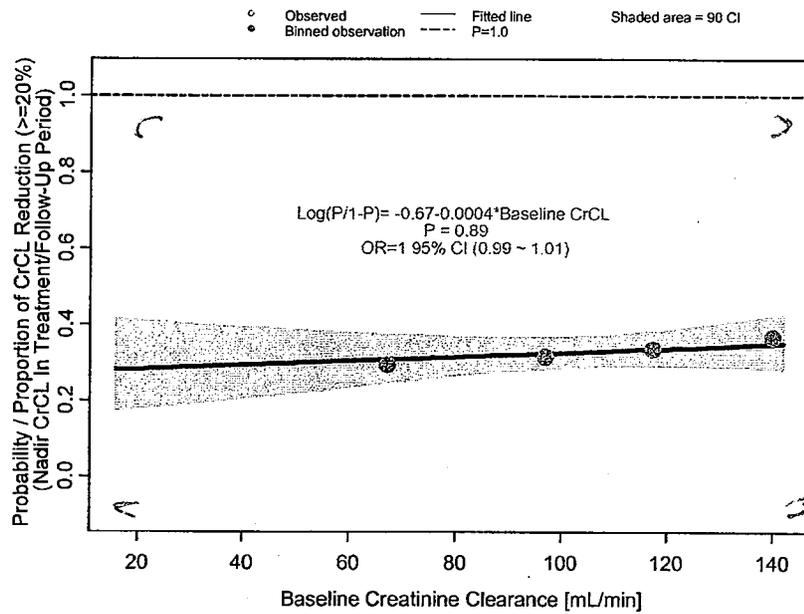
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Figure 11 Univariate logistic regression model fitting for last renal function reduction rate versus telavancin exposure (AUC_{0-48hr})



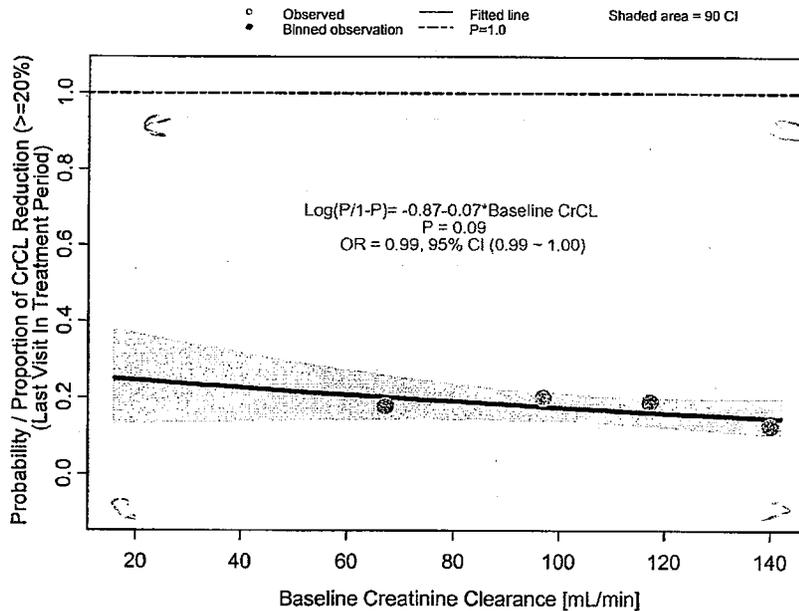
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Figure 12 Univariate logistic regression model fitting for worst renal reduction rate versus baseline CrCL



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Figure 13 Univariate logistic regression model fitting for last renal function reduction rate versus baseline CrCL



b(4)

Table 1 Clinical cure rate at the test of cure on treatment in patients post amendment

Days on Treatment	TLV (N= 712)		VANC (N= 711)		Difference (TLV - VANC)
	% (s/n[1])	95% CI[2]	% (s/n[1])	95% CI[2]	Difference (95% CI)[3]
Day 7	94.0 (94 /100)	(89.3, 98.7)	95.2 (79 /83)	(90.6, 99.8)	-1.2 (-3.0, 6.0) ^A
Day 8	97.6 (166 /170)	(95.4, 99.9)	90.7 (136 /150)	(86.0, 95.3)	7.0 (1.6, 12.3) ^A
Day 9	89.5 (51 /57)	(81.5, 97.4)	92.0 (46 /50)	(84.5, 99.5)	-2.5 (-13.8, 9.3) ^A
Day 10	92.3 (72 /78)	(86.4, 98.2)	90.1 (64 /71)	(83.2, 97.1)	2.2 (-7.3, 11.7) ^A
Day 11	88.9 (48 /54)	(80.5, 97.3)	94.4 (51 /54)	(88.3, 100.0)	-5.6 (-16.3, 5.6) ^A
Day 12	94.3 (33 /35)	(86.6, 100.0)	87.5 (42 /48)	(78.1, 96.9)	6.8 (-7.1, 18.9) ^A
Day 13	85.7 (30 /35)	(74.1, 97.3)	100.0 (34 /34)	(100.0, 100.0)	-14.3 (-26.5, -0.4) ^A
Day 14-15	85.2 (156 /183)	(80.1, 90.4)	82.8 (183 /221)	(77.8, 87.8)	2.4 (-4.7, 9.6)

Table 2 Microbiologic eradication rates at test of cure by days on treatment in patients with 7 to 14 days of treatment post amendment

Days on Treatment	TLV (N= 504)		VANC (N= 517)		Difference (TLV - VANC)
	% (s/n[1])	95% CI[2]	% (s/n[1])	95% CI[2]	Difference (95% CI)[3]
Day 7	94.2 (65 /69)	(88.7, 99.7)	95.4 (62 /65)	(90.3, 100.0)	-1.2 (-9.3, 7.2) ^A
Day 8	97.3 (109 /112)	(94.3, 100.0)	88.9 (88 /99)	(82.7, 95.1)	8.4 (1.2, 15.5) ^A
Day 9	87.2 (34 /39)	(76.7, 97.7)	90.9 (30 /33)	(81.1, 100.0)	-3.7 (-18.3, 11.9) ^A
Day 10	92.3 (48 /52)	(85.1, 99.6)	90.2 (46 /51)	(82.0, 98.4)	2.1 (-9.5, 13.6) ^A
Day 11	85.0 (34 /40)	(73.9, 96.1)	91.7 (33 /36)	(82.6, 100.0)	-6.7 (-21.0, 8.8) ^A
Day 12	96.9 (31 /32)	(90.8, 100.0)	85.0 (34 /40)	(73.9, 96.1)	11.9 (-3.0, 24.6) ^A
Day 13	82.6 (19 /23)	(67.1, 98.1)	95.7 (22 /23)	(87.3, 100.0)	-13.0 (-30.9, 6.9) ^A
Day 14-15	90.5 (124 /137)	(85.6, 95.4)	86.5 (147 /170)	(81.3, 91.6)	4.0 (-3.1, 11.1)

Table 3 Baseline MIC distribution in the analysis dataset from Study 0017 and Study 0018. (Only 230 of 344 patients with PK data)

GROUP	1	2	3	4	5	6	7
MIC	4	1	0.5	0.25	0.12	0.06	0.03
Percentage	0.40%	6.10%	51.70%	36.10%	2.20%	2.60%	0.90%

4 INTRODUCTION

4.1 BACKGROUND

Telavancin (AMI-6424, TD-6424) is derived from a synthetic modification of vancomycin, and is a purified lipoglycopeptide antibacterial agent. Telavancin exerts concentration-dependent, bactericidal activity against Gram-positive organism. The bactericidal activity of telavancin results from a multifunctional mechanism of action that contributes to enhanced activity and low potential for selection of resistant mutants of Gram-positive bacteria. The multifunctional mechanism of action of telavancin includes: 1.) inhibition of bacterial cell wall synthesis, and 2.) disruption of the functional integrity of the bacterial plasma membrane.

This submission is a New Drug Application (NDA) to obtain marketing approval for the indication of the treatment of patients with complicated skin and skin structure infections (cSSSI) caused by susceptible strains of the following Gram-positive microorganisms: Staphylococcus aureus (methicillin-resistant and –susceptible strains (MRSA and MSSA),  Streptococcus pyogenes, Streptococcus agalactiae, Strptococcus anginosus group (including S. anginosus, S. intermedius and S. constellatus), and Enterococcus faecalis (vancomycin-susceptible isolates only).

b(4)

4.2 STUDIES

There were 4 major clinical effectiveness and safety studies (2 Phase II study and 2 Phase III study) that the sponsor included in this submission, they were summarized as the following:

Study 0017 (Phase III):

Study 0017 was a randomized, double blind, active-controlled, parallel-group, multicenter, multinational Phase 3 trial comparing telavancin 10 mg/kg IV q 24h to standard therapy (vancomycin 1 g IV q 12h) in subjects with complicated skin and skin structure infections, with emphasis on infections caused by MRSA (methicillin-resistant staphylococcus aureus). The primary objective was to compare the effectiveness and safety of telavancin to vancomycin in the treatment of target patients. A total of 862 patients were randomized and 855 patients received either telavancin or vancomycin in the study and pharmacokinetic samples were drawn from 244 patients.

Baseline evaluations were performed within 24 hours prior to treatment. During the study treatment phase, patients were evaluated daily for the occurrence of treatment emergent adverse events. On Day 4 (+/- a 1 day window), PK sampling was conducted at selected sites. The duration of the treatment was from 7 to 15 days. For all patients, post-treatment

visits included an End-of-Therapy (EOT) visit (conducted no later than 3 days after the last dose of study medication) and a Follow-Up visit (conducted within 7 to 14 days after the EOT visit). A Test-of-Cure (TOC) assessment was conducted for patients who were a clinical cure or indeterminate at the EOT visit. Both the EOT and Follow-Up Visit procedures included an assessment of adverse events. Primary efficacy was evaluated as the clinical response determined by the investigator at TOC. The secondary effectiveness variables included microbiologic response, overall therapeutic response, clinical signs and symptoms of infection, duration of treatment with study medication, time to resolution of fever, and size of primary infection site. Pharmacokinetic samples were taken at the following time points: just prior to an infusion, 0.25 – 0.5 hours following the start of the infusion (during the infusion) and at 1 – 1.5, and 2 – 3.5 hours following the start of the infusion. For patients whose infusion times were longer than 60 minutes, an alternative sampling schedule was employed, as follows: just prior to an infusion (pre-dose), 0.5 – 1 hours following the start of the infusion (during the infusion), 2 – 2.5 hours following the start of the infusion, 3 – 4.5 hours following the start of the infusion.

Study 0018 (Phase III)

Study 0018 was a Phase 3, randomized, double-blind, multinational trial of intravenous 10mg/kg of telavancin versus 1g q 12 hr. of vancomycin for the treatment of complicated gram-positive skin and skin structure infections with a focus on patients with infections due to methicillin-resistant *staphylococcus aureus*. The primary objective of this study was to compare the efficacy and safety of telavancin to vancomycin in the treatment. A total of 1035 patients were randomized into the study; of these, 1012 received at least one dose of study medication. Blood samples were taken from 141 subjects.

Baseline evaluations were performed within 24 hours prior to treatment start. During the study treatment phase, patients were evaluated daily for the occurrence of treatment-emergent adverse events. On Day 4 (+/- a 1 day window), PK sampling was collected at selected sites. The overall treatment duration is about 7-15 days. For all patients, post-treatment visits included an End-of-Therapy (EOT) visit (conducted no later than 3 days after the last dose of study medication) and a Follow-Up visit (conducted within 7 to 14 days after the EOT visit). A Test-of-Cure (TOC) assessment was conducted for patients who were a clinical cure or indeterminate at the EOT visit. Primary effectiveness was evaluated as the clinical response determined by the investigator at TOC. Up to 4 samples were collected in the following time points: just prior to an infusion, 0.25 – 0.5 hours following the start of the infusion (during the infusion) and at 1 - 1.5, and 2 - 3.5 hours following the start of the infusion. For patients whose infusion times were longer than 60 minutes, an alternative sampling schedule was employed, as follows: just prior to an infusion (pre-dose), 0.5 - 1 hours following the start of the infusion (during the infusion), 2 - 2.5 hours following the start of the infusion, 3 - 4.5 hours following the start of the infusion.

Study 16424-202a (Phase II)

Study 16424-202a was a randomized, double-blind, active-controlled, parallel-group, multicenter, multinational Phase 2 study. The primary objective was to assess the safety and tolerability, and to explore the effectiveness (clinical and microbiologic) of telavancin in the treatment of adults with complicated skin and skin structure infections (cSSSI) due to Gram-positive bacteria. Patients with complicated Gram-positive skin and skin structure infections were treated with telavancin 7.5-mg/kg/day IV or standard therapy, defined as vancomycin 1 g q 12 hours IV or an antistaphylococcal (semisynthetic) penicillin (nafcillin or oxacillin 2 g q 6 hours IV or cloxacillin 0.5 – 1 g q 6 hours IV). A total of 169 patients were randomized; of these, 167 received study treatment (84 received telavancin, 83 received standard therapy). The duration of treatment was up to 14 days. The primary effectiveness variable was the clinical response at the test-of-cure (TOC) visit. For PK subgroup, plasma samples were collected at selected study centers and a total of 7 samples were obtained per subject on either Day 3, 4, or 5 at the following sampling time points relative to the active infusion on that day: prior to the infusion (trough); immediately following the completion of the infusion, at 30 minutes, and at 1, 3, 8, and 23 hours following the completion of the infusion. There was to be a window of +/- 2 hours to obtain the 8-hour pharmacokinetic sample. Blood samples were taken from 169 subjects and the PK profiles from 51 subjects were included in the population PK analysis.

Study 16424-202b (Phase II)

Study 16424-202b was a phase 2, randomized, double-blind, active-controlled, multinational trial of intravenous telavancin versus standard therapy for treatment of complicated Gram-positive skin and skin structure infections. Patients with complicated Gram-positive skin and skin structure infections were treated with telavancin or standard therapy, defined as vancomycin 1 g q 12 hours or antistaphylococcal penicillin. Under the original protocol, telavancin was administered at a dose of 7.5 mg/kg IV once daily. Patients enrolled after approval of Protocol Amendment 1 were administered a telavancin dose of 10 mg/kg IV once daily. Up to 400 patients were to be enrolled Post Amendment 1. A total of 201 patients were randomized; of these, 195 received study treatment (100 received telavancin, 95 received standard therapy). The duration of the study was up to 14 days. The primary effectiveness variable was the clinical response at the test-of-cure (TOC) visit. Pharmacokinetic sampling was performed at selected sites. A total of 7 samples were obtained per subject on either Day 3, 4, or 5 at the following sampling time points relative to the active infusion on that day: prior to the infusion (trough); immediately following the completion of the infusion, at 30 minutes, and at 1, 3, 8, and 23 hours following the completion of the infusion. There was to be a window of +/- 2 hours to obtain the 8-hour pharmacokinetic sample. Blood samples were taken from 79 subjects and were used in the population PK analysis.

4.3 AIM OF ANALYSIS

The aim for the population PK analysis was to describe the pharmacokinetics of telavancin in healthy subjects and subjects with complicated Gram-positive skin and skin

structure infections following i.v. infusion and to identify the source of interindividual variability in the pharmacokinetics of telavancin. Furthermore, the exposure-response relationships for effectiveness and safety were to be investigated. Dose adjustment for special patient population would be evaluated.

5 SPONSOR'S ANALYSIS

5.1 BACKGROUND

Telavancin (AMI-6424, TD-6424) is derived from a synthetic modification of vancomycin. This NDA submission was to obtain marketing approval for the indication of the treatment of patients with complicated skin and skin structure infections (cSSSI) caused by susceptible strains of the Gram-positive microorganisms. The sponsor proposed dosing for telavancin is 10mg/kg administered over a 60-minute period by intravenous infusion once every 24 hours for 7 to 14 days. A dosage adjustment is required for patients with creatinine clearance ≤ 50 mL/min (Table 4). From the population PK analysis, the sponsor proposed no dosage adjustment based on age and gender in the labeling.

Table 4 Dosage adjustment for patients with renal impairment

Creatinine Clearance* (mL/min)	Dose and Dosage Interval
> 50	10 mg/kg every 24 hours
30 – 50	7.5 mg/kg every 24 hours
< 30	10 mg/kg every 48 hours

*As calculated using the Cockcroft-Gault formula (12.3)

b(4)

5.2 SPONSOR'S POPULATION PK ANALYSIS

The sponsor submitted 2 population PK reports, including report No.06-6424-pop-PK-01 (A Population Pharmacokinetic Analysis of Phase I data of Telavancin), and report No. 6424-pop-PK-02 (A Population Pharmacokinetic Analysis of Telavancin Phase 1, 2, 3 Data). They were summarized as following:

Report 06-6424-pop-PK-01

Report 06-6424-pop-PK-01 presented a population PK modeling using data from 7 phase I studies, i.e. 101a, 103a, 104a, 105a, 107a, 108a, and 0016, with the objective to describe the pharmacokinetic process of telavancin in health subjects, subjects with varying degree of renal function and subjects with impaired hepatic function and to identify sources of interindividual variability in the pharmacokinetics of telavancin. Plasma samples were obtained from 236 subjects after being administered single or multiple doses of 0.25 - 15 mg/kg q.d. of telavancin by intravenous infusion over 30, 60 or 120 minutes. A two compartment open model with first order elimination was determined to provide the best fit to the data. The structural model parameters were assumed to be log normally

distributed. Estimates of interindividual variability for telavancin pharmacokinetic parameters ranged from 24 to 31%. A combination of additive and proportional residual error model was used. Covariate analysis determined that telavancin clearance was influenced primarily by renal function. There was a significant linear relationship between estimated creatinine clearance and estimated telavancin clearance. The distribution volumes of telavancin were influenced linearly by body weight and inversely by CLcr. Therefore, reduced telavancin clearance in subjects with severe renal impairment may necessitate adjustment of dosing regimens to match systemic exposures with those in subjects with normal renal function and lesser degrees of renal dysfunction. The relationships between body weight and volume of distribution support the dosing of telavancin on a mg/kg basis.

Report 06-6424-pop-PK-02

Report 06-6424-pop-PK-02 presented a population PK modeling to describe the pharmacokinetics of telavancin in healthy subjects and subjects with complicated Gram-positive skin and skin structure infections, and to identify sources of interindividual variability in the pharmacokinetics of telavancin. Data for the analysis were obtained from 749 adult subjects in 7 Phase I (236 subjects), 2 Phase II and 2 Phase III clinical trials (513 subjects). Population PK modeling based on 236 subjects in the 7 Phase I trials were reported in 06-6424-pop-PK-01. For the Phase II and Phase III trials, up to 7 plasma samples were collected from each of the 513 subjects, after being administered a dose of 7.5 or 10 mg/kg once daily as 1 hour infusions. In Phase III trials, telavancin was administered at 10mg/kg every other day in subjects with CLcr below 30 mL/min. The present analysis confirmed that the two compartment model with first order elimination, which was presented in report 06-6424-pop-PK-01, described the observed data best. In addition to the covariates identified in the report 06-6424-pop-PK-01, body weight, gender and a flag for bacterial eradication were found to correlate with telavancin clearance. Telavancin clearance increased with body weight, was about 10% lower in female subjects, and was higher in subjects achieving bacterial eradication. Telavancin volume of distribution was also found to increase in subjects who underwent surgery. There were no clinically relevant differences in telavancin pharmacokinetics between elderly (>65 or >75 years) and non-elderly subjects. Therefore, the sponsor concluded that the increase in dosing interval (q 48h vs q 24h) utilized in the phase III in subjects with severe renal impairment was in accordance with the observed change in telavancin clearance. No dose adjustment is warranted based on gender and age alone. No clinically relevant differences were observed in the pharmacokinetics of telavancin in obese subjects, defined as subjects with BMI of 35 or greater, and non-obese subjects, BMI of less than 35.

5.3 POPULATION PK METHOD AND RESULTS

5.3.1 Population PK results in healthy subjects (Study Report 06-6424-pop-PK-01)

In the study report 06-6424-pop-PK-01, the sponsor tested one and two compartment open models with first order elimination, using first order estimation in NONMEM. The results showed that plasma telavancin concentration-time data were best described using a two compartment open model with first order elimination.

The structural pharmacokinetic model for the two-compartment model consists of four parameters: clearance (CL), volume of the central compartment (V1), intercompartment clearance (Q) and volume of the peripheral compartment (V2). All pharmacokinetic parameters were assumed to be log-normally distributed and exponential interindividual variability terms were included on the pharmacokinetic parameters in the model. Various residual error models were tested. A combined additive and proportional residual error model provided the best fit to the data, based on reduction of objective function

The final basic model was rerun using first order conditional estimation with interaction (FOCEI). The population telavancin clearance was estimated to be 0.944 L/h and the volume of the central compartment was 4.51 L.

All covariates (age, body weight, height, CLcr, BMI, race and gender) were plotted for relationships with telavancin clearance (CL), volume of the central compartment (V1), intercompartment clearance (Q) and volume of the peripheral compartment (V2). Covariates were also plotted against each other to identify correlated covariates. Body weight and BMI were strongly correlated. Also, a strong correlation between CLcr and age was observed. Therefore, age was not included as a continuous covariate in the analysis. All possible parameter-covariate relationships were screened separately for each parameter in NONMEM. The final model was obtained by a sequential process of stepwise additions of significant covariates to the base model. The impact of the covariate on the model was assessed using the likelihood ratio test. The final model was rerun using first order conditional estimation with interaction (FOCEI).

The final clearance model included effect of creatinine clearance. Body weight and CLcr were determined to be a significant source of interindividual variability in both V1 and V2. Q was also influenced by the creatinine clearance but to a much lesser extent. The PK parameter estimates were shown in Table 5, and can be expressed as following:

$$CL = 0.68 + 0.00251 * CLcr$$

$$V1 = 2.17 - 0.0229 * CLcr + 0.0638 * WT$$

$$Q = 3.6 + 0.0136 CLcr$$

$$V2 = 1.87 - 0.00514 * CLcr + 0.0514 * WT$$

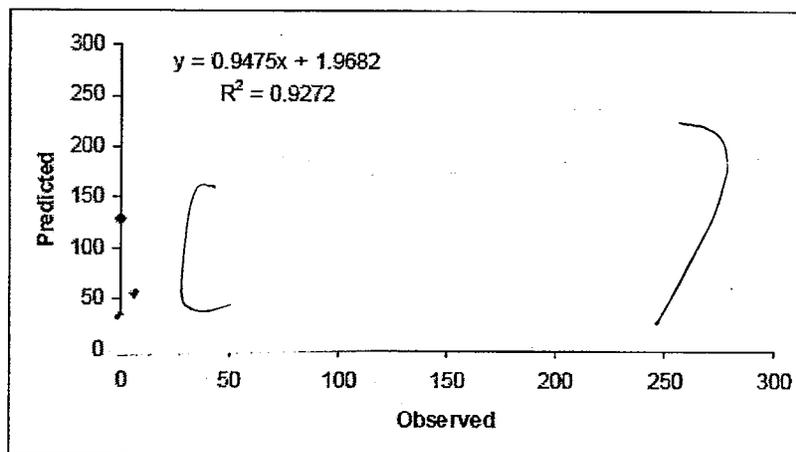
where:

CLcr = estimated creatinine clearance (mL/min)

WT is body weight (kg)

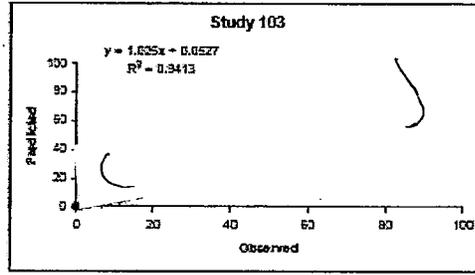
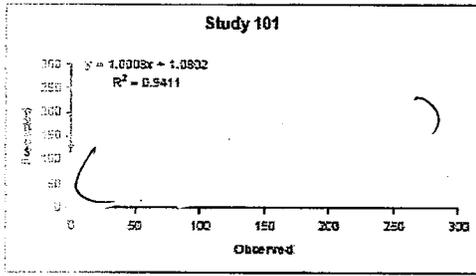
The model performance was checked by comparing the predicted versus observed concentrations (Figure 14), and the weighted residual was plotted against the predicted concentration values (Figure 15). Furthermore, the ability of the final population model to describe the observed data was investigated using data from a separate Phase 1 study (Study 0032). Assuming that the model accurately describes the observed data, 90% of the observed data should fall within the boundaries of the 95th and 5th quantiles of the predicted data. The results of the model evaluation are shown graphically in Figure 16. Overall 90% of the observed data fell within the range of the 95th and 5th quantiles of the predicted data, supporting the goodness of the model.

Figure 14 Model predicted versus observed concentration in healthy subjects from 7 clinical studies

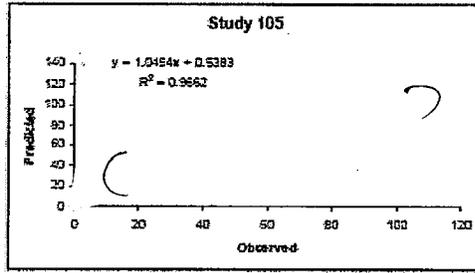
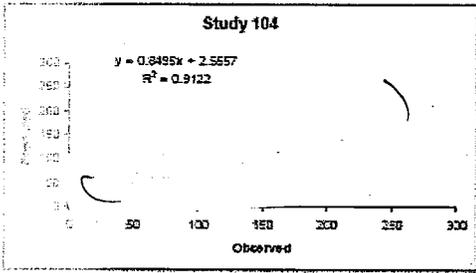


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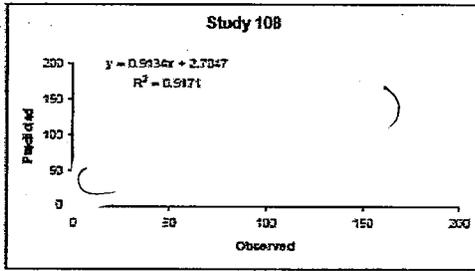
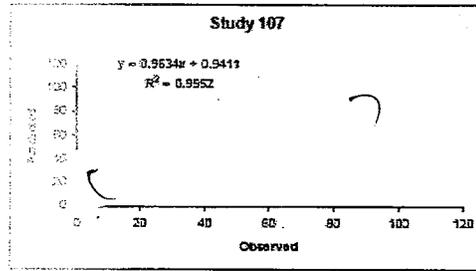
(A)



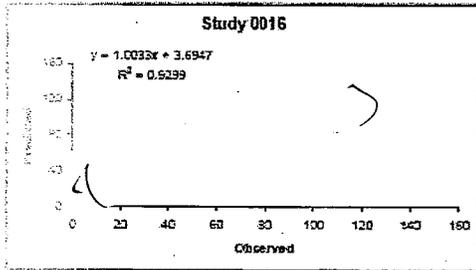
b(4)



b(4)



b(4)



b(4)

(B)

NOTE: (A) is from the pooled data using 7 phase I studies.

(B) is from 7 phase I studies separately.

Figure 15 Weighted residual versus model predicted plasma concentration

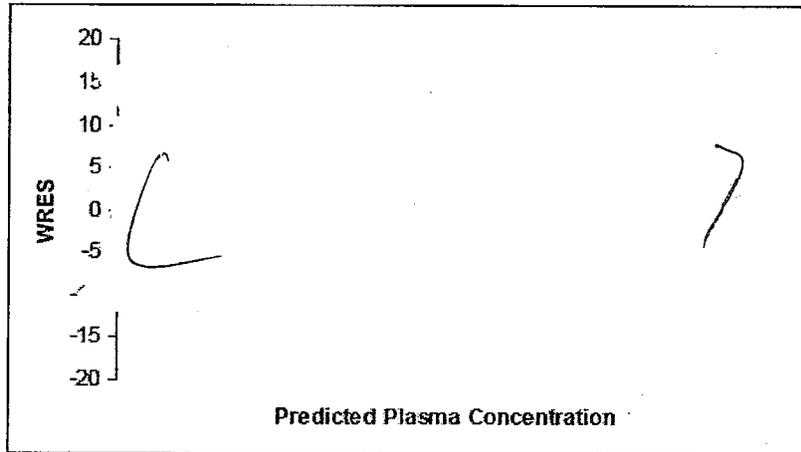


Figure 16 Predicted versus observed concentration from validation run

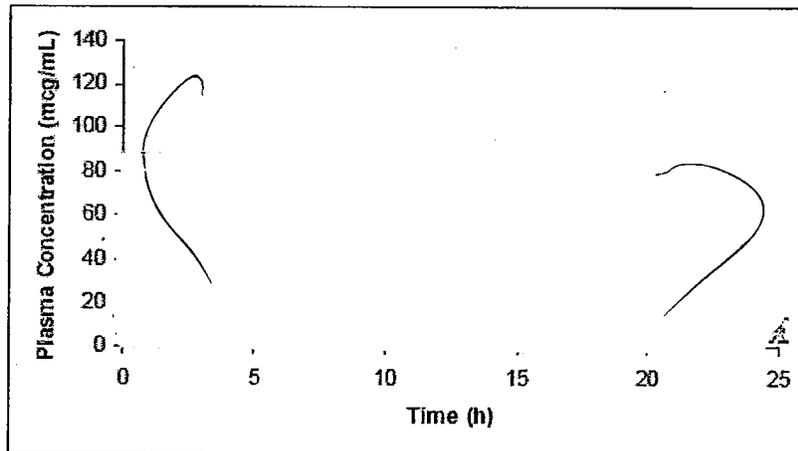


Table 5 Population PK parameters from healthy subjects (Study report 06-6424-pop-PK-01)

Pharmacokinetic Parameter	Median Value	Inter-individual CV (RSE)
CL (L/h)	0.94	28.90 (48.9)
V ₁ (L)	4.40	22.85 (30.8)
Q (L/h)	4.93	26.02 (49.6)
V ₂ (L)	5.24	19.80 (20.0)
Residual Error Parameters	Estimate (RSE)	Intra-individual Error
Additive	0.100 (28.2)	0.316 µg/mL
Proportional	0.0137 (14.7)	11.7 (%CV)

5.3.2 Population PK analysis in healthy subjects and subjects with complicated skin and skin structure infection (Study report 06-6424-pop-PK-02)

In study report 06-6424-pop-PK-02, the two-compartment model developed previously (report 06-6424-pop-PK-02) was fit to the telavancin plasma concentration-time data from seven Phase 1, two Phase 2, and two Phase 3 clinical studies. The structural pharmacokinetic model for the two-compartment model consisted of four parameters: clearance (CL), volume of the central compartment (V₁), intercompartment clearance (Q) and volume of the peripheral compartment (V₂). All pharmacokinetic parameters were assumed to be log-normally distributed and exponential interindividual variability terms were included in the pharmacokinetic parameters in the model. A combined additive and proportional residual error model was used.

Table 6 Population PK parameters from 7 phase I trials, 2 phase II trials, and 2 phase III trials (Study report 06-6424-pop-PK-02)

Pharmacokinetic Parameter	Median Value	Interindividual CV (RSE)
CL (L/h)	1.15	27.15 (16.1)
V ₁ (L)	5.65	41.11 (25.0)
Q (L/h)	6.91	20.57 (178.5)
V ₂ (L)	6.59	30.03 (25.9)
Residual Error Parameters	Estimate (RSE)	Intraindividual Error
Additive	1.09 (65.4)	1.044 µg/mL
Proportional	0.0269 (13.8)	16.4 (%CV)

Method FO was used.

Parameter-covariate relationships screened in NONMEM included covariates incorporated in the Phase 1 final model, selected covariates identified using the General additive model of S-Plus and renal function variables. Covariates were also plotted

against each other to identify correlated covariates. The final models for telavancin clearance (CL), volume of the central compartment (V1), intercompartment clearance (Q) and volume of the peripheral compartment (V2) were as described as follows, and the major parameter estimates were listed in Table 6:

$$\begin{aligned} CL &= (0.286 + 0.00456 * CLcr + 0.0039 * WT) * Y + 0.0847 * ERAD \\ V1 &= 1.64 - 0.0336 * CLcr + 0.0858 * WT + 1.34 * SURG \\ Q &= 2.58 + 0.0419 * CLcr \\ V2 &= 2.85 + 0.0498 * WT \end{aligned}$$

where:

Y=1 for males and 0.907 for females

CLcr = estimated creatinine clearance (mL/min)

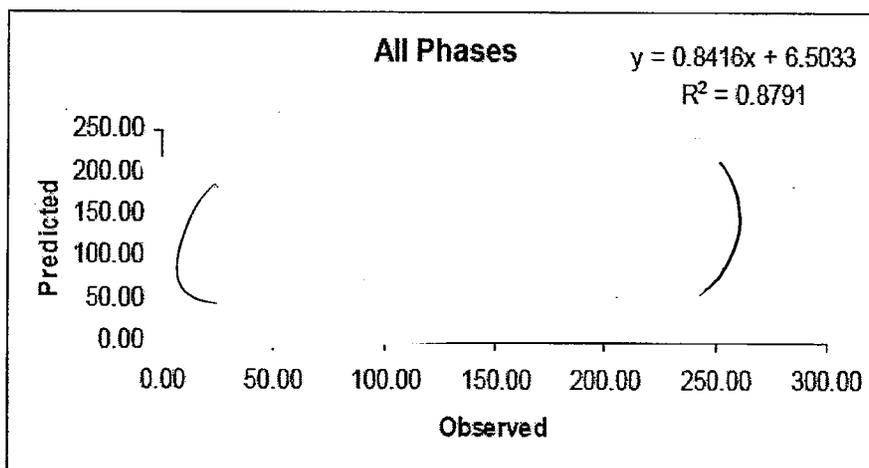
WT is body weight (kg)

ERAD is flag for Eradication (0=no eradication, 1= eradication)

SURG is a flag for surgery (0=no surgery, 1=surgery)

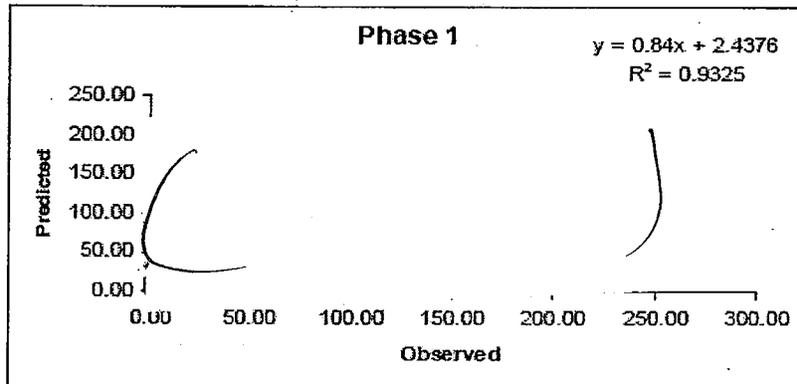
The final population pharmacokinetic model parameter estimates, including median population values, RSE, interindividual variability and residual variability, are presented in Table 6. The final model satisfied all modeling assumptions and parameter estimates were precise. Diagnostic plots show good fit of the final model to telavancin plasma concentrations. Predicted and observed plasma concentration-time profiles for selected subjects are also depicted. The individual telavancin pharmacokinetic parameters were predicted using Bayesian estimation. The parameter estimates obtained with Monte Carlo simulations and bootstrap are in accordance with the estimates from the population model, supporting the validity of the final model (Table 7 and Table 8).

Figure 17 Model predicted versus observed concentration in healthy subjects from 7 phase I studies, 2 phase II studies, and 2 phase III studies

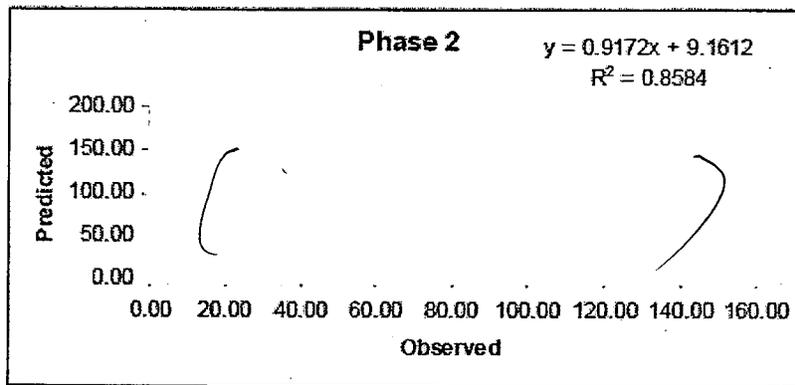


(A)

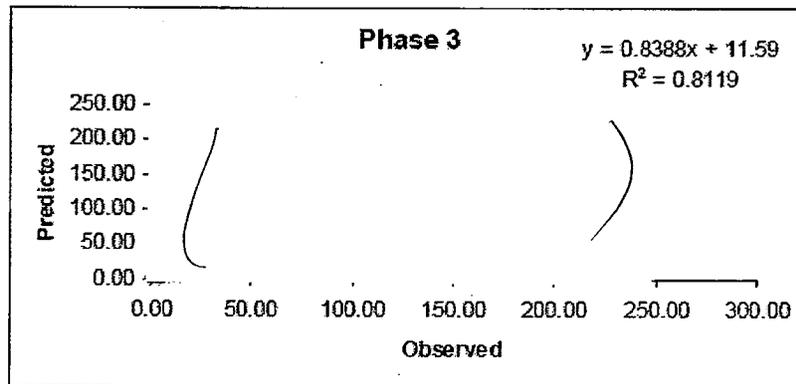
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b(4)

(B)

Note: (A) is from the pooled outcome with all phases of concentration observations
(B) is the outcome separated by 7 phase I clinical trials, 2 phase II trials, and 2 phase III trials.

Figure 18 Weighted residual versus model predicted concentration

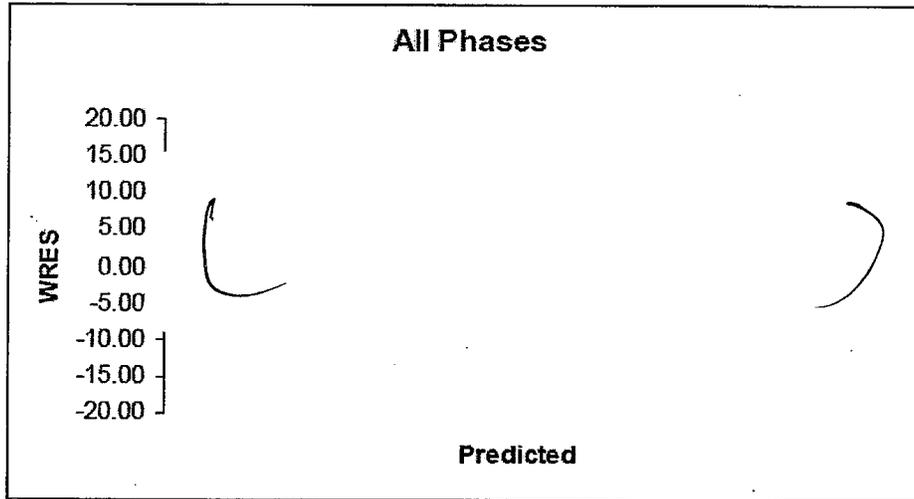


Table 7 Final estimates for the population pharmacokinetic parameters and 201 bootstrap replicates

Parameter	NONMEM	201 Bootstrap Replicates	
	Estimate	Mean	95% PI
Structural Model			
θ1	0.286	0.275	0.0837 – 0.466
θ2	1.64	1.51	-0.350 – 3.38
θ3	2.58	3.46	1.104 – 5.808
θ4	2.85	2.42	0.648 – 4.20
θ5	0.00456	0.00462	0.00328 – 0.00595
θ6	0.0858	0.0815	0.0530 – 0.110
θ7	-0.0336	-0.0286	-0.0426 – -0.0146
θ8	0.0419	0.0280	-0.69 – 0.0630
θ9	0.0498	0.0545	0.0331 – 0.0759
θ10	0.907	0.927	0.798 – 1.057
θ11	0.0039	0.00399	0.00168 – 0.00631
θ12	0.0847	0.0899	-0.0428 – 0.223
θ13	1.34	1.49	-0.168 – 3.155
Statistical model			
ω ² CL	0.0737	0.0758	0.0498 – 0.102
ω ² V ₁	0.169	0.165	0.0912 – 0.239
ω ² Q	0.0423	0.113	-0.0998 – 0.327
ω ² V ₂	0.0902	0.0975	0.035 – 0.160
σ ² prop	0.0269	0.0244	0.0174 – 0.0314
σ ² add	1.09	1.04	-0.383 – 2.47

PI=prediction interval is computed as $\bar{X}_n \pm AS_n \sqrt{1 + (1/n)}$, where A is the $100(1 - (p/2))^{th}$ percentile of Student's t-distribution with $n - 1$ degrees of freedom. \bar{X}_n and S_n are the mean and standard deviation, respectively.

Table 8 Final estimates for the population pharmacokinetic parameters based on Monte Carlo simulation and compared to the estimates from the final model

Parameter	Monte Carlo simulated datasets		Model-building datasets	
	Estimate	SE	Estimates	SE
Structural Model				
θ_1	0.304	0.0628	0.286	0.104
θ_2	1.11	0.718	1.64	1.04
θ_3	2.91	0.409	2.58	0.965
θ_4	2.60	0.818	2.85	0.922
θ_5	0.00378	0.000358	0.00456	0.000702
θ_6	0.0845	0.00671	0.0858	0.0155
θ_7	-0.0282	0.00449	-0.0336	0.00776
θ_8	0.0382	0.00429	0.0419	0.0151
θ_9	0.0689	0.0108	0.0498	0.0110
θ_{10}	0.890	0.0298	0.907	0.0639
θ_{11}	0.00408	0.000675	0.0039	0.00124
θ_{12}	0.126	0.0259	0.0847	0.07
θ_{13}	1.26	0.228	1.34	0.742
Statistical model				
ω^2_{CL}	0.0662	0.00464	0.0737	0.0119
$\omega^2_{V_1}$	0.166	0.0158	0.169	0.0423
ω^2_Q	0.0563	0.0258	0.0423	0.0755
$\omega^2_{V_2}$	0.0936	0.0109	0.0902	0.0234
σ^2_{prop}	0.0286	0.00117	0.0269	0.00371
σ^2_{add}	1.58	0.185	1.09	0.713

5.4 SPONSOR'S CONCLUSIONS

I. Based on the population PK report 06-6424-pop-PK-01, the sponsor found:

- The pharmacokinetics of telavancin was modeled using data from seven Phase I studies.
- The final population model was a two-compartment linear model with first order elimination and included four parameters: CL, V1, Q, and V2. Interindividual variability was present for all parameters. Residual variability was expressed as a combined additive and proportional error model.

The following conclusions can be drawn from the population pharmacokinetic analysis:

- Telavancin clearance is estimated to be primarily a linear function of estimated creatinine clearance.
- Both V1 and V2 were associated with body weight, indicating that the apparent rate of telavancin distribution into the peripheral (extracellular) compartment increases with body weight.
- Both V1 and V2 were inversely related to CL_{cr}, indicating that telavancin distribution increased in subjects with impaired renal function.

The relationships between body weight and telavancin volumes of distribution support the dosing of telavancin on a mg/kg basis. The significant correlation between

creatinine clearance and telavancin clearance suggests that subjects with severe renal impairment or end stage renal disease may require adjusted dosing regimens to match systemic exposures with those seen in subjects with normal renal function.

2. Based on the population PK report 06-6424-pop-PK-02, the sponsor found:

- The pharmacokinetics of telavancin were evaluated using data from seven Phase 1, two Phase 2 and two Phase 3 studies.
- The final population model was a two-compartment linear model with first order elimination and included four parameters: CL, V1, Q, and V2. Interindividual variability was present on all parameters. Residual variability was expressed as a combined additive and proportional error model.

The following conclusions can be drawn from the population pharmacokinetic analysis:

- Telavancin clearance is estimated to be primarily a linear function of estimated creatinine clearance. Clearance decreased in moderate to severe impaired renal function
- Both V1 and V2 were associated with body weight, indicating that the apparent rate of telavancin distribution into the peripheral (extracellular) compartment increase with body weight
- V1 was inversely related to CLcr, indicating that telavancin distribution increased in subjects with impaired renal function
- No dose adjustment is needed based on gender or age alone
- The dose adjustments for renal impairment utilized in Phase 3 protocols (7.5 mg/kg for moderate renal impairment and 10 mg/kg q48h for severe renal impairment) seems appropriate based on the observed reductions in telavancin clearance in subjects with moderate and severe renal impairment
- No dose adjustment is warranted in obese subjects

5.5 REVIEWER'S COMMENTS ON SPONSOR ANALYSIS

- The population pharmacokinetic analysis based on 7 phase I clinical trials (Study report 06-6424-pop-PK-01) is acceptable.
- The population pharmacokinetic analysis based on 7 phase I clinical trials, 2 phase II clinical trials, and 2 phase III clinical trials (Study report 06-6424-pop-PK-02) is acceptable.
- Should there be additional clinical trials for this drug, we recommend that the sponsor:
 - provide standard goodness-of-fit plots in order to support the validity of the final model. These plots consist of 1.) population predicted versus observed concentration, 2.) individual predicted versus observed concentration, 3.) weighted residual or conditional weighted residual versus time, and 4.) weighted residual or conditional weighted residual versus population predicted concentration.
 - perform assumption check for the random effects. For example, the sponsor can provide the QQ plots to compare the interindividual variability with the standard normal distribution.
 - collect sparse PK samples from all patients in the pivotal clinical trials in order to further investigate the exposure-response relationship.

6 REVIEWER'S ANALYSIS

FDA reviewer's analysis was to explore the exposure-effectiveness and safety relationship following telavancin therapy.

6.1 DATA

The original data was provided by the sponsor on April 26, 2007 upon request from the reviewer. The sponsor provided 2 major exposure-effectiveness and exposure-safety datasets - pkexpeff.xpt, and pkexpcl.xpt.

Clinical response at the test-of-cure (TOC) was evaluated by the clinical investigator and was used by sponsor as the primary effectiveness variable in the pivotal trials. The clinical responses from 346 subjects (PK subset) in Studies 0017 and 0018 were provided in the pkexpeff.xpt dataset. Since 2 subjects in this dataset have no PK information, the clinical response analysis dataset includes 344 subjects.

Microbiological response at the TOC was used by the sponsor as the secondary effectiveness variable in the pivotal trials. We derived the analysis dataset by removing the subjects with no PK or no microbiological response observations from the pkexpeff.xpt dataset. Totally 266 subjects were included in the exposure-microbiological analysis dataset.

Renal function change in the telavancin treatment and follow-up periods was measured by the sponsor as creatinine clearance (CrCL). We derived the analysis dataset by removing the subjects and observations with no PK, no baseline CrCL or no CrCL observations from the pkexpcl.xpt dataset. There are 380 subjects in the final analysis dataset.

6.2 METHODS AND RESULTS

We performed exposure-clinical response rate, exposure-microbiological response rate, and exposure-renal function reduction rate analyses using data from PK subgroup in the two pivotal clinical trials (0017 and 0018). In our analyses, the exposure is defined as the steady state AUC over 48 hr ($AUC_{ss(0-48)}$). As stated in the protocols of Study 0017 and Study 0018, 7.5 mg/kg or 10 mg/kg telavancin was administered once every 24 hr. In patients with severe renal impairment, telavancin was given once every 48 hr. Therefore, the steady state AUC over 48 hr is employed as exposure measures. $AUC_{ss(0-48hr)}$ distribution is shown in Figure 19. The distributions of telavancin exposure are similar between the two pivotal trials. The treatment duration was also plotted in Figure 20. The treatment duration distribution is different from Study 0017 to Study 0018-more than 40% of the patients in Study 0017, as compared to about 15% of the patients in Study 0018, stayed in the trial until Day 14. In summary, analysis data obtained from Study 0017 and Study 0018 provides sufficient range of telavancin exposure in order for us to perform relevant analyses.

Figure 19 Telavancin Steady state AUC (0-48hr) distribution from Studies 0017 and 0018

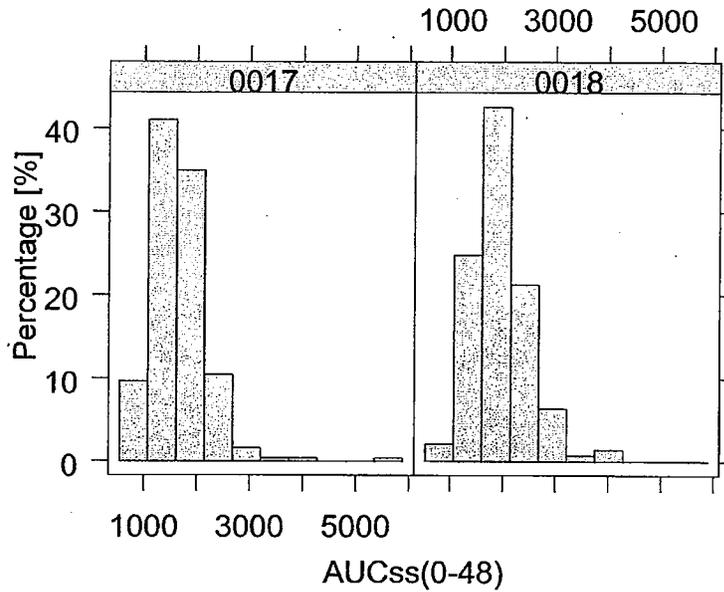
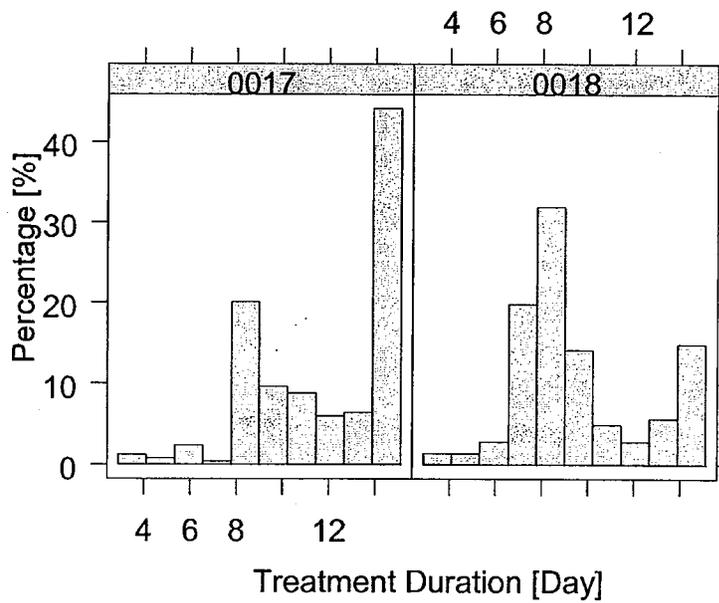


Figure 20 Telavancin treatment duration in the PK subset of patient from Studies 0017 and 0018



6.2.1 Exposure-clinical response rate analysis

We investigated the exposure-clinical response rate relationship from the PK subgroup in the two pivotal clinical trials (0017 and 0018).

Clinical response rate is defined as clinical cure rate. Clinical response at the test-of-cure (TOC) was measured by the clinical investigator and was used as the primary effectiveness variable by the sponsor in the statistical analysis. Based on the study protocol of 0017 and 0018, the clinical response was defined as “cured”, “not cured”, “indeterminate”, and “missing”. In our exposure-clinical response analysis, we pooled the “indeterminate” and “missing” into “not cured”, as the sponsor summarized the percentage of clinical cure rate. We then analyzed the percentage of subjects who were clinically cured as a function of telavancin exposure.

At a scrutiny of the raw data, we found that similar $AUC_{SS\ 0-48hr}$ distribution is observed in patients who were cured as compared to those who were not cured at the TOC (Figure 21). However, the patients who were clinically cured appears to have longer treatment duration time as compared to the patients who were not cured at the TOC (Figure 22).

Figure 21 $AUC_{(0-48)}$ distribution for the patients who were cured as compared to those who were not cured at the TOC

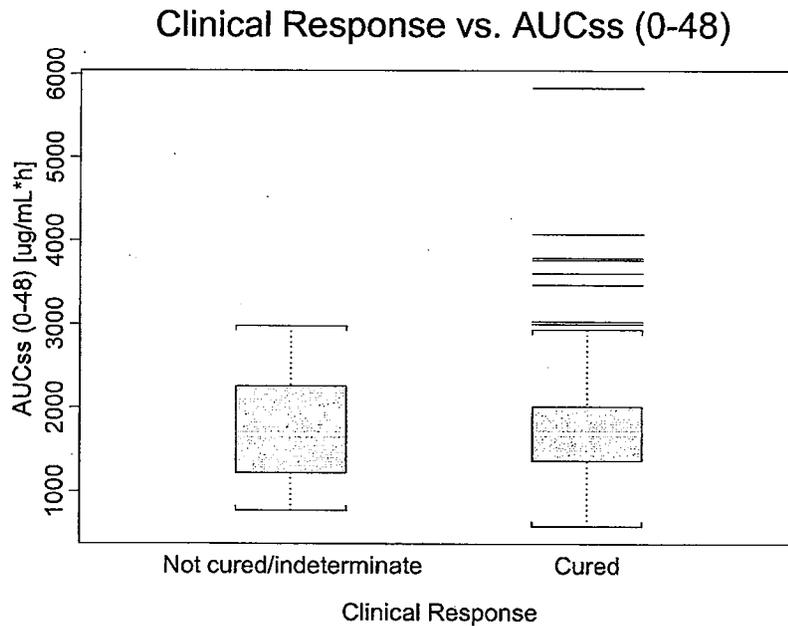
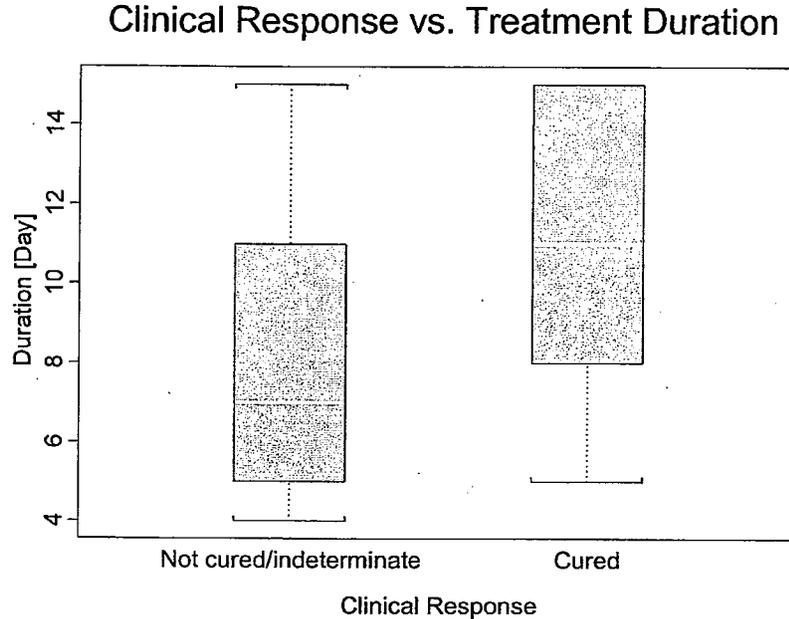


Figure 22 Treatment duration distribution for the patients who were cured as compared to the patients who were not cured at the TOC



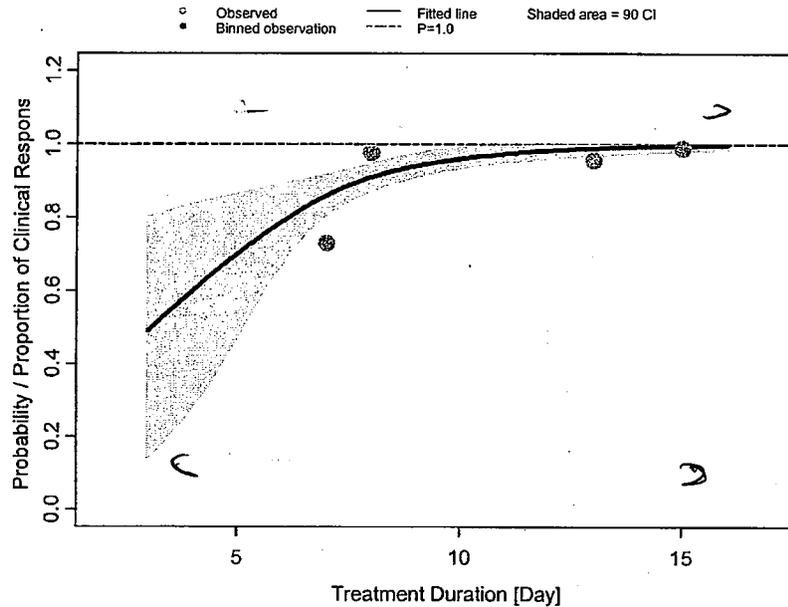
We used logistic regression model to explore the relationship between telavancin exposure and the clinical cure rate following telavancin treatment. Factors, such as telavancin exposure ($AUC_{SS\ 0-48hr}$) (log-transformed), treatment duration time, and patient body weight, were screened using stepwise selection. Only treatment duration time is proved to be a significant factor for the model ($P = 0.0001$), and the parameter estimates were listed in Table 9. As demonstrated in Figure 23, the model adequately describes the relationship between clinical response and the telavancin treatment duration time.

Table 9 Parameter estimates (Clinically cured ~ treatment duration)

Parameter	Estimate	P value	Odds ratio	95% CI
Intercept	-1.28	0.18	-	-
Treatment Duration	0.44	0.0001 (***)	1.56	1.25 ~ 1.95

***: Statistically significant

Figure 23 Logistic regression model fitting for clinical response and treatment duration time



b(4)

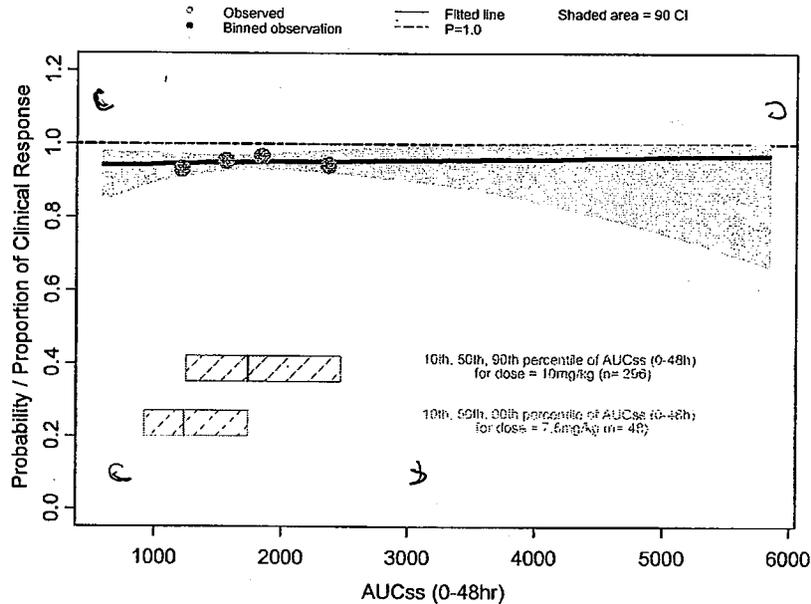
We further employed a logistic regression model to characterize the telavancin exposure and clinical cure rate relationship. The model parameters were listed in Table 10, and no statistically significant telavancin exposure effect is demonstrated. The model fitted curve was shown in Figure 24. The fitted curve sufficiently describes the observed data. No trend between clinical response rate and telavancin exposure can be identified. The 10th, 50th, and 90th percentile of telavancin exposure following 7.5 mg/kg and 10 mg/kg (tested dose) telavancin administration was illustrated respectively as boxes in the plot. No superior clinical response rate can be shown for the dose at 10 mg/kg as compared to 7.5 mg/kg.

Table 10 Parameter estimates (Clinically cured ~ telavancin exposure (AUC_{0-48hr}))

Parameter	Estimate	P value	Odds ratio	95% CI
Intercept	- 0.12	0.98	-	-
Log ₂ AUC _{ss (0-48hr)}	0.28	0.61 [#]	1.33	0.45 ~ 3.95

#: Not statistically significant

Figure 24 Logistic regression model fitting for clinical response and telavancin exposure (AUC_{0-48hr})



b(4)

6.2.2 Exposure-microbiological response rate analysis

We also investigated the exposure-microbiological response rate relationship from the PK subgroup in the two pivotal clinical trials (0017 and 0018).

Microbiological response rate is defined as microbiological eradication rate. Microbiological response at the TOC was used as the secondary effectiveness variable in the pivotal trials by the sponsor. Based on the study protocol of 0017 and 0018, the microbiological response was defined as “eradicated”, “not eradicated”, and “indeterminate”. In our exposure-microbiological response analysis, we pooled the “not eradicated” and “indeterminate” into “not eradicated”, as the sponsor conducted in the statistical analysis. We then analyzed the percentage of subjects who were proved to be microbiologically eradicated as a function of telavancin exposure.

At a scrutiny of the raw data, similar AUC_{ss 0-48hr} distribution is observed in patients who were microbiologically eradicated as compared to those who were not microbiologically eradicated at the TOC (Figure 25). However, the patients who were microbiologically eradicated appears to have longer treatment duration time as compared to the patients who were not microbiologically eradicated at the TOC (Figure 26).

Figure 25 AUC (0-48) distribution for the patients who were microbiologically eradicate as compared to those who were not microbiologically eradicate at the TOC

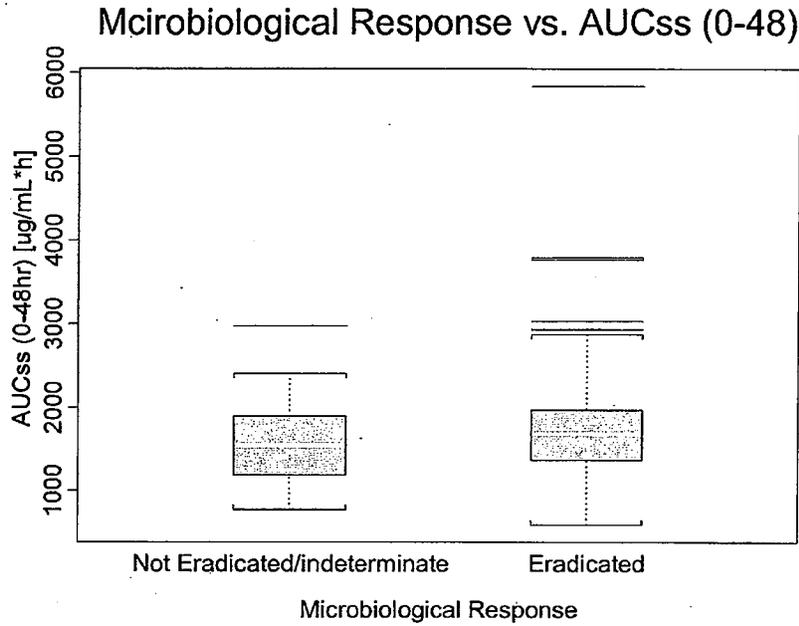
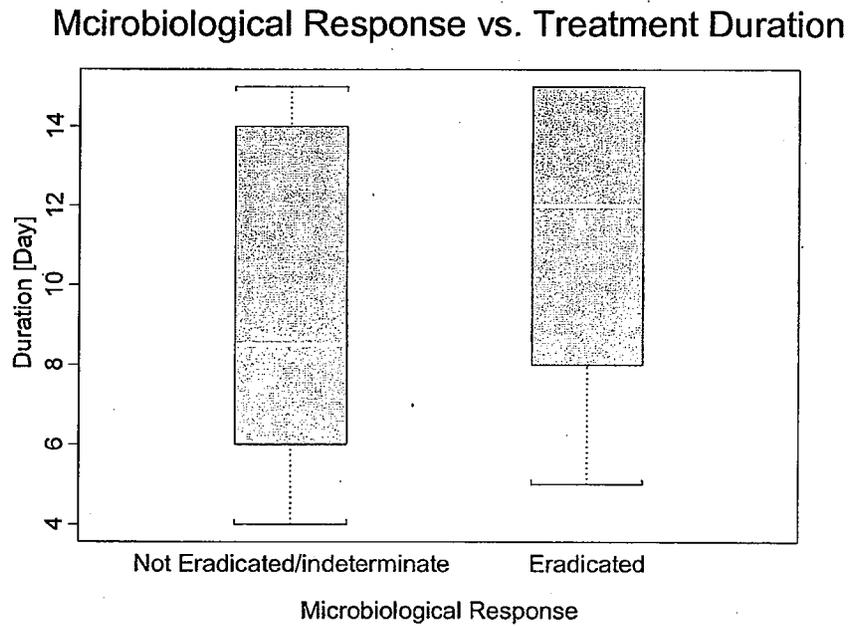


Figure 26 Treatment duration distribution for the patients who were microbiologically eradicate as compared to those who were not microbiologically eradicate at the TOC



We performed univariate logistic regression models to further identify the relationship between the microbiological response rate with telavancin exposure and treatment

duration. Microbiological response rate were modeled separately with AUCss (0-48) (Figure 27) and with treatment duration (Figure 28). The fitted curve describes the observed data well. An increased trend of higher microbiological response rate was identified when a patient has higher telavancin exposure or longer treatment duration.

Figure 27 Univariate logistic regression model fitting for microbiological response versus telavancin exposure (AUCss (0-48hr))

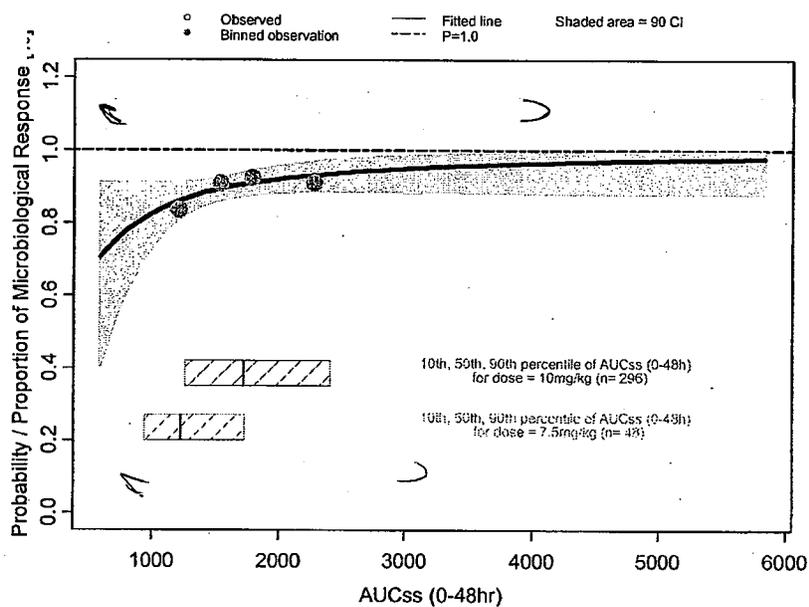
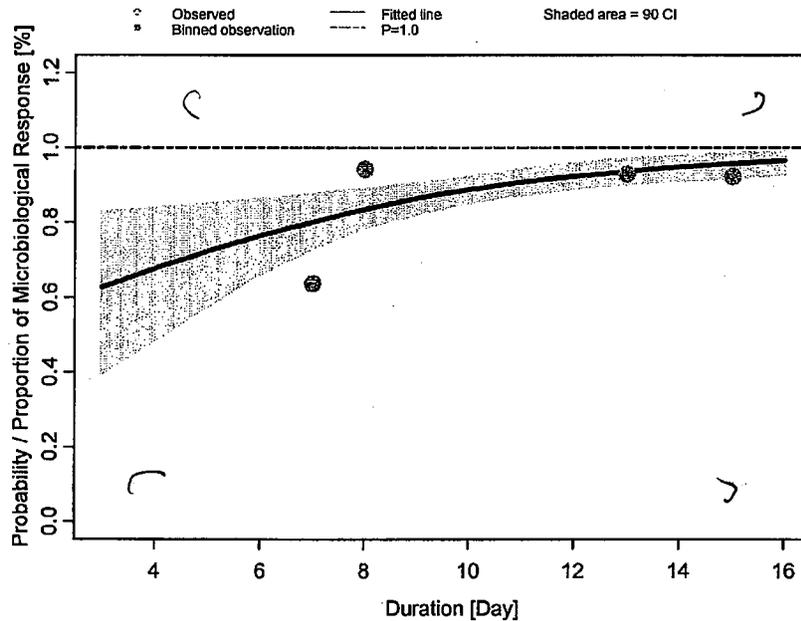


Figure 28 Univariate logistic regression model fitting for microbiological response versus telavancin treatment duration



b(4)

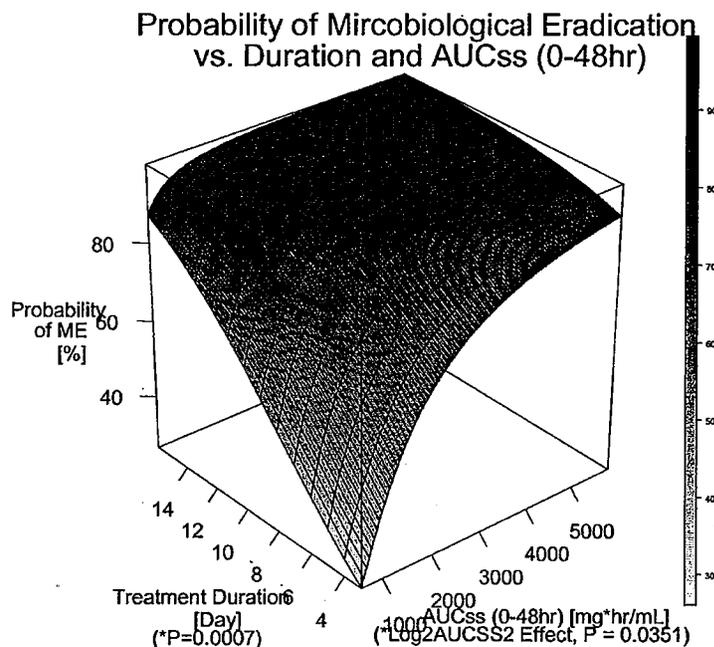
Subsequently, factors, such as telavancin exposure (AUC_{0-48hr}) (log-transformed), treatment duration time, and patient body weight, were screened using stepwise selection. Both treatment duration and telavancin exposure are proved to be significant factors for the final model ($P < 0.05$). The final multivariate logistic regression model parameters were listed in Table 11.

Table 11 Parameter estimates (Microbiological response ~ treatment duration + exposure)

Parameter	Estimate	P value	Odds ratio	95% CI
Intercept	-11.29	0.035	-	-
$\text{Log}_2 AUC_{0-48hr}$	1.04	0.035 (**)	2.83	1.08 ~ 7.44
Treatment Duration	0.23	0.0007 (***)	1.26	1.10 ~ 1.43

** or ***: Statistically significant.

Figure 29 Multivariate logistic regression model fitting for microbiological response and treatment duration and telavancin exposure



Our multivariate logistic regression analysis indicated that the microbiological eradication rate is governed by both the telavancin exposure and treatment duration. The combination effect for the telavancin exposure and patient treatment duration on the microbiological response was shown in Figure 29. A general trend can be identified that a patient with higher exposure and longer treatment duration yields higher microbiological response rate.

6.2.3 Exposure-renal function reduction rate analysis

We performed the exposure-renal function reduction rate analysis from the PK subgroup in the two pivotal clinical trials (0017 and 0018).

The renal toxicity was described by renal function reduction rate, which is defined as the percentage of subjects who experienced at least 20% creatinine clearance (CrCL) reduction comparing to baseline. The CrCL values higher than 140 mL/min are physiologically implausible. Any CrCL values greater than 140 mL/min were treated as 140 mL/min. The percentage reduction from baseline (P.CHG) was calculated by the following method. Patients with P.CHG > (-)20% were designated as 'yes' (reduced renal function), else 'no'.

$$P.CHG = \frac{TBCLCR - TCLCR}{TBCLCR} \times 100\%$$

Where P.CHG represents the CrCL percentage reduction from baseline, TBCLCR is the truncated (truncated to 140 mL/min, when baseline creatinine clearance > 140 mL/min)

baseline creatinine clearance, TCLCR is the truncated (truncated to 140 mL/min, when CrCL > 140 mL/min at any visit) CrCL.

Renal function reduction was analyzed at two different scenarios. In the first scenario, we performed the analysis using the lowest CrCL value observed during the treatment and follow-up periods (worst CrCL scenario). In the second occasion, we performed similar analysis using the last CrCL value observed during the treatment period (last CrCL scenario).

6.2.3.1 Exposure- worst renal function reduction rate analysis

We performed exposure-renal function reduction rate analysis for the worst CrCL reduction during any visit in the treatment and follow-up periods of each subject (worst CrCL scenario).

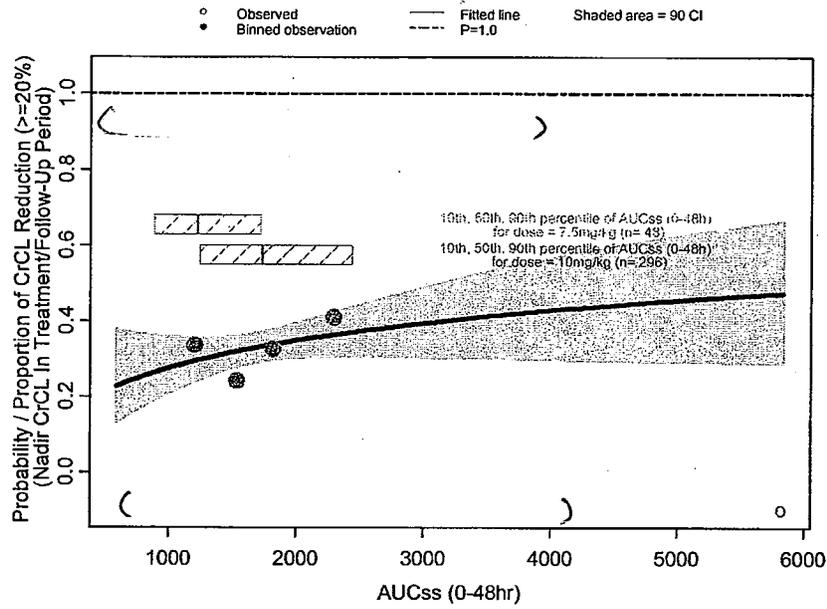
We used logistic regression model to explore the relationship between telavancin exposure and the worst renal function reduction following telavancin treatment. Factors, such as telavancin exposure (AUC_{0-48hr}) (log-transformed), treatment duration time, patient body weight, and baseline CrCL were screened using stepwise selection. No factor was selected as a significant effect at 0.05 level.

We further investigated the effect of telavancin exposure, treatment duration, and baseline CrCL on renal function reduction separately by using univariate logistic regression modeling approach. The model parameter estimates were presented in Table 13. The model fitted curves were illustrated from to Figure 32. The model fitted curves sufficiently describe the observed data. We also identified the following:

- A slightly increased trend can be observed as higher telavancin exposure (AUC_{0-48hr}) yields relatively higher incidence of renal function reduction (defined as CrCL > 20% reduction from baseline) – the renal function reduction rate is about 29.8% when the exposure is 1225 ug/mL*hr (equivalent to the median exposure at the dose of 7.5 mg/kg), whereas the rate is increased to 33.1% when exposure is increased to 1731 ug/mL*hr (equivalent to the median exposure at the dose of 10 mg/kg) (Figure 30). This suggests that reducing dose from 10 mg/kg to 7.5 mg/kg provides a slight reduction (4-5%) of risk for a patient to experience renal function reduction. However, this increased trend is not statistically significant ($P = 0.19$, OR = 1.39 with 95% CI (0.85 ~ 2.28)).
- The incidence of renal function reduction does not appear to be treatment duration dependent ($P = 0.996$, OR = 1 with 95% CI (0.93 ~ 1.07)) (Figure 31). Therefore, increasing treatment duration does not appear to increase the risk for a patient to experience worst renal function reduction rate.
- Baseline CrCL does not appear to be related to the renal function reduction based on the analysis ($P = 0.89$, OR = 1 with 95% CI (0.99 ~ 1.01)) (Figure 32). This might be because that 1.) we truncated both baseline CrCL and CrCL where they

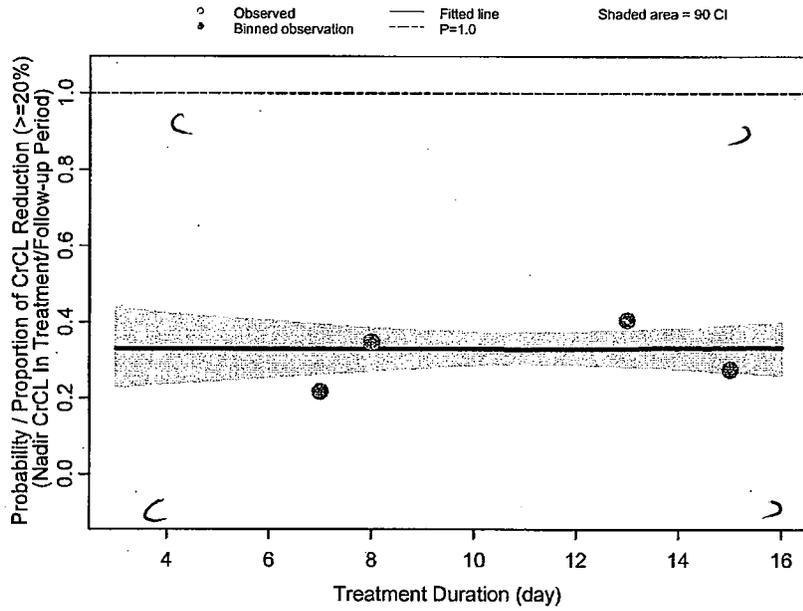
are greater than 140, and 2.) we used percentage change from baseline CrCL in constructing the dataset.

Figure 30 Univariate logistic regression model fitting for worst renal reduction rate versus telavancin exposure (AUCss (0-48hr))



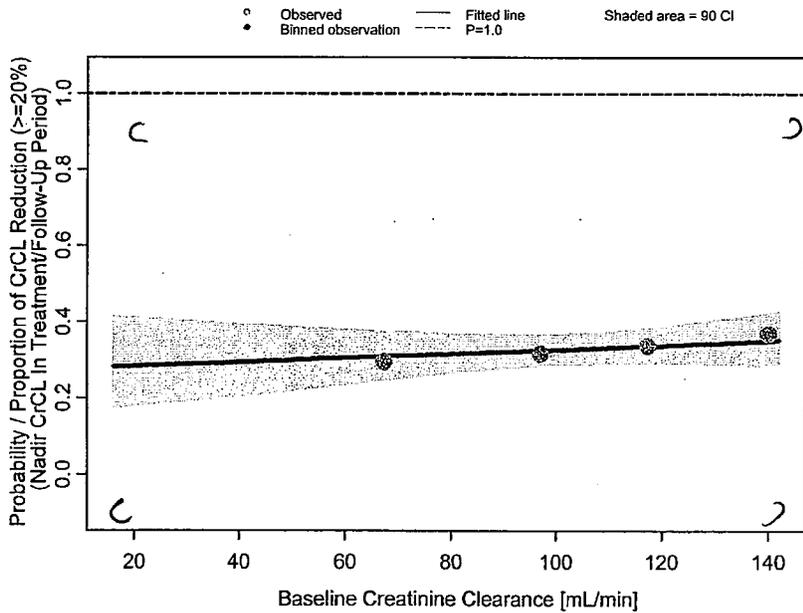
b(4)

Figure 31 Univariate logistic regression model fitting for worst renal reduction rate versus telavancin treatment duration



b(4)

Figure 32 Univariate logistic regression model fitting for worst renal reduction rate versus baseline CrCL



b(4)

Table 12 Univariate model parameter estimates for worst renal function reduction rate versus telavancin exposure, treatment duration, and baseline CrCL

Model: Log (P/1-P) ~ Log₂ AUC_{ss} (0-48hr)				
Parameter	Estimate	P value	Odds ratio	95% CI
Intercept	-4.26	0.12	-	-
Log ₂ AUC _{ss} (0-48hr)	0.33	0.19 (#)	1.39	0.85 ~2.28
Model: Log(P/1-P) ~ Treatment duration				
Parameter	Estimate	P value	Odds ratio	95% CI
Intercept	-0.72	0.08	-	-
Treatment duration	-0.0002	0.996 (#)	1	0.93 ~ 1.07
Model: Log(P/1-P) ~ Baseline CrCL				
Parameter	Estimate	P value	Odds ratio	95% CI
Intercept	-0.67	0.06	-	-
Baseline CrCL	-0.0004	0.89 (#)	1	0.99 ~ 1.01

P: probability of subjects with $\geq 20\%$ reduction in CrCL comparing to baseline

#: No statistical significance ($\alpha = 0.05$).

6.2.3.2 Exposure- last renal function reduction rate analysis

We performed exposure-renal function reduction analysis for the last visit in the actual treatment period of each subject (last CrCL scenario).

We used logistic regression model to explore the relationship between telavancin exposure and the last renal function reduction following telavancin treatment. Factors, such as telavancin exposure (AUC_{0-48hr}) (log-transformed), treatment duration time, patient body weight, and baseline CrCL were screened using stepwise selection. No factor was selected as a significant effect at 0.05 level.

We further investigated the effect of telavancin exposure, treatment duration, and baseline CrCL on renal function reduction separately by using univariate logistic regression modeling approach. The model parameter estimates were presented in Table 13.

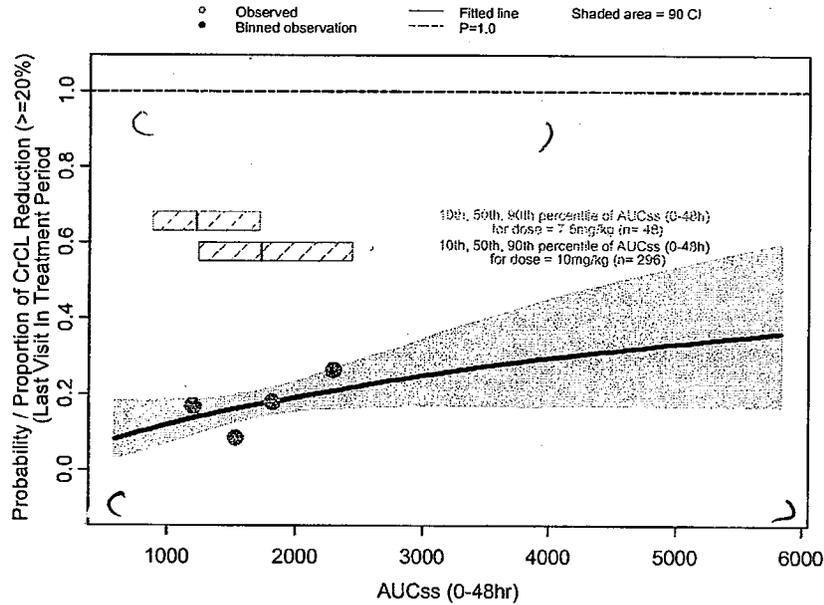
The model fitted curves were illustrated from Figure 33 and Figure 35. The model fitted curves sufficiently describe the observed data. We also identified the following:

- A slightly increased trend can be observed as higher telavancin exposure (AUC_{ss} (0-48)) yields relatively higher incidence of renal function reduction (defined as CrCL > 20% reduction from baseline) – the renal function reduction rate is about 13.7% when the exposure is 1225 ug/mL*hr (equivalent to the median exposure at the dose of 7.5 mg/kg), whereas the rate is increased to 17.4% when exposure is increased to 1731 ug/mL*hr (equivalent to the median exposure at the dose of 10 mg/kg) (Figure 33). This suggests that reducing dose from 10 mg/kg to 7.5 mg/kg

provides a slight reduction (4-5%) of risk for a patient to experience renal function reduction. However, this increased trend is not statistically significant ($P = 0.07$, OR = 1.76 with 95% CI (0.96 ~ 3.26)).

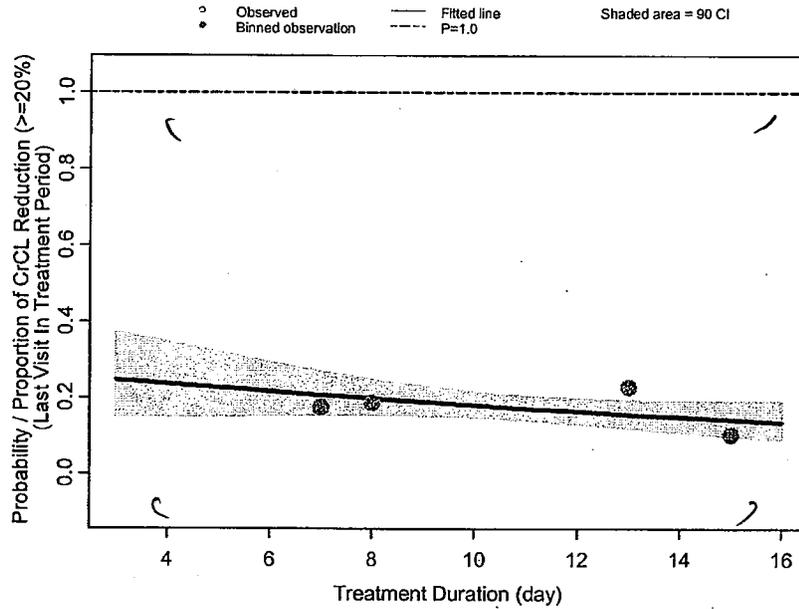
- The incidence of renal function reduction does not appear to be treatment duration dependent ($P=0.17$, OR = 0.94 with 95% CI (0.87 ~ 1.03)) (Figure 34). Therefore, increasing treatment duration does not appear to increase the risk for a patient to experience last renal function reduction rate.
- Baseline CrCL does not appear to be related to the renal function reduction based on the analysis ($P = 0.09$, OR = 0.99 with 95% CI (0.99 ~ 1.00)). This might be because that 1.) we truncated both baseline CrCL and CrCL where they are greater than 140, and 2.) we used percentage change from baseline CrCL in constructing the dataset.

Figure 33 Univariate logistic regression model fitting for last renal function reduction rate versus telavancin exposure (AUCss (0-48hr))



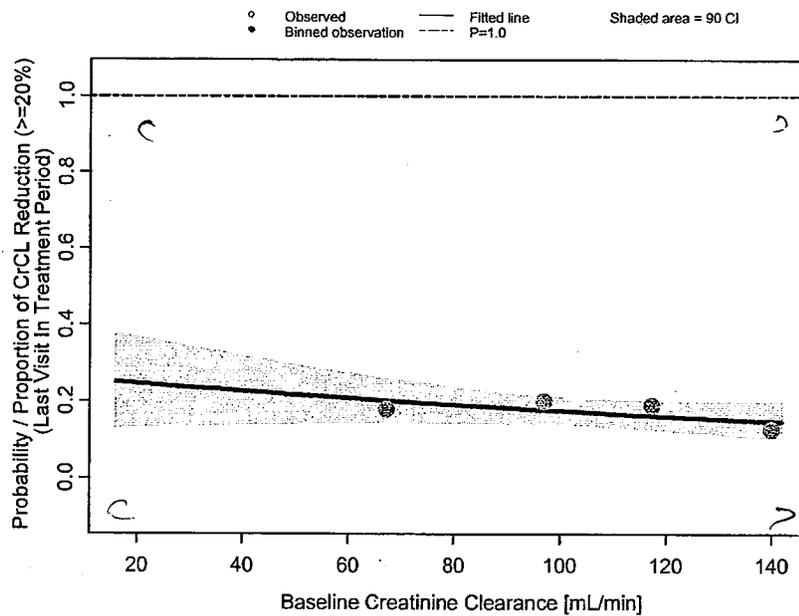
b(4)

Figure 34 Univariate logistic regression model fitting for last renal function reduction rate versus telavancin treatment duration



b(4)

Figure 35 Univariate logistic regression model fitting for last renal function reduction rate versus baseline CrCL



b(4)

Table 13 Univariate model parameter estimates for last renal function reduction rate versus telavancin exposure, treatment duration, and baseline CrCL

Model: Log (P/1-P) ~ Log₂ AUC_{ss} (0-48hr)				
Parameter	Estimate	P value	Odds ratio	95% CI
Intercept	-7.65	0.02	-	-
Log ₂ AUC _{ss} (0-48hr)	0.57	0.07 (#)	1.76	0.96 ~ 3.26
Model: Log(P/1-P) ~ Treatment duration				
Parameter	Estimate	P value	Odds ratio	95% CI
Intercept	-0.91	0.06	-	-
Treatment duration	-0.06	0.17 (#)	0.94	0.87 ~ 1.03
Model: Log(P/1-P) ~ Baseline CrCL				
Parameter	Estimate	P value	Odds ratio	95% CI
Intercept	-0.87	0.04	-	-
Baseline CrCL	-0.007	0.09 (#)	0.99	0.99 ~ 1.00

P: probability of subjects with $\geq 20\%$ reduction in CrCL comparing to baseline

#: No statistical significance ($\alpha = 0.05$).

7 PHARMACOMETRIC REVIEW CONCLUSIONS

The following summarizes the pharmacometric findings from telavancin exposure-effectiveness and exposure-renal toxicity analyses in PK subgroup.

The recommendations based on the telavancin exposure-effectiveness and -renal toxicity analyses, in the subgroup with PK measurements, are provided in this review.

Specifically, we found that:

- 10mg/kg dose, as proposed by the sponsor, is acceptable.
 - The clinical cure rate is similar between 7.5 mg/kg and 10 mg/kg groups. The exposures seem to be at the plateau region of the exposure-response curve.
 - Microbiological eradication rate is higher for the 10 mg/kg dose versus 7.5 mg/kg. The expected microbiological response rate for a patient with the exposure of 1239 mg*hr/mL (median exposure at the dose of 7.5 mg/kg) is 72.8%, whereas the response rate increased to 81.6% for a patient with the exposure of 1739 mg*hr/mL (median exposure at the dose of 10 mg/kg)
 - 10 mg /kg yields only marginally (and numerically) higher risk of renal function reduction (defined as at least 20% reduction in creatinine clearance from baseline at any time during the trial) compared to 7.5 mg/kg (14% vs. 17.6%).
- Treatment duration of 7-14 days is acceptable.
 - The clinical cure and microbiological eradication rates seem to have achieved the maximum between 7-14 days. Patients treated for less than 7 days have lower probability of treatment success.

8 APPENDICES

(None)

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

/s/

Hao Zhu
8/31/2007 09:06:11 AM
BIOPHARMACEUTICS

Jogarao Gobburu
8/31/2007 09:31:04 AM
BIOPHARMACEUTICS
Pharmacometrics Review (Also see Dr. Tworzyanski's ClinPharm review)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	22-110
Submission Date(s)	06DEC2006, 16MAR2007, 26APR2007, 22MAY2007, 16AUG2007, 27AUG2007
Brand Name	TBD
Generic Name	Telavancin
Primary Reviewer	Jeffrey J. Tworzyanski, Pharm.D.
Team Leader (Acting)	Charles R. Bonapace, Pharm.D.
Pharmacometrics Reviewer	Hao Zhu, Ph.D.
Pharmacometrics Team Leader	Jogaroo Gobburu, Ph.D.
Thorough QT Study Reviewer	Hao Zhu, Ph.D.
QT Secondary Reviewer	Christine Garnett, Pharm.D.
OCP Division	DCP4
OND Division	DAIOP
Applicant	Theravance, Inc., San Francisco, CA 94080
Relevant IND(s)	IND 60,237
Submission Type; Code	Original NDA, New Molecular Entity, Standard Review
Formulation; Strength(s)	Sterile lyophilized powder for injection, 250 mg and 750 mg vials
Indication	Treatment of patients with complicated skin and skin structure (cSSSI) infections caused by susceptible strains of designated microorganisms.

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1. EXECUTIVE SUMMARY

Theravance, Inc., submitted a New Drug Application for telavancin for injection on December 19, 2006. The FDA granted this submission a standard review cycle. Telavancin is a semisynthetic, lipoglycopeptide antibiotic that has *in vitro* activity against a broad range of clinically relevant aerobic and anaerobic Gram-positive bacterial pathogens. The mechanism of action of telavancin is by inhibition of bacterial cell wall synthesis and disruption of the functional integrity of the bacterial plasma membrane. Theravance is requesting approval for the indication of complicated skin and skin structure infections (cSSSI) caused by *Staphylococcus aureus* (methicillin-resistant and susceptible strains), *Streptococcus pyogenes*, *Enterococcus faecalis* (vancomycin-susceptible isolates only), *Streptococcus agalactiae*, and *Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius* and *S. constellatus*). The proposed intravenous dosage regimen is 10mg/kg infused over 60 minutes every 24 hours for 7 to 14 days depending upon the severity of the infection.

A total of 12 Phase 1 clinical pharmacology studies were conducted to investigate the single-dose and multiple-dose pharmacokinetics, metabolic disposition, effect of special populations (renal impairment and hepatic impairment), impact of age and gender, drug-drug interactions (piperacillin-tazobactam, aztreonam, and midazolam), and the potential of telavancin to prolong cardiac repolarization. Eleven of the Phase 1 studies were evaluated in this review; one study was not reviewed because it was not pertinent to this indication.

Two Phase 2 and two Phase 3 studies were submitted to support the safety and efficacy of telavancin for the treatment of cSSSI. Since sparse samples were obtained from all four studies, a population pharmacokinetic analysis was performed to compare the pharmacokinetics of telavancin in patients with infection to healthy subjects as well as assess the impact of covariates. In addition, an exposure-response analysis was conducted to evaluate the relationship between telavancin exposure and clinical & microbiological cure and renal toxicity. The results of this analysis support the sponsor's proposed dosage regimen of telavancin 10 mg/kg q24h and duration of therapy of 7-14 days for the treatment of cSSSI.

1.1. Recommendation

The Office of Translational Sciences, Office of Clinical Pharmacology, Division of Clinical Pharmacology 4 has reviewed NDA 22-110 and the submission is acceptable from a Clinical Pharmacology point of view.

The proposed labeling comments in Section 3 should to be communicated to the sponsor.

1.2. Phase IV Commitments

No Phase IV commitments are recommended.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Pharmacokinetics:**Distribution:**

Telavancin is approximately 90% plasma protein bound. The degree of penetration of telavancin into skin blister fluid was approximately 40% as measured by the ratio of the AUC in blister fluid to the AUC in serum.

Metabolism:

In vitro assays with human liver microsomes showed that none of the following CYP450 isoforms metabolized telavancin: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, and CYP4A11. Thus, the clearance of telavancin is not anticipated to be altered by inhibitors of these enzymes in vivo.

A metabolite of telavancin (AMI-11352) has been identified although its formation pathway has not been identified. In the mass balance study (Study 0027), the amount of AMI-11352 recovered in urine based on total radioactivity was 6-11% of the administered dose.

Excretion:

Telavancin is eliminated primarily by the kidney. In the mass balance study approximately 80% of the administered dose was recovered from the urine based upon total radioactivity and less than 1% was recovered from feces.

Intrinsic Factors:**Gender**

The impact of gender on the pharmacokinetics of telavancin was evaluated in 16 elderly male and female healthy subjects following administration of a single dose of telavancin 7.5 mg/kg infused over 60 minutes. The pharmacokinetics of telavancin were similar between male and female subjects. No dosage adjustment is recommended based on gender.

Age

A formal Phase 1 study evaluating the impact of age was not performed by the sponsor. The reviewer compared the pharmacokinetics of telavancin from healthy elderly male and female subjects to a control group (Study I6424-107a) of healthy young male and female subjects. The pharmacokinetics of telavancin were similar between young and elderly subjects. No dosage adjustment is recommended based on age.

Renal impairment

The impact of renal impairment on the pharmacokinetics of telavancin was investigated in a clinical study of 28 subjects with varying degrees of renal impairment. The mean clearance was 11%, 19%, and 55% lower in subjects with mild, moderate, and severe renal impairment, respectively compared to normal renal function. Among subjects with end-stage renal disease who received hemodialysis immediately following administration of telavancin, the mean plasma clearance was 40% lower than subjects with normal renal function. A dosage adjustment is recommended for patients with moderate renal impairment (7.5 mg/kg q24h) and severe renal impairment (10 mg/kg q48h).

Hepatic impairment

The impact of hepatic impairment on the pharmacokinetics of telavancin was investigated in a clinical study comparing eight adult subjects with normal hepatic function to eight adult subjects with moderate hepatic impairment (Childs-Pugh B). The mean clearance was 8% higher and $AUC_{0-\infty}$ 7% lower in subjects with moderate hepatic impairment compared subjects with normal hepatic function. No dosage adjustment is recommended for patients with mild or moderate hepatic impairment.

Extrinsic Factors:

In vitro metabolism studies with human liver microsomes demonstrated that telavancin is not an inhibitor of CYP450 1A2, 2C9, 2C19, 2D6, 3A4, 3A5, and 4A11 isoforms. Thus, telavancin is not anticipated to alter the clearance of co-administered drugs metabolized by one or more of these enzymes *in vivo*.

Aztreonam

The impact of telavancin on the pharmacokinetics of aztreonam and the impact of aztreonam on the pharmacokinetics of telavancin were assessed in a clinical study of 11 healthy subjects. Subjects received a single dose of telavancin 10 mg/kg alone, aztreonam 2 gm alone, and telavancin 10 mg/kg and aztreonam 2 gm in combination. Co-administration of aztreonam and telavancin did not significantly impact the C_{max} and $AUC_{0-\infty}$ of either drug. No dosage adjustments are recommended when aztreonam and telavancin are co-administered.

Piperacillin-Tazobactam

The impact of telavancin on the pharmacokinetics of piperacillin/tazobactam and the impact of piperacillin/tazobactam on the pharmacokinetics of telavancin were assessed in a clinical study of 12 healthy subjects. Subjects received a single dose of telavancin 10 mg/kg alone, piperacillin/tazobactam 4.5 gm alone, and telavancin 10 mg/kg and piperacillin/tazobactam 4.5 gm in combination. Co-administration of piperacillin/tazobactam and telavancin did not significantly impact the C_{max} and $AUC_{0-\infty}$ of any of the three drugs. No dosage adjustments are recommended when piperacillin/tazobactam and telavancin are co-administered.

Midazolam

The pharmacokinetics of midazolam and 1'-hydroxy-midazolam with and without coadministration of telavancin was evaluated in a clinical study of 16 subjects. A single dose of telavancin 10 mg/kg did not significantly impact the C_{max} and $AUC_{0-\infty}$ of midazolam and 1'-hydroxy-midazolam. No dosage adjustment of midazolam is recommended when co-administered with telavancin.

Cardiac Repolarization:

The sponsor conducted a thorough QT/QTc study to evaluate the effect of telavancin on cardiac repolarization following administration of 7.5 mg/kg q24h and 15 mg/kg q24h infused over 60 minutes for three days. At steady-state for both doses, the baseline- and placebo-corrected QTcF interval was lengthened greater than 10 msec. The expected mean change in the baseline- and placebo-corrected QTcF interval for the proposed clinical dose (10 mg/kg) is 12 to 15 msec.

Exposure-Response:

The exposure-effectiveness analysis found that the treatment duration of 7-14 days is acceptable. A sufficient duration of treatment is necessary to ensure the benefit of telavancin in terms of clinical cure rate and microbiological eradication rate. The exposure-response analysis showed that the microbiological eradication rate is higher for the 10mg/kg dose versus 7.5 mg/kg at the same treatment duration of 7-14 days. The exposure-renal function analysis showed that 10 mg/kg dose yields only a marginal increase (about 4%) risk of renal function reduction compared to the 7.5 mg/kg dose.

2. QUESTION BASED REVIEW

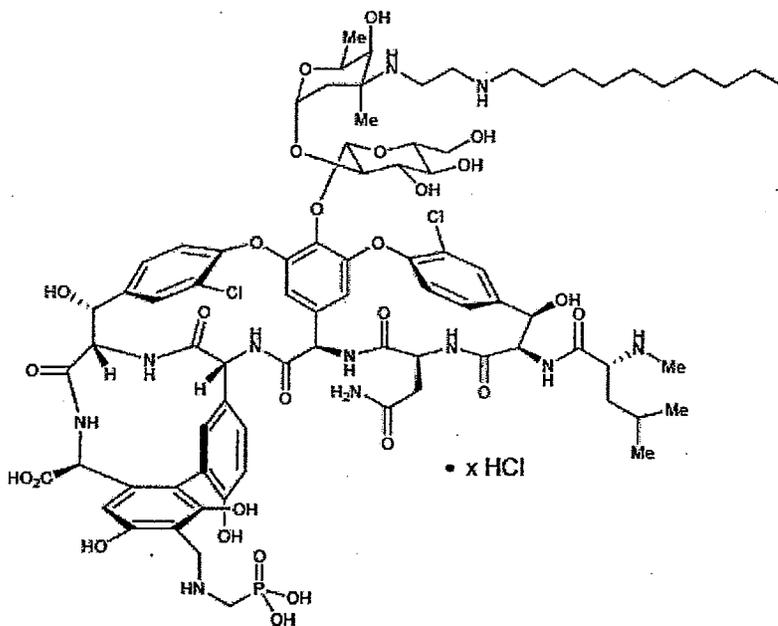
2.1. General Attributes of the Drug

2.1.1. *What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?*

Telavancin hydrochloride is derived from a synthetic modification of vancomycin and is a purified lipoglycopeptide antibacterial product. The chemical structure and physical-chemical properties of telavancin hydrochloride are described below.

Structural Formula: $C_{80}H_{106}Cl_2N_{11}O_{27}P \cdot xHCL$ (where $x=1-3$)

Chemical Structure:



Chemical Name:

Vancomycin, *N*3'-[2-(decylamino)ethyl]-29-[[[(phosphonomethyl)amino]methyl]-hydrochloride

Molecular Weight: 1755.63 (free base)

Solubility Profile:

Telavancin in water is classified as soluble at \rightarrow , slightly soluble at \dashrightarrow and very slightly soluble above pH 4.5.

b(4)

Drug Product:

Telavancin for injection is supplied as a sterile lyophilized powder for IV injection. The unit composition of telavancin for injection is presented in Table 1. The same formulation was used throughout the clinical development program (Phase 1, 2, and 3 clinical trials).

b(4)

Table 1. Unit Composition of Telavancin for Injection

Component	Reference to Quality Standard	Function / Explanatory Notes	Amount per 250 mg vial (mg)	Amount per 750 mg vial (mg)
Telavancin Hydrochloride (free base equivalent)	Theravance Specifications	Drug substance	250	750
Hydroxypropylbetadex ^a	Ph Eur		2500	7500
Mannitol	USP		312.5	937.5
Sodium Hydroxide	NF		q.s. ^b	q.s. ^b
Hydrochloric Acid ^b	NF		q.s. ^b	q.s. ^b
	USP			
	NF			
Total Weight				

b(4)

^a Also referred to as hydroxypropyl-beta-cyclodextrin, hydroxypropyl-β-cyclodextrin, HP-β-CD, HPBCD, HPbCD.

b(4)

^b reagent are added for pH adjustment to 4.5 as needed

2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

Telavancin is a semisynthetic, lipoglycopeptide antibiotic that has in vitro activity against aerobic Gram-positive pathogens including *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus*, *grp.* (including *S. anginosus*, *S. intermedius* and *S. constellatus*), and *Enterococcus faecalis* (vancomycin-susceptible isolates only). The bactericidal activity of telavancin is due to two mechanisms of action: 1) inhibition of bactericidal cell wall synthesis and 2) disruption of the functional integrity of the bacterial plasma membrane. Telavancin inhibits cell wall biosynthesis by binding to late-stage peptidoglycan precursors, including lipid II, which prevents both the polymerization of precursor into peptidoglycan and subsequent cross-linking events. Telavancin also binds to bacterial membranes and causes depolarization of membrane potential and an increase in membrane permeability. These actions of telavancin to inhibit protein, RNA and lipid synthesis consequently result in bacterial cell death. The proposed indication for telavancin is for the treatment of complicated skin and skin structure infections (cSSSI).

b(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?*

The primary efficacy variable in phase 2 and phase 3 studies was the clinical response (cure) rate at the Test of Cure (TOC) visit in the Clinically Evaluable (CE) Population. Intent-to-treat (ITT) analyses were performed as supportive efficacy analyses. Bacteriological response rates were evaluated in most of the studies. These endpoints are based on FDA guidelines for developing antimicrobial drugs for the treatment of cSSSI.

2.2.3. *Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?*

The known active moiety of telavancin hydrochloride is telavancin. An inactive metabolite AMI-11352 and \curvearrowright AMI-999 have been identified. Liquid Chromatography Mass Spectrometry (LC-MS/MS) and HPLC methods have been used exclusively for analysis of telavancin and metabolites. The assays are acceptable. See Section 2.6 for further details.

b(4)

2.2.4. *Exposure-Response*

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

The exposure-response relationship for telavancin has been evaluated using in vitro time-kill studies, in vivo animal models of infection, Monte Carlo simulations, and an exposure-response analysis based on the pharmacokinetic subgroup in the two Phase 3 clinical trials to evaluate the relationship between telavancin exposure and clinical & microbiologic cure.

2.2.4.1.1. *Time-Kill Studies*

Time-kill kinetic studies were performed to assess the bactericidal activity with static telavancin concentrations. With this method, both the extent and rate of bacterial killing can be measured. Clinical isolates of *S. aureus* from SSSI, wounds and respiratory sites were obtained from various sources and included 2 MSSA, 3 MRSA (one non-susceptible patient with daptomycin (DAPNS)) and a vancomycin intermediate *staphylococcus aureus* (VISA) strain. Additionally, a strain of *S. epidermidis* from a catheter-related bloodstream infection was included. Figures 1-3 show the bactericidal activity of telavancin against various strains of organisms. The graph on the left depicts bactericidal activity as a function of telavancin concentration and the graph on the right depicts the bactericidal activity of telavancin and comparator antibiotics at 8X their respective MIC as shown in Figure 1.

Figure 1. Bactericidal Activity of telavancin and Comparators against *S. aureus* ATC 29213

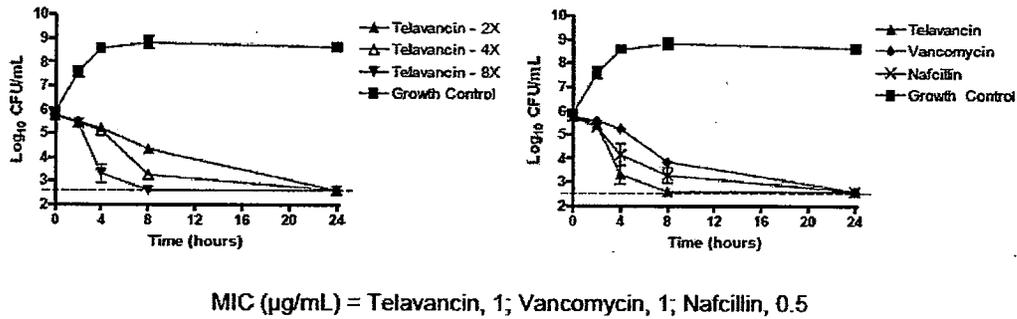


Figure 2. Bactericidal Activity of Telavancin and Comparators against MSSA H335629

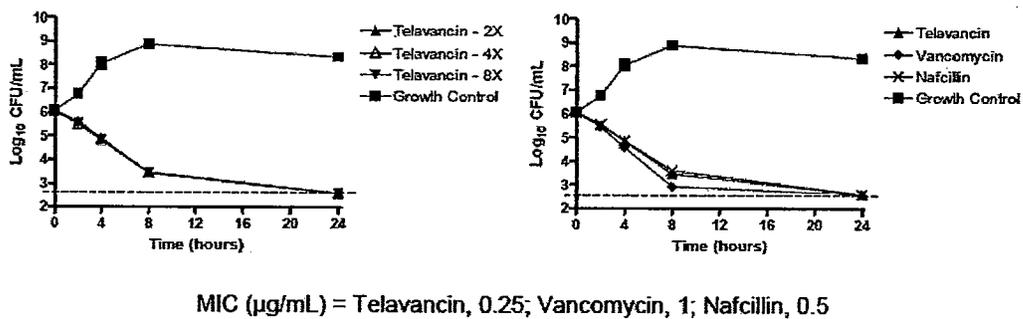
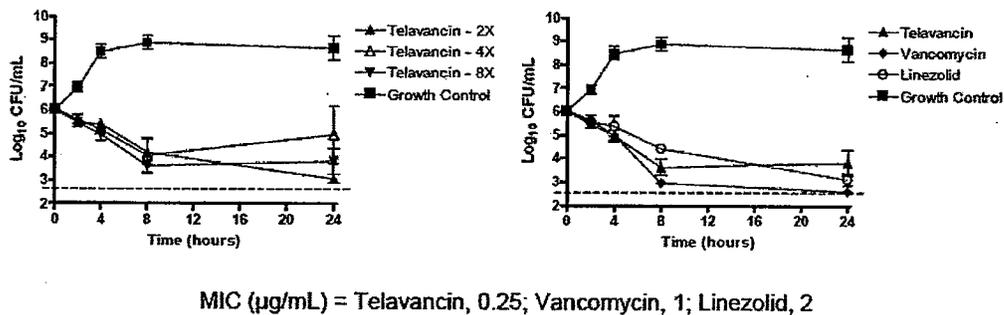


Figure 3. Bactericidal Activity of Telavancin and Comparators against MRSA 1345084



Telavancin MIC values increase by 1- to 2-doubling dilutions in the presence of 50% human serum or 40 mg/mL human serum albumin. Telavancin MBC values are within 1- to 2-doubling dilutions of the values obtained without added serum or serum proteins.

2.2.4.1.2. Animal Models of Infection

To determine possible PK/PD relationships for telavancin and clinical target PK/PD parameter(s), an efficacy study with telavancin against a single strain of *S. aureus* (telavancin MIC = 1 µg/mL) in the neutropenic mouse thigh infection model was utilized (Study 01-6424-PH-08). The pre-treatment thigh bacterial titer was 4.7 ± 0.3 log CFU/g. In vehicle treated controls the titer after 24h was 8.4 ± 0.3 log CFU/g. Figure 4 shows a dose-dependent reduction in thigh bacterial titer at 24 hrs when telavancin (1, 2, 3, 5, 10 and 15 mg/kg, IV) was dosed as a single dose (q24h), two divided doses (q12h), three divided doses (q8h) or four divided doses (q6h). The estimated ED₅₀s (95% CI) for telavancin were 3.8 (2.6-5.6), 2.8 (2.2-3.6), 3.8 (0.4-35.9) and 3.5 (2.8-4.3) at dosing regimens of q24h, q12h, q8h, q6h, respectively. Table 3 summarizes the PK/PD parameters at varying doses and dosing regimens of telavancin.

Figure 4. Effect of Dose-Fractionation on the Efficacy of Telavancin against MRSA 33591 in the Murine Neutropenic Thigh Model

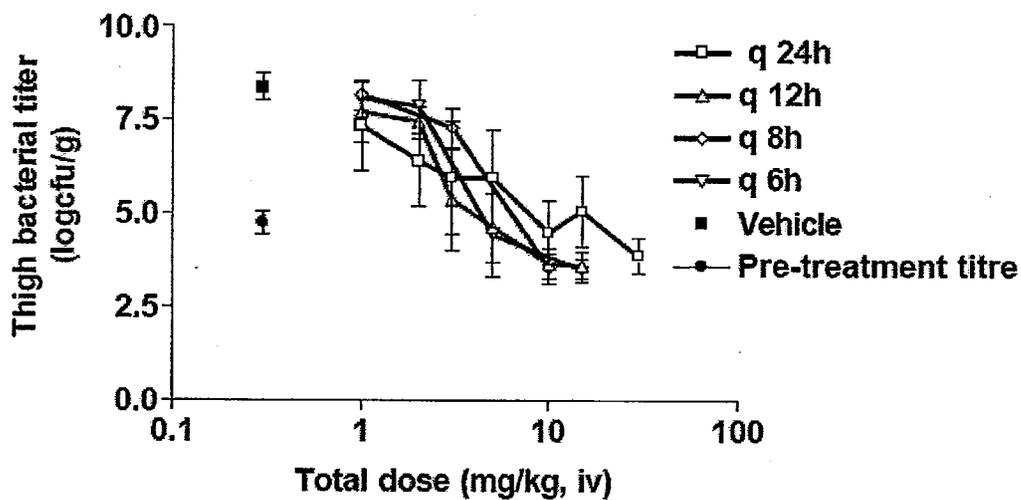


Table 3. The Pharmacodynamics (log CFU/g) and Pharmacokinetics (T>MIC; AUC) of Telavancin

Total Dose (mg/kg)	Log CFU/g	T>MIC (hr)	AUC (µg.hr/mL)
q 24 h			
1	7.328	1.5	8.1
2	6.415	2.25	20.6
3	5.942	3.25	32.25
5	5.935	4	49.6
10	4.484	14	107.5
15	5.027	17	189.4
30	3.848	24	322.5
q 12 h			
1	7.687	2	11.6
2	7.429	3	21.446
3	5.37	4.5	31.91
5	4.624	5.75	50.202
10	3.64	19.5	134.2
15	3.591	24	189.6
q 8 h			
1	8.165	2	11.9
3	7.272	6	32.3
10	3.513	20	134.4
q 6 h			
1	8.045	2	11.9
2	7.851	3	22
5	4.408	8.75	52
15	3.465	24	189

Figure 5 shows a relationship between log CFU/g and dose with an R^2 of 0.97. Figure 6 A, B, and C shows the relationship between three PK parameters (C_{max} , AUC and T > MIC) and log CFU/g. There was a correlation between C_{max} and log CFU/g ($R^2 = 0.66$). In contrast, a significant ($P < 0.01$) correlation was noted between AUC and T > MIC vs. log CFU/g ($R^2 = 0.94$ and 0.91 , respectively) which was described by a sigmoidal curve. These findings suggest that AUC is the primary pharmacodynamically linked variable. Since the telavancin MIC of the *S. aureus* isolate was 1 µg/mL, the AUC_{0-24}/MIC ratio (based on total telavancin concentrations) associated with maximal bacterial killing of this isolate is approximately 100.

Figure 5. Dose (mg/kg) vs log CFU/g of AMI-6424 Administered q24h

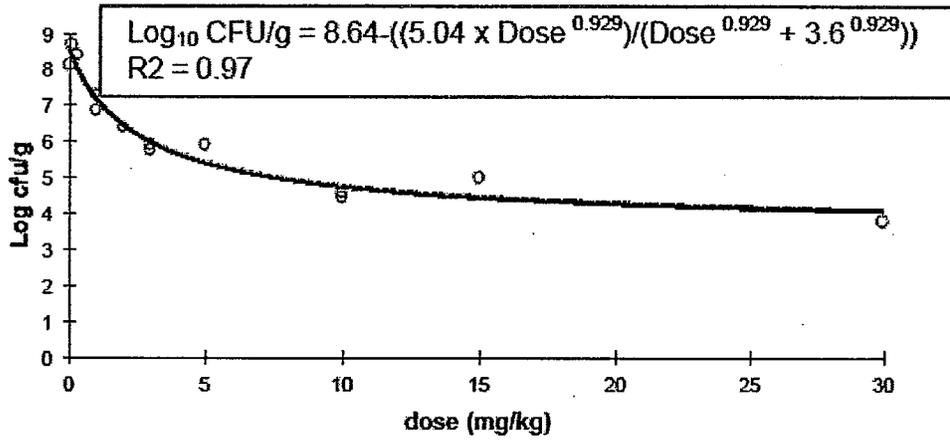


Figure 6. Relationship Between log CFU/g and C_{max} (A), AUC₀₋₂₄ (B), and T>MIC (C)

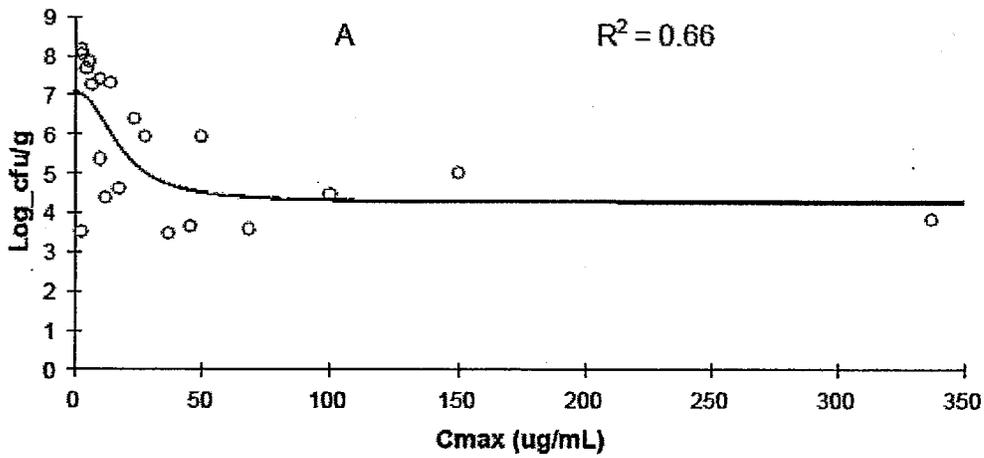
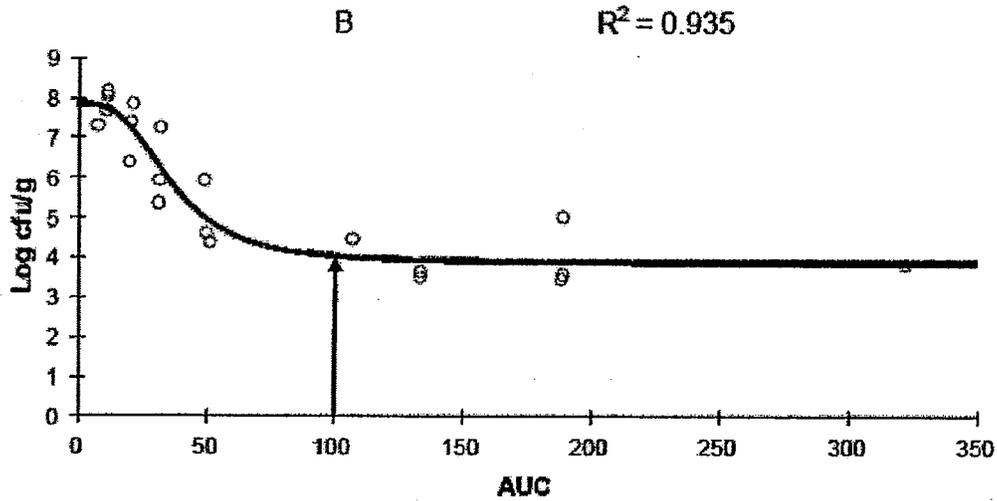
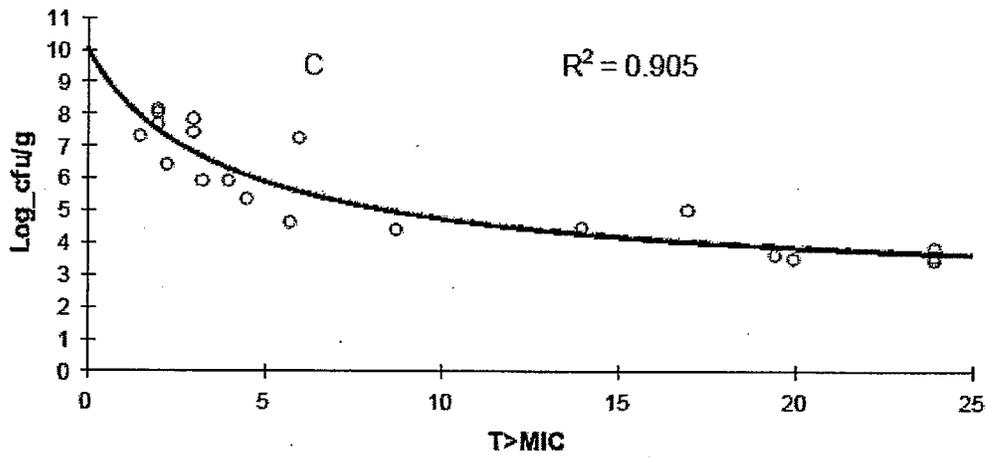


Figure 6 (con't). Relationship Between log CFU/g and C_{max} (A), AUC_{0-24} (B) and $T>MIC$ (C)



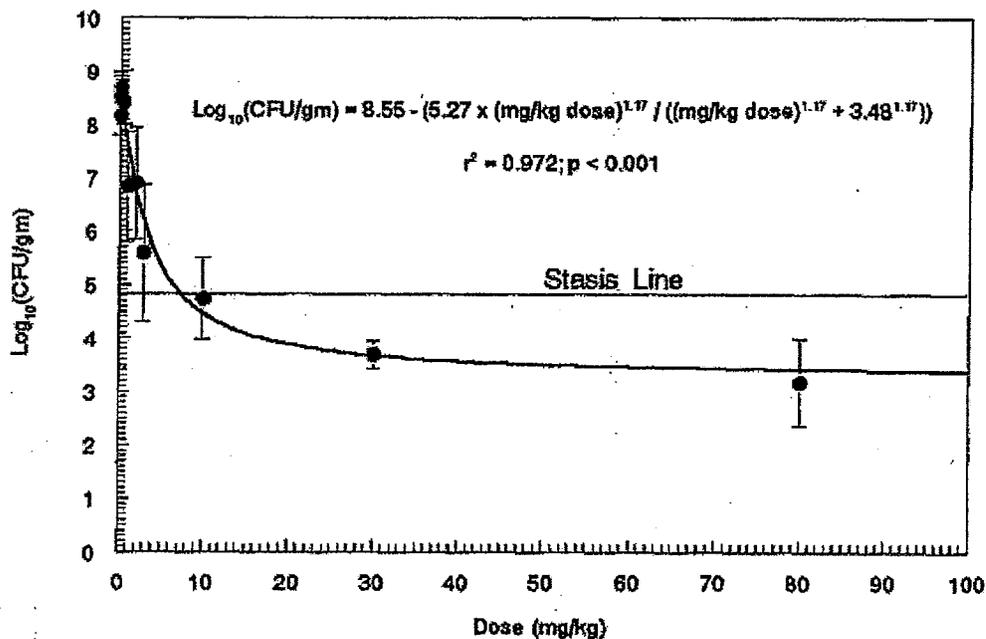
NOTE: The arrow above represents an AUC_{0-24}/MIC ratio of approximately 100 and was associated with maximal bacterial killing.



The sponsor conducted a study in a neutropenic mouse thigh infection model (Study 01-6424-PH02) to assess the relationship between telavancin dose and CFUs in thigh muscle. In this study, dose response experiments were carried out against MRSA ATCC 33591 resulting in the data displayed in Figure 7. A correlation was found between administered dose and reduction in thigh CFUs. The intravenous dose required for a 1 log₁₀ reduction in CFUs from the stasis line (i.e. log₁₀ 4.8 to 3.8) was approximately 24 mg/kg. An AUC₀₋₁ of 91 µg.hr/mL was observed following a 10 mg/kg dose in mice (Study 01-6424-PK-03). Therefore, the AUC₀₋₂₄ for a dose of 24 mg/kg in this species is estimated to be approximately 219 µg.hr/mL. Since the MIC of the strain of MRSA used in the thigh infection model (ATCC 33591) was 1 µg/mL, the AUC₀₋₂₄/MIC for a 1-log net reduction of the initial inoculum is 219.

Reviewer Note: This AUC₀₋₂₄/MIC ratio of 219 obtained from study Study 01-6424-PH02 is not consistent with the AUC₀₋₂₄/MIC ratio of 100 obtained from Study 01-6424-PH-08. Thus, the use of an AUC₀₋₂₄/MIC ratio of 100 would predict a dose lower than those evaluated in the Phase 3 clinical trials (7.5 and 10 mg/kg).

Figure 7. Telavancin Effect Against MRSA in a Mouse Thigh Model



The sponsor conducted an additional study (Study 01-6424-PH-09) to determine the efficacy of telavancin against multiple strains of clinically relevant gram positive organisms in the neutropenic mouse thigh infection model. In this study the sponsor used MRSA strain No. 33591 and MSSA strain No. 13709. Telavancin 0.1, 0.3, 1, 3, 10, and 50 mg/kg was administered once daily. Table 4 shows the telavancin doses required to attain a static effect (no net killing or regrowth), one log₁₀ net killing, and two log₁₀ net killing).

Table 4. Doses of AMI-6424 Required to Attain Different Pharmacodynamic Endpoints Against Multiple Gram Positive Organisms in the Mouse Neutropenic Thigh Model

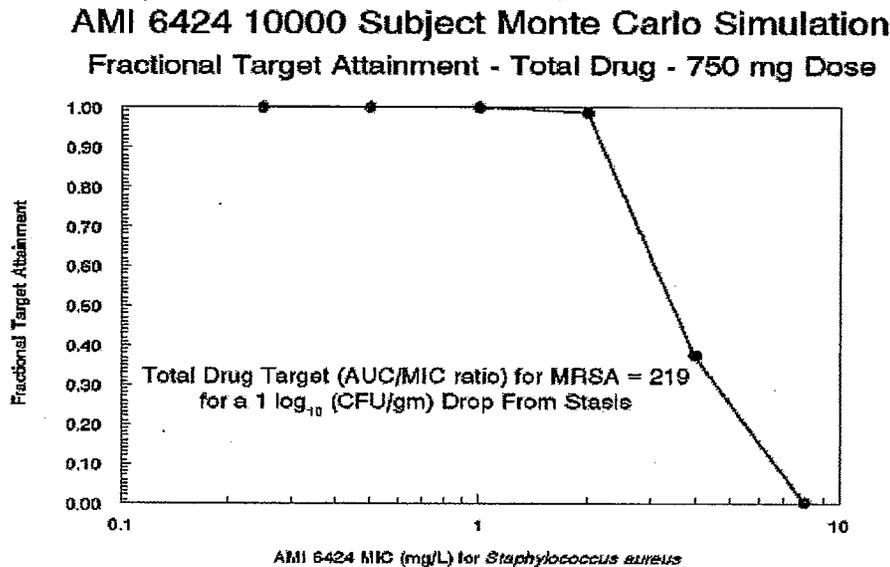
Organism	Doses of AMI-6424 (mg/kg, IV)				
	ED ₅₀	Stasis	1 log kill	2 log kill	3 log kill
MRSA 33591 (MIC 1 µg/ml)	2.5	6.3	27.5	-	-
MSSA 13709 (MIC 1 µg/ml)	1.7	2.5	5.5	58.9	

2.2.4.1.3. Monte-Carlo Simulations

Monte-Carlo simulations were performed by the sponsor to calculate the probability of attaining an AUC₀₋₂₄/MIC target of 219 with a fixed dose of telavancin (750 mg) over a range of MIC values. The sponsor states that the AUC₀₋₂₄/MIC target of 219 is required for a one log₁₀ reduction in CFUs against a MRSA strain with a MIC of 1 µg/mL in the murine neutropenic thigh model. However, the reviewer is unable to concur with this target and identified an AUC₀₋₂₄/MIC target of 100 associated with maximal killing (Figure 6) based on a single isolate of methicillin-resistant *Staphylococcus aureus*. The use of the higher AUC₀₋₂₄/MIC target (i.e., 219) would require a higher dose of telavancin to obtain the same probability of target attainment.

Monte Carlo simulations were performed for 10,000 simulated subjects to estimate the probability of target attainment (AUC₀₋₂₄/MIC target of 219) with a telavancin dose of 750 mg (approximately 10 mg/kg) against varying MIC values. Based on the Monte Carlo simulations, a 750 mg dose (approximately 10 mg/kg for average adult body weight) was associated with target attainment rates ≥ 99% for organisms with MIC values as high as 2 µg/mL (Figure 8). Since the protein binding of telavancin is similar in human and mouse plasma, the PK/PD analysis should support the dose evaluated in both Phase 3 clinical trials.

Figure 8. Fractional Target Attainment of One log₁₀ CFU/g Net Killing Based on the Total Drug Concentrations of Telavancin (AMI-6424) in Plasma



2.2.4.1.4. Summary of Efficacy

Below is a summary of terms describing the different patient populations used in the statistical analyses. The primary efficacy analysis in the pivotal Phase 3 clinical trials was the clinical cure rate at the test-of-cure (TOC) visit based on the clinically evaluable population.

All-Treated (AT) population: Comprised of all randomized patients with a confirmed cSSSI diagnosis who received at least one dose of study medication.

Modified All-Treated (MAT) population: Comprised of all patients in the AT population who also had a pathogen recovered from baseline cultures.

Clinically Evaluable (CE) population: Comprised of all patients in the AT population who (a) complied with all exclusion and inclusion criteria, or were approved for enrollment by the DCRI study physician and (b) had a clinical response (analysis value) of either “cure” or “failure”.

Microbiologically Evaluable (ME) population: Comprised of all patients in the CE population who also had a Gram-positive pathogen recovered from baseline cultures.

Phase 2 Studies:

Study I6424a-202a: A Phase 2, Randomized, Double-Blind, Multinational Trial of Intravenous TD-6424 versus Standard Therapy for Treatment of Complicated Gram-Positive Skin and Skin Structure Infections

Patients with complicated Gram-positive skin and skin structure infections were treated with telavancin 7.5 mg/kg/day IV Q24h or standard therapy, defined as vancomycin 1g q12h or an antistaphylococcal (semisynthetic) penicillin (nafcillin or oxacillin 2 g q6h IV or cloxacillin 0.5-1 g q6h IV). 200 patients were planned to be enrolled. A total of 169 patients were randomized, and of these 167 received study treatment (84 received telavancin, 83 received standard therapy). In the clinically evaluable (CE) population at the test of cure (TOC) visit, the clinical cure rate was 91.7% for telavancin (n=72) and 95.7% for standard therapy (n=69). In the microbiologically evaluable population at the TOC visit, the microbiological eradication rate for telavancin was 75% (n=48) versus (n=49) 84% for standard therapy.

Study I6424-202b: A phase 2, Randomized, Double-Blind, Multinational trial of Intravenous Telavancin versus Standard Therapy for Treatment of Complicated Gram-Positive Skin and Skin Structure Infections

Patients with complicated Gram-positive skin and skin structure infections were treated with telavancin or standard therapy, defined as vancomycin 1 g q12h or an antistaphylococcal penicillin. Under the original protocol, telavancin was administered at a dose of 7.5 mg/kg IV once daily. Patients enrolled after the approval of a protocol amendment were administered a telavancin dose of 10mg/kg IV once daily. The rationale for increasing the dose was based upon the results of Study I6424-202a in conjunction with the results of Monte Carlo demonstrating that a 750 mg dose was found to result in target attainment rates \geq 99% for organisms with MIC values as high as 2 μ g/ml. Up to 400 patients were to be enrolled Post Amendment. A total of 201 patients were randomized; of these 195 received study treatment (100 received telavancin, 95 received standard therapy). In the CE population at TOC, the clinical cure rate was 96.1% for telavancin (n=77) and 93.5% for standard therapy (n=77). In the ME population at TOC, the microbiological eradication rate (n=61) for telavancin was 93% versus 81% for standard therapy (n=53).

Phase 3 Studies:

Study 0017: A Phase 3, randomized, Double-Blind, Multinational trial of Intravenous Telavancin Versus Vancomycin for Treatment of Complicated Gram-Positive Skin and Skin Structure Infections with a Focus on Patients with Infections Due to Methicillin-resistant *Staphylococcus aureus* (primarily due to MRSA)

The patients were randomized to receive telavancin 10mg/kg IV once daily or vancomycin 1g IV q12. Approximately 750 patients were to be enrolled in order to obtain 600 clinically evaluable patients (300 per arm). A total of 862 patients were randomized into the study post amendment; of these 855 received at least one dose of study medication. In both treatment groups, the majority of patients received 7-14 days of study drug. In this study the primary efficacy analysis was to test both the clinical non inferiority and the superiority of telavancin to vancomycin with respect to clinical response at the Test of Cure assessment. For purposes of assessing clinical non-inferiority, both the AT and CE analysis populations were considered co-primary. For purposes of assessing clinical superiority, the AT population was of primary interest. Telavancin was demonstrated to be clinically non-inferior to vancomycin using the pre-specified non-inferiority margin of 10%, as evidenced by the lower bound of the 95% CI around the difference (telavancin-vancomycin) in cure rates being greater than -10%. For the primary efficacy parameter, Clinical Response at Test-of-Cure in the co-primary all treated (AT) Population, cure rates were 75.8% and 74.8% in the telavancin and vancomycin treatment groups, respectively, representing a difference of 1% (95% CI, -4.8% to 6.8%). Table 5 shows the efficacy parameters.

Table 5. Summary of Key Efficacy Parameters at Test-of Cure (Study 0017)

Efficacy Parameter	Analysis Population	Telavancin 10 mg/kg	Vancomycin	Diff (95% CI) [1]
		Number (%) of Patients		
Clinical Cure Rate	AT	N = 426 323 (75.8%)	N = 429 321 (74.8%)	1.0% (-4.8%, 6.8%)
	CE	N = 346 304 (87.9%)	N = 349 302 (86.5%)	1.3% (-3.6%, 6.3%)
Clinical Cure Rate by Pathogen	ME			
<i>Staphylococcus aureus</i>	-	N = 203 179 (88.2%)	N = 227 194 (85.5%)	2.7% (-3.7%, 9.1%)
MRSA	-	N = 116 101 (87.1%)	N = 138 118 (85.5%)	1.6% (-6.9%, 10.0%)
MSSA	-	N = 90 80 (88.9%)	N = 91 77 (84.6%)	4.3% (-5.6%, 14.1%)
<i>Streptococcus pyogenes</i>	-	N = 12 11 (91.7%)	N = 13 12 (92.3%)	-0.6% (-26.1%, 24.2%)
<i>Streptococcus agalactiae</i>	-	N = 10 9 (90%)	N = 5 4 (80%)	10.0% (-27.6%, 51.5%)
<i>Streptococcus anginosus</i>	-	N = 5 5 (100%)	N = 3 3 (100%)	
<i>Enterococcus faecalis</i>	-	N = 13 13 (100%)	N = 14 11 (78.6%)	21.4% (-6.4%, 43.0%)
By-Patient Microbiologic Eradication Rate	MAT	N = 307 240 (78.2%)	N = 322 241 (74.8%)	3.3% (-3.3%, 10.0%)
	ME	N = 237 212 (89.5%)	N = 255 219 (85.9%)	3.6% (-2.2%, 9.4%)
Overall Therapeutic Response Rate	MAT	N = 307 235 (76.5%)	N = 322 239 (74.2%)	2.3% (-4.4%, 9.1%)
	ME	N = 237 210 (88.6%)	N = 255 218 (85.5%)	3.1% (2.8%, 9.0%)

[1] Difference (telavancin – vancomycin); two-sided 95% CI

*All Treated (AT), Modified All Treated (MAT), Clinically Evaluable (CE), Microbiologically Evaluable (ME)

Study 0018: A Phase 3, randomized, Double-Blind, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Complicated Gram-Positive Skin and Skin Structure Infections with a focus on Patients with Infections Due to Methicillin-resistant *Staphylococcus aureus* (primarily due to MRSA)

The patients were randomized to receive either telavancin 10mg/kg IV once daily or vancomycin 1g q12h. A total of 1035 patients were randomized into this study post amendment; of these 1012 received at least one dose of study medication. Of the 1012 patients randomized into the study to receive drug, there were 502 in the telavancin treatment group and 510 in the vancomycin treatment group. The primary efficacy analysis was to test both the clinical non inferiority and the superiority of telavancin to vancomycin with respect to clinical response at the Test of Cure assessment. For purposes of assessing clinical non-inferiority, both the AT and CE populations were considered co-primary. For purposes of assessing clinical superiority, the AT population was of primary interest. The telavancin and vancomycin groups were comparable with regard to the percentage of patients included in each efficacy analysis population, overall and in each randomization stratum per the sponsor. Telavancin 10 mg/kg IV

administered once daily was effective in treating complicated skin and skin structure infections caused by Gram-positive pathogens. For the primary efficacy parameter, Clinical Response at Test-of-Cure in the co-primary AT Population, cure rates were 77.1% and 73.7% in the telavancin and vancomycin treatment groups, respectively (difference, 3.4%; 95% CI, -1.9% to 8.7%). Table 6 shows the efficacy parameters.

Table 6. Summary of Key Efficacy Parameters at Test-of Cure (Study 0018)

Efficacy Parameter	Analysis Population	Telavancin 10 mg/kg	Vancomycin	Diff (95% CI) [1]
		Number (%) of Patients		
Clinical Cure Rate	AT	N = 502 387 (77.1%)	N=510 376 (73.7%)	3.4% (-1.9%, 8.7%)
	CE	N = 399 354 (88.7%)	N = 395 346 (87.6%)	1.1% (-3.4%, 5.6%)
Clinical Cure Rate by Pathogen	ME			
<i>Staphylococcus aureus</i>	-	N = 253 231 (91.3%)	N = 246 217 (88.2%)	3.1% (-2.2%, 8.4%)
MRSA	-	N = 162 151 (93.2%)	N = 163 142 (87.1%)	6.1% (-0.3%, 12.5%)
MSSA	-	N = 91 80 (87.9%)	N = 85 77 (90.6%)	-2.7% (-11.9%, 6.8%)
<i>Streptococcus pyogenes</i>	-	N = 11 10 (90.9%)	N = 12 11 (91.7%)	-0.8% (-27.9%, 25.7%) ^a
<i>Streptococcus agalactiae</i>	-	N = 9 6 (66.7%)	N = 14 13 (92.9%)	-26.2% (-56.6%, 8.9%) ^b
<i>Streptococcus anginosus</i>	-	N = 6 6 (100%)	N = 5 5 (100%)	--
<i>Enterococcus faecalis</i>	-	N = 14 12 (85.7%)	N = 20 17 (85%)	0.7% (-25.6%, 24.4%)
By-Patient Microbiologic Eradication Rate	MAT	N = 373 287 (76.9%)	N=381 285 (74.8%)	2.1% (-4.0%, 8.2%)
	ME	N = 290 261 (90.0%)	N = 281 249 (88.6%)	1.4% (-3.7%, 6.5%)
Overall Therapeutic Response Rate	MAT	N = 373 281 (75.3%)	N = 381 276 (72.4%)	2.9% (-3.4%, 9.2%)
	ME	N = 290 257 (88.6%)	N = 281 244 (86.8%)	1.8% (-3.6%, 7.2)

[1] Difference (telavancin – vancomycin); two-sided 95% CI

*All Treated (AT), Modified All Treated (MAT), Clinically Evaluable (CE), Microbiologically Evaluable (ME)

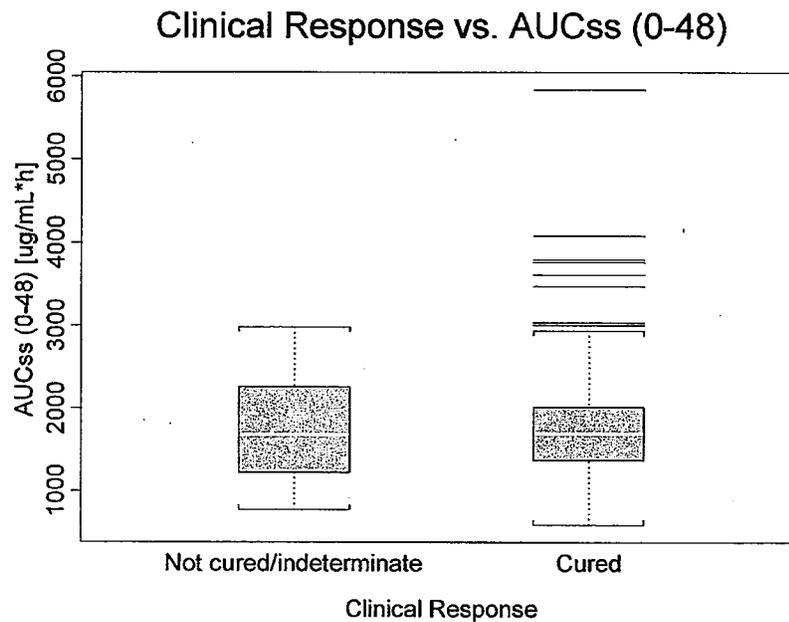
2.2.4.1.5. Exploratory PK/PD Analyses

An exposure-response analysis was performed on the pharmacokinetic subgroup in the two pivotal Phase 3 clinical trials (Studies 0017 and 0018) to evaluate the relationship between telavancin exposure (AUC_{0-48} based on total concentrations or duration of therapy) and clinical & microbiologic cure and renal toxicity. In the exposure-response analysis for efficacy, the telavancin exposure was measured by the steady state AUC over 48 hours (AUC_{0-48}). Efficacy was measured by the clinical cure rate (primary efficacy variable in the sponsor's analysis) and the microbiological eradication rate (the secondary efficacy variable in the sponsor's analysis). The following is summarized from the Pharmacometric review.

1. Exposure-clinical response rate analysis

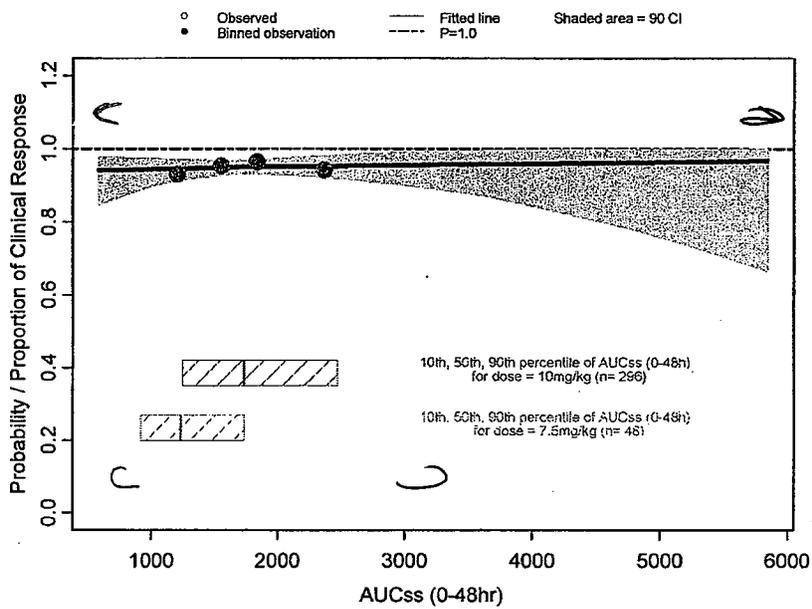
Based on the Phase 3 protocols, the clinical response was defined as “cured”, “not cured”, “indeterminate”, and “missing”. In the exposure-response analysis for clinical efficacy, patient’s with an outcome of “indeterminate” and “missing” were pooled with patient’s who had an outcome of “not cured”. Similar AUC_{0-48} values were observed in patients who were cured as compared to those patients who were not cured at the TOC visit (primary endpoint, Figure 9).

Figure 9. AUC_{0-48} distribution for the patients who were cured as compared to those who were not cured at the TOC visit



A logistic regression model was used to characterize the telavancin exposure (AUC_{0-48}) and clinical cure rate relationship. The model fitted curve is shown in Figure 10 and sufficiently describes the observed data. No trend between clinical response rate and telavancin exposure could be identified. The 10th, 50th, and 90th percentile of telavancin exposure following administration of telavancin 7.5 mg/kg and 10 mg/kg are illustrated as boxes in the plot. No appreciable difference in the clinical response rate could be shown for telavancin 10 mg/kg q24h (proposed dosage regimen) compared to 7.5 mg/kg q24h.

Figure 10. Logistic regression model fitting for clinical response and telavancin exposure (AUC₀₋₄₈)



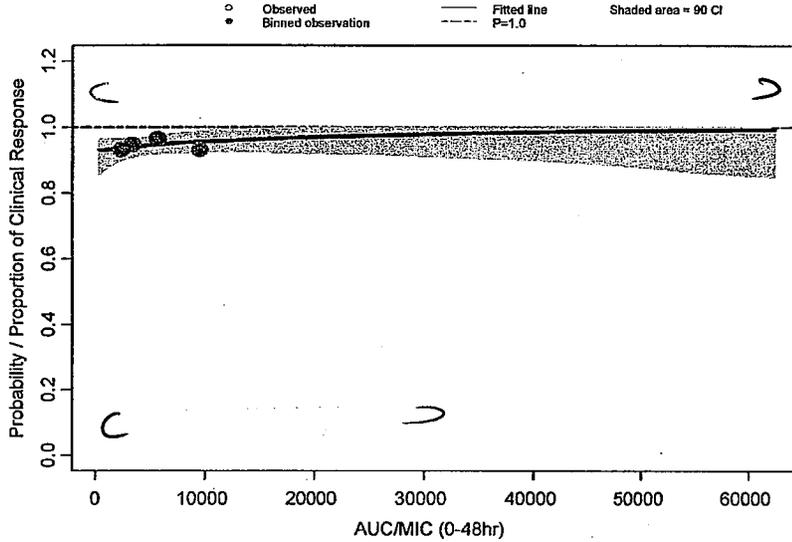
b(4)

Univariate logistic regression was used to characterize the telavancin exposure (AUC₀₋₄₈/MIC) and clinical cure rate relationship. The MIC distribution in the analysis dataset derived from Studies 0017 and 0018 is presented in Table 7. The modeling results are presented in Figure 11. The AUC₀₋₄₈/MIC as the exposure measure did not explain any more variability in the exposure-response relationships compared to AUC₀₋₄₈ alone. Thus, telavancin 10 mg/kg q24h does not appear to provide any additional benefit compared to telavancin 7.5 mg/kg q24h in terms of the clinical cure rate.

Table 7. Baseline MIC distribution in the analysis dataset from Studies 0017 and 0018 (MIC values from 230 patients with PK data)

GROUP	1	2	3	4	5	6	7
MIC (mcg/ml)	4	1	0.5	0.25	0.12	0.06	0.03
Percentage	0.40%	6.10%	51.70%	36.10%	2.20%	2.60%	0.90%

Figure 11. AUC₀₋₄₈/MIC versus clinical cure rate relationship

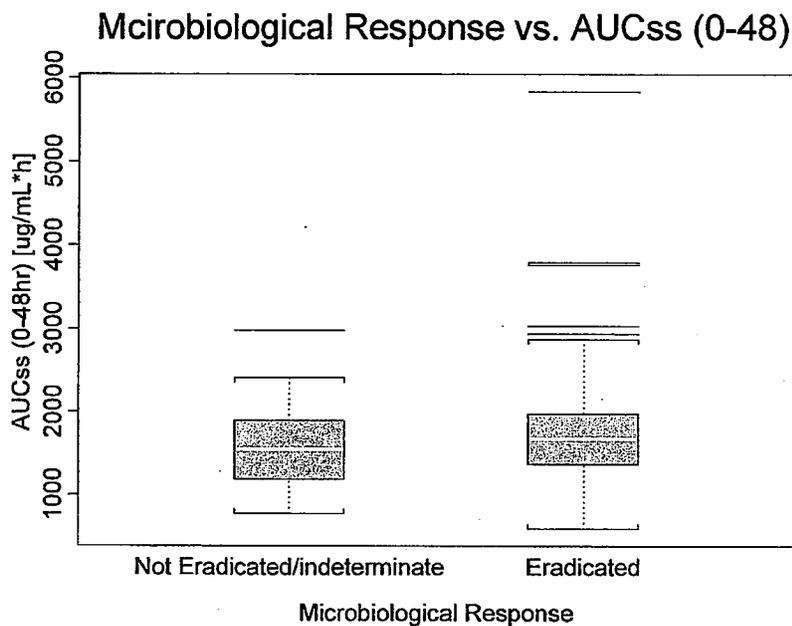


b(4)

2. Exposure-microbiological response rate analysis

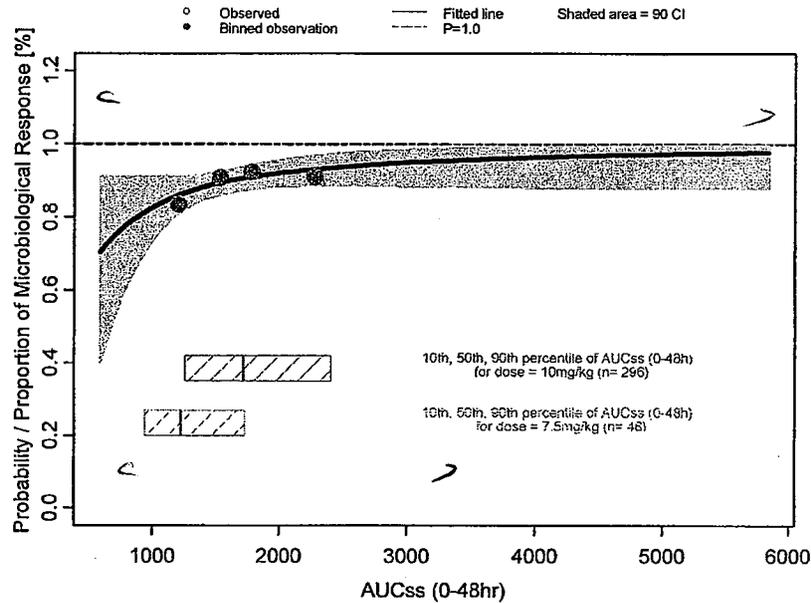
Based on the Phase 3 protocols, the microbiological response rate was defined as microbiological eradication rate. Microbiological response at the TOC visit was used as the secondary effectiveness variable in the pivotal Phase 3 trials conducted by the sponsor. The microbiological response was defined as “eradicated”, “not eradicated”, and “indeterminate”. In the exposure-response analysis for microbiologic efficacy, patients with an outcome of “indeterminate” were pooled with patients with an outcome of “not eradicated”. As previously shown for clinical response, similar AUC₀₋₄₈ values were observed in patients whose organisms were eradicated as compared to those patients whose organisms were not eradicated at the TOC visit (Figure 12).

Figure 12. AUC₀₋₄₈ distribution from patients whose organisms were eradicated as compared to those patients whose organisms were not eradicated at the TOC visit



Univariate logistic regression was used to further identify the relationship between the microbiological response rate and telavancin exposure (Figure 13). The fitted curve describes the observed data well. A trend toward a higher microbiological response rate was identified with higher telavancin exposures. Thus, telavancin 10 mg/kg q24h results in a higher microbiological eradication rate than telavancin 7.5 mg/kg q24h.

Figure 13. Univariate logistic regression model fitting for microbiological response versus telavancin exposure (AUC₀₋₄₈)



b(4)

2.2.4.2. *What are the characteristics of exposure-response relationships (dose-response, concentration-response) for safety?*

An integrated assessment of safety data from the Phase 1 clinical pharmacology and biopharmaceutics studies for telavancin reports the most frequently reported treatment-emergent adverse events were dysgeusia (53%) [described as metallic or soapy taste], urine abnormality (15%) [described as foamy urine], headache (15%), nausea (13%), and somnolence (8%) were the most frequently reported treatment-emergent adverse events among subjects treated with telavancin in the clinical pharmacology studies. Of these events, urine abnormality (generally referred to foaming in the bowl on urination) was considered to be related to the presence in the urine of hydroxypropylbetadex from the vehicle for telavancin. An integrated assessment of safety data from the Phase 2 and 3 clinical studies for telavancin shows that the overall incidence of treatment-emergent adverse events, 77% in the telavancin group and 71% in the vancomycin group, was generally similar between treatment groups in the efficacy and safety studies in cSSSI, with most adverse events being mild or moderate in intensity. Overall, fewer than 10% of patients in either treatment group experienced a treatment-emergent event that was severe. The only two treatment-emergent adverse events that exhibited a strong suggestion of a dose response between telavancin 7.5mg/kg and telavancin 10 mg/kg were dysgeusia (11% versus 32%) and urine abnormality (3% versus 12%). Dysgeusia, nausea, headache, vomiting and urine abnormality were the most frequently reported (>10%) treatment-emergent adverse events in patients treated with telavancin overall in these studies. Table 8 shows the treatment-emergent adverse events in the efficacy and safety studies of telavancin.

Table 8. Treatment-Emergent Adverse Events with an Incidence of $\geq 1\%$ in Telavancin or Vancomycin (Based on Total Column)-All Efficacy and Safety Studies in cSSSI-Safety Population

MedDRA System Organ Class/ Preferred Term Number (%) of Patients	Studies 0017, 0018, 202b Original Protocol and 202a				Studies 0017, 0018, 202b Post-Amendment				All Efficacy and Safety Studies in cSSSI			
	TLV 7.5 mg/kg (N=192)		Vanc ¹ (N=189)		TLV 10 mg/kg (N=1029)		Vanc ¹ (N=1033)		TLV (N=1221)		Vanc ¹ (N=1222)	
Any event	144	(75)	138	(73)	791	(77)	730	(71)	935	(77)	868	(71)
BLOOD AND LYMPHATIC SYSTEM DISORDERS												
Any event	10	(5)	6	(3)	37	(4)	37	(4)	47	(4)	43	(4)
ANAEMIA	6	(3)	4	(2)	26	(3)	22	(2)	32	(3)	26	(2)
GASTROINTESTINAL DISORDERS												
Any event	73	(38)	70	(37)	422	(41)	328	(32)	495	(41)	398	(33)
ABDOMINAL PAIN	5	(3)	5	(3)	17	(2)	26	(3)	22	(2)	31	(3)
ABDOMINAL PAIN UPPER	0		2	(1)	8	(<1)	16	(2)	8	(<1)	18	(1)
CONSTIPATION	14	(7)	11	(6)	101	(10)	68	(7)	115	(9)	79	(6)
DIARRHOEA	9	(5)	12	(6)	73	(7)	81	(8)	82	(7)	93	(8)
DRY MOUTH	4	(2)	2	(1)	21	(2)	22	(2)	25	(2)	24	(2)
DYSPEPSIA	6	(3)	5	(3)	21	(2)	25	(2)	27	(2)	30	(2)
LOOSE STOOLS	1	(<1)	2	(1)	11	(1)	13	(1)	12	(<1)	15	(1)
NAUSEA	48	(25)	40	(21)	265	(26)	148	(14)	313	(26)	188	(15)
VOMITING	21	(11)	17	(9)	135	(13)	75	(7)	156	(13)	92	(8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS												
Any event	42	(22)	39	(21)	250	(24)	226	(22)	292	(24)	265	(22)
ASTHENIA	1	(<1)	2	(1)	13	(1)	16	(2)	14	(1)	18	(1)
FATIGUE	5	(3)	3	(2)	42	(4)	31	(3)	47	(4)	34	(3)
INFUSION SITE ERYTHEMA	3	(2)	4	(2)	26	(3)	27	(3)	29	(2)	31	(3)
INFUSION SITE PAIN	6	(3)	6	(3)	42	(4)	40	(4)	48	(4)	46	(4)
INFUSION SITE PHLEBITIS	0		0		19	(2)	21	(2)	19	(2)	21	(2)
INFUSION SITE PRURITUS	1	(<1)	0		9	(<1)	18	(2)	10	(<1)	18	(1)
INFUSION SITE REACTION	1	(<1)	0		14	(1)	14	(1)	15	(1)	14	(1)
NON-CARDIAC CHEST PAIN	2	(1)	1	(<1)	16	(2)	12	(1)	18	(1)	13	(1)
OEDEMA PERIPHERAL	5	(3)	2	(1)	13	(1)	14	(1)	18	(1)	16	(1)
PYREXIA	4	(2)	2	(1)	17	(2)	16	(2)	21	(2)	18	(1)
RIGORS	7	(4)	4	(2)	47	(5)	23	(2)	54	(4)	27	(2)
INFECTIONS AND INFESTATIONS												
Any event	27	(14)	23	(12)	138	(13)	101	(10)	165	(14)	124	(10)
URINARY TRACT INFECTION	6	(3)	5	(3)	20	(2)	9	(<1)	26	(2)	14	(1)
VAGINAL MYCOSIS	3	(2)	0		10	(<1)	13	(1)	13	(1)	13	(1)
INVESTIGATIONS												
Any event	30	(16)	29	(15)	74	(7)	93	(9)	104	(9)	122	(10)
ALANINE AMINOTRANSFERASE INCREASED	7	(4)	14	(7)	11	(1)	17	(2)	18	(1)	31	(3)
ASPARTATE AMINOTRANSFERASE INCREASED	9	(5)	16	(8)	11	(1)	13	(1)	20	(2)	29	(2)

Table 8 (cont'd.). Treatment-Emergent Adverse Events with an Incidence of $\geq 1\%$ in Telavancin or Vancomycin (Based on Total Column)-All Efficacy and Safety Studies in cSSSI-Safety Population

MedDRA System Organ Class/ Preferred Term Number (%) of Patients	Studies 0017, 0018, 202b Original Protocol and 202a				Studies 0017, 0018, 202b Post-Amendment				All Efficacy and Safety Studies in cSSSI			
	TLV 7.5 mg/kg (N=192)		Vanc ¹ (N=189)		TLV 10 mg/kg (N=1029)		Vanc ¹ (N=1033)		TLV (N=1221)		Vanc ¹ (N=1222)	
BLOOD CREATININE INCREASED	4	(2)	2	(1)	14	(1)	6	(<1)	18	(1)	8	(<1)
METABOLISM AND NUTRITION DISORDERS												
Any event	25	(13)	15	(8)	96	(9)	92	(9)	121	(10)	107	(9)
ANOREXIA	4	(2)	3	(2)	17	(2)	11	(1)	21	(2)	14	(1)
DECREASED APPETITE	1	(<1)	0		27	(3)	19	(2)	28	(2)	19	(2)
HYPOGLYCAEMIA	2	(1)	1	(<1)	18	(2)	11	(1)	20	(2)	12	(<1)
HYPOKALAEMIA	8	(4)	1	(<1)	11	(1)	23	(2)	19	(2)	24	(2)
HYPOMAGNESAEMIA	3	(2)	6	(3)	8	(<1)	16	(2)	11	(<1)	22	(2)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS												
Any event	12	(6)	18	(10)	77	(7)	75	(7)	89	(7)	93	(8)
ARTHRALGIA	5	(3)	0		20	(2)	13	(1)	25	(2)	13	(1)
BACK PAIN	4	(2)	3	(2)	20	(2)	17	(2)	24	(2)	20	(2)
PAIN IN EXTREMITY	1	(<1)	6	(3)	13	(1)	12	(1)	14	(1)	18	(1)
NERVOUS SYSTEM DISORDERS												
Any event	61	(32)	38	(20)	441	(43)	240	(23)	502	(41)	278	(23)
DIZZINESS	15	(8)	6	(3)	58	(6)	55	(5)	73	(6)	61	(5)
DYSGEUSIA	21	(11)	5	(3)	325	(32)	62	(6)	346	(28)	67	(5)
HEADACHE	26	(14)	20	(11)	138	(13)	124	(12)	164	(13)	144	(12)
HYPOAESTHESIA	3	(2)	6	(3)	6	(<1)	12	(1)	9	(<1)	18	(1)
PARAESTHESIA	3	(2)	4	(2)	6	(<1)	12	(1)	9	(<1)	16	(1)
SOMNOLENCE	3	(2)	3	(2)	11	(1)	6	(<1)	14	(1)	9	(<1)
PSYCHIATRIC DISORDERS												
Any event	38	(20)	30	(16)	151	(15)	137	(13)	189	(15)	167	(14)
AGITATION	5	(3)	8	(4)	9	(<1)	8	(<1)	14	(1)	16	(1)
ANXIETY	11	(6)	10	(5)	27	(3)	22	(2)	38	(3)	32	(3)
INSOMNIA	23	(12)	17	(9)	103	(10)	89	(9)	126	(10)	106	(9)
RENAL AND URINARY DISORDERS												
Any event	19	(10)	13	(7)	181	(18)	66	(6)	200	(16)	79	(6)
HAEMATURIA	3	(2)	2	(1)	12	(1)	3	(<1)	15	(1)	5	(<1)
RENAL INSUFFICIENCY	3	(2)	0		10	(<1)	2	(<1)	13	(1)	2	(<1)
URINE ABNORMALITY	6	(3)	4	(2)	125	(12)	27	(3)	131	(11)	31	(3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS												
Any event	29	(15)	13	(7)	112	(11)	88	(9)	141	(12)	101	(8)
COUGH	5	(3)	3	(2)	19	(2)	21	(2)	24	(2)	24	(2)
DYSPNOEA	8	(4)	3	(2)	17	(2)	12	(1)	25	(2)	15	(1)
PHARYNGOLARYNGEAL PAIN	2	(1)	1	(<1)	23	(2)	18	(2)	25	(2)	19	(2)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS												
Any event	34	(18)	40	(21)	175	(17)	262	(25)	209	(17)	302	(25)
DRY SKIN	0		5	(3)	8	(<1)	11	(1)	8	(<1)	16	(1)
ERYTHEMA	2	(1)	3	(2)	9	(<1)	19	(2)	11	(<1)	22	(2)
HYPERHIDROSIS	4	(2)	5	(3)	16	(2)	13	(1)	20	(2)	18	(1)
PRURITUS	14	(7)	14	(7)	60	(6)	128	(12)	74	(6)	142	(12)
PRURITUS GENERALISED	4	(2)	4	(2)	28	(3)	60	(6)	32	(3)	64	(5)
RASH	6	(3)	4	(2)	37	(4)	43	(4)	43	(4)	47	(4)
RASH GENERALISED	0		1	(<1)	6	(<1)	12	(1)	6	(<1)	13	(1)
VASCULAR DISORDERS												
Any event	13	(7)	18	(10)	64	(6)	72	(7)	77	(6)	90	(7)
FLUSHING	1	(<1)	3	(2)	10	(<1)	16	(2)	11	(<1)	19	(2)
HYPERTENSION	4	(2)	5	(3)	16	(2)	14	(1)	20	(2)	19	(2)
HYPOTENSION	7	(4)	4	(2)	19	(2)	13	(1)	26	(2)	17	(1)

¹Includes 27 patients (20 in 202a and 7 in 202b Post-Amendment) who received an antistaphylococcal penicillin instead of vancomycin

Exposure-response relationship for renal toxicity

An exposure-response analysis was performed to assess the relationship between telavancin exposure (AUC_{0-48}) or duration of therapy and renal toxicity. For the analysis, renal toxicity was defined as at least a 20% reduction in creatinine clearance (CrCL) compared to the baseline CrCL. All CrCL values greater than 140 mL/min were treated as 140 mL/min.

The exposure-renal function reduction analysis was performed using two scenarios. In the first scenario, the analysis was performed using the lowest CrCL value observed during the treatment and follow-up periods (worst CrCL scenario). In the second occasion, the analysis was performed using the last CrCL value observed during the treatment period (last CrCL scenario). The findings of the two analyses are discussed below.

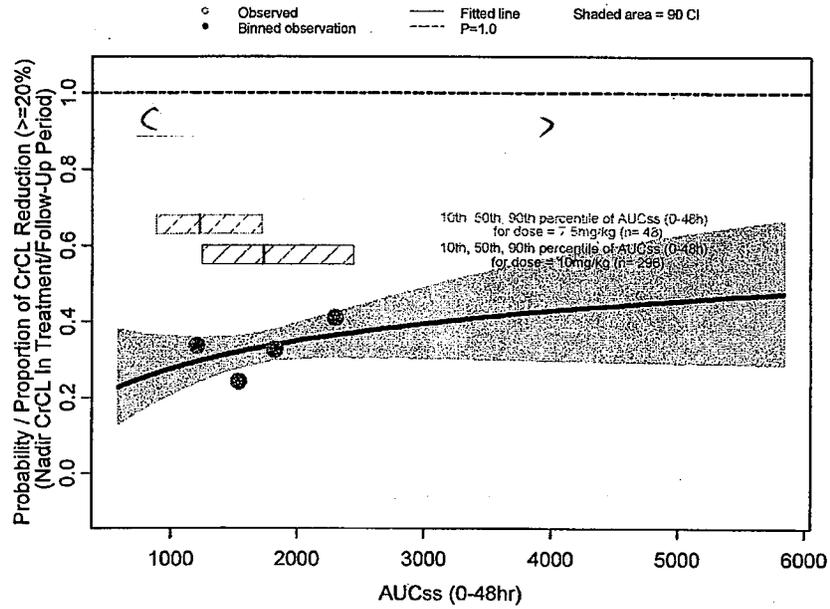
1. Exposure-worst renal function reduction rate analysis

The effect of telavancin exposure and treatment duration was evaluated separately using a univariate logistic regression modeling approach. The model fitted curves are illustrated in Figures 14 and 15. The model fitted curves sufficiently describe the observed data.

A trend was observed as higher telavancin exposure (AUC_{0-48}) yields a relatively higher incidence of renal toxicity. This suggests that reducing the dose from 10 mg/kg to 7.5 mg/kg provides a slight reduction (4-5%) of risk for a patient to experience renal toxicity. However, this increased trend was not statistically significant ($p=0.19$, $OR=1.39$ with 95% CI (0.85 ~ 2.28)).

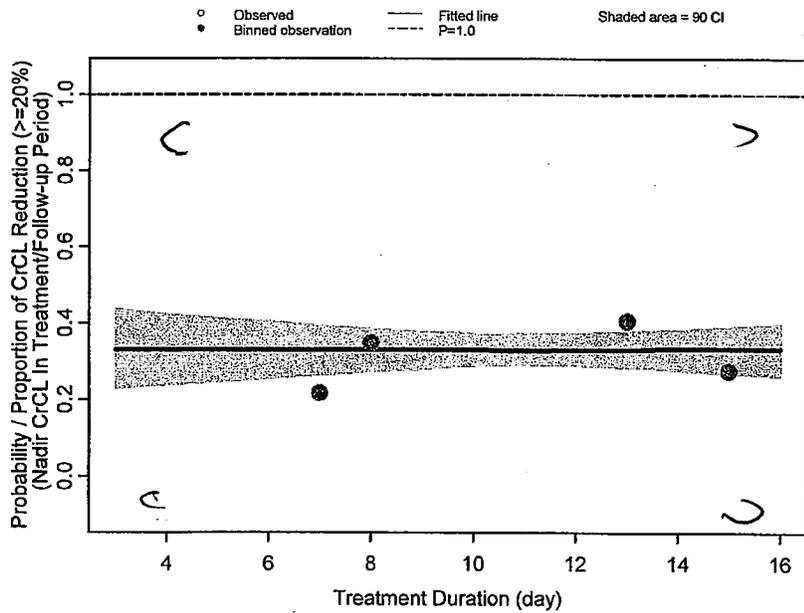
The incidence of renal toxicity does not appear to be treatment duration dependent ($p=0.996$, $OR=1$ with 95% CI (0.93 ~ 1.07)). Therefore, increasing treatment duration does not appear to increase the risk for a patient to experience renal toxicity.

Figure 14. Univariate logistic regression model fitting of the rate of renal toxicity versus telavancin exposure (AUC₀₋₄₈)



b(4)

Figure 15. Univariate logistic regression model fitting of the rate of renal toxicity versus telavancin treatment duration



b(4)

2. Exposure-last renal function reduction rate analysis

A logistic regression model was used to explore the relationship between telavancin exposure and the last renal function reduction following telavancin treatment. Factors, such as telavancin exposure (AUC_{0-48} , log-transformed), treatment duration time, patient body weight, and baseline CrCL were screened using stepwise selection. No factor was selected as a significant effect at 0.05 level.

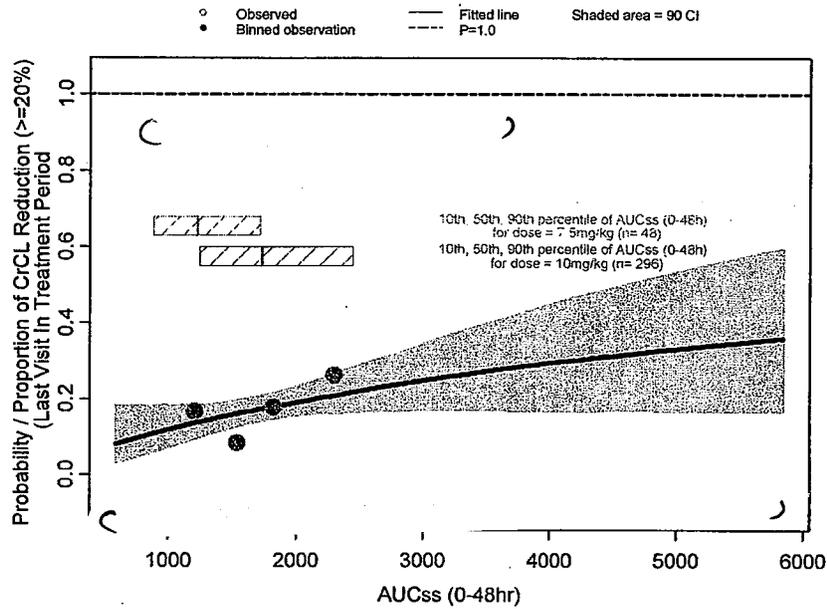
The effect of telavancin exposure and treatment duration was investigated separately by using univariate logistic regression modeling approach. The model fitted curves are illustrated in Figures 16 and 17. The model fitted curves sufficiently describe the observed data.

A trend was observed as higher telavancin exposure (AUC_{0-48}) yields a relatively higher incidence of renal toxicity. This suggests that reducing the dose from 10 mg/kg to 7.5 mg/kg provides a slight reduction (4-5%) of risk for a patient to experience renal toxicity. However, this increased trend is not statistically significant ($p=0.07$, OR=1.76 with 95% CI (0.96 ~ 3.26)).

The incidence of renal toxicity does not appear to be treatment duration dependent ($p=0.17$, OR=0.94 with 95% CI (0.87 ~ 1.03)). Therefore, increasing treatment duration does not appear to increase the risk for a patient to experience renal toxicity.

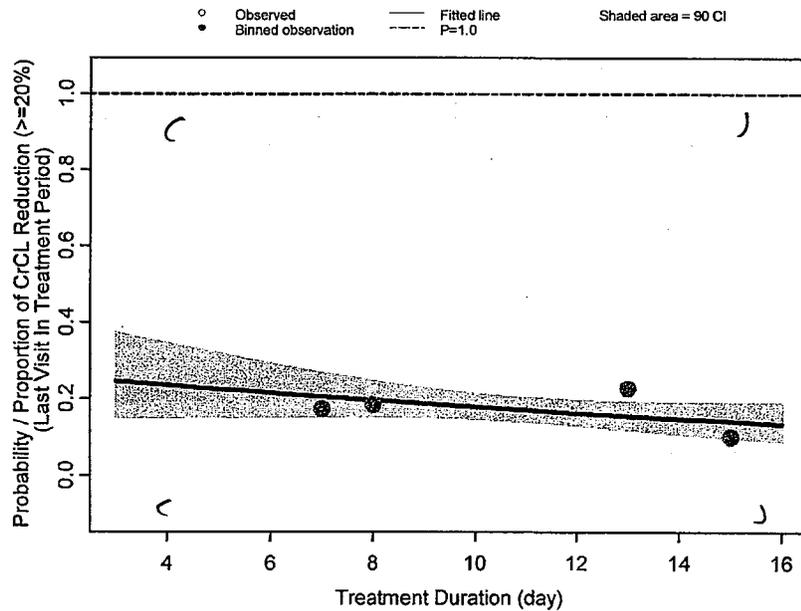
Thus, telavancin 10 mg/kg q24h yields only marginally (and numerically) higher risk of renal toxicity (defined as at least 20% reduction in creatinine clearance from baseline at any time during the trial) compared to telavancin 7.5 mg/kg q24h (14% vs. 17.6%).

Figure 16. Univariate logistic regression model fitting of the rate of renal toxicity versus telavancin exposure (AUC₀₋₄₈)



b(4)

Figure 17. Univariate logistic regression model fitting of the rate of renal toxicity versus telavancin treatment duration



b(4)

2.2.4.3. Does telavancin prolong QT or QTc interval?

A thorough QT (TQT) study was conducted with telavancin (I6424-104a). This study was reviewed by the Interdisciplinary Review Team for QT studies at the FDA. The study was a randomized, double-blind, parallel-group, gender-stratified, multi-dose Phase 1 study with negative and positive control arms in 160 healthy volunteers. Subjects (40/group) were randomized to receive placebo for telavancin (negative control), moxifloxacin 400mg IV infused over 60 minutes (positive control), telavancin 7.5 mg/kg infused over 60 minutes, or telavancin 15 mg/kg IV infused over 60 minutes. The primary objective of this study was to assess the safety (including the effect of telavancin on ECG intervals and morphology with focus on the QTc interval) and tolerability of telavancin administration to healthy male and female subjects. In this 'thorough QT/QTc study' the effects of once daily dosing of telavancin at 7.5 mg/kg and 15 mg/kg, infused intravenously over 60 minutes, were assessed at steady state after three days. At both doses, the baseline- and placebo-corrected QTcF interval was lengthened greater than 10 msec, the threshold of regulatory concern (Table 9). The mean C_{max} of the suprathreshold dose (15 mg/kg) represents a 50% increase in exposure over the highest clinical dose of 10 mg/kg (expected steady-state mean C_{max} of 122 µg/ml based on linear pharmacokinetics).

Table 9. Maximum Mean Effect by Dose Group (E14 Primary Analysis)

Dosing Regimen	Mean C _{max} , µg/ml	Time of maximum ΔΔQTcF	Mean ΔΔQTcF, msec	90 % Confidence Interval, msec
7.5 mg/kg	88	Immediately post infusion	14	8, 20
15 mg/kg	186	Immediately post infusion	18	11, 25
400 mg Moxifloxacin	Not applicable	Immediately post infusion	24	18, 30

ΔΔQTcF = baseline- and placebo-corrected QTcF interval

Telavancin undergoes minimal metabolism and is predominantly excreted unchanged in the urine. Therefore, subjects with impaired renal function are expected to have the highest exposure to telavancin. In a single-dose renal impairment study (Study I6424-103a), subjects with severe renal impairment had <10% increase in C_{max} and 118% increase in AUC. Based on the mean elimination half-life for these subjects, the steady state mean C_{max} is expected to be approximately 190 µg/ml. Hence, the observed exposures after administration of repeated doses of 15 mg/kg of telavancin encompass the highest anticipated exposures for patients receiving 10mg/kg.

A step-wise linear mixed-effects model described the relationship between telavancin concentrations and ΔΔQTcF (defined as baseline-corrected, placebo corrected), (Figure 18). The observed median values (and inter-quartile range) for the change from baseline QTcF immediately after infusion at T_{max} was similar for both dose groups suggesting a non-linear concentration-QTcF relationship. Based on this relationship, the expected mean ΔΔQTcF for the 10 mg/kg dose is 12 to 15 msec (Table 10).

Figure 18. Goodness-of-Fit Plots for Step-wise Linear Model (Left Panel: Model Developed from 7.5mg/kg Dose Group, Right Panel: Model Developed from 15 mg/kg Dose group)

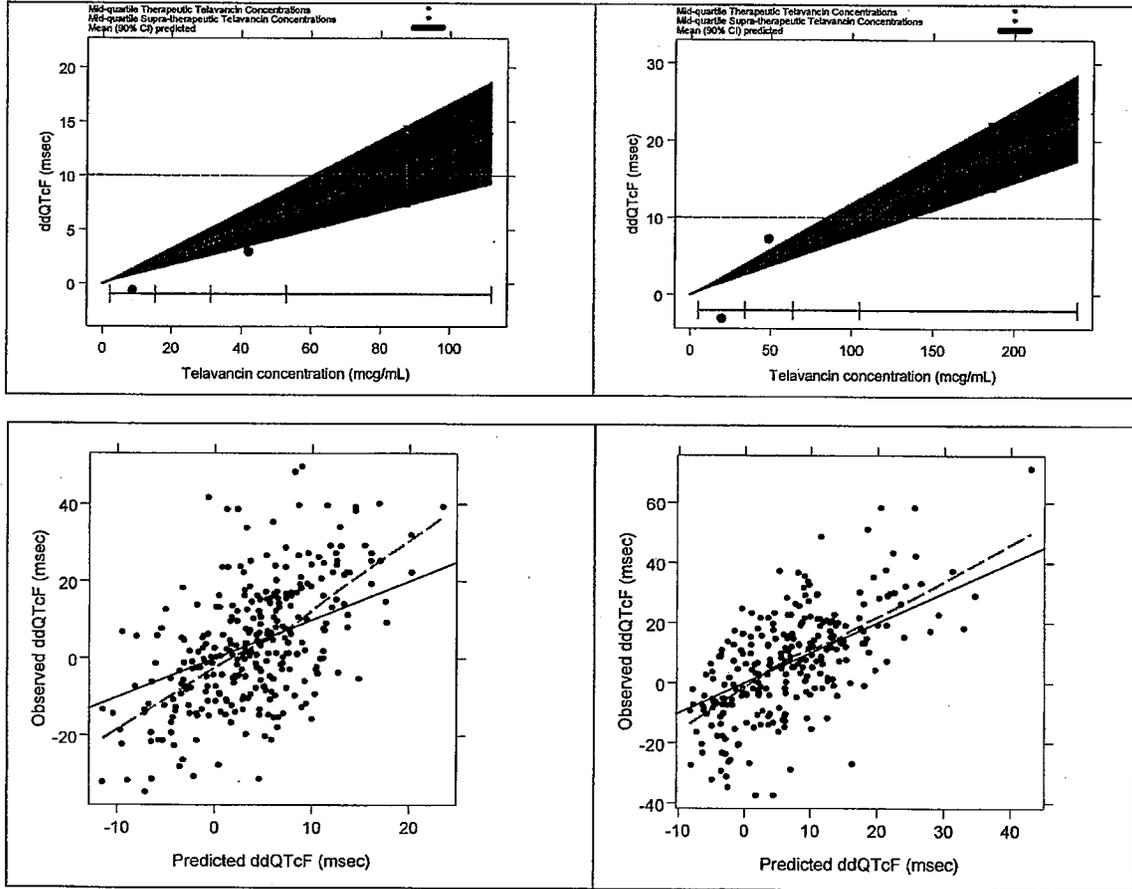


Table 10. Predicted Change of $\Delta\Delta$ QTcF Interval at Mean C_{max}

Dose Group	Predicted change in $\Delta\Delta$ QTcF interval (msec)	
	Mean	90% Confidence Interval
7.5 mg/kg qd (steady-state)		
Mean C_{max} (87.5 μ g/ml)	10.90	(7.37, 14.42)
10 mg/kg (steady-state) *1		
Mean C_{max} (121.6 μ g/ml)	15.15	(10.24, 20.05)
10 mg/kg		
Mean C_{max} 121.6 μ g/ml) *2	11.7	(8.9, 14.5)
15 mg qd (single dose)		
Mean C_{max} (186.2 μ g/ml)	17.9	(13.6, 22.1)

*1: Steady-state mean C_{max} of 10mg/kg dose was obtained by using linear imputation; the QTc interval prolongation value was calculated from model developed based on 7.5 mg/kg dose group.

*2: Steady-state mean C_{max} of 10mg/kg dose was obtained by using linear imputation; the QTc interval prolongation value was calculated from model developed based on 10 mg/kg dose group. The impact of telavancin on the baseline-corrected QTcF interval was evaluated in the Phase 2/3 clinical trials of telavancin. The investigators used 12-lead ECGs that were obtained in triplicate at pretreatment, Study Day 4, and end of therapy. German sites obtained ECGs every third day during treatment, at study days 4, 7, 10, and 13, as appropriate. ECGs were to be transmitted to the central ECG lab for analysis. Table 11 shows the summary of ECG changes in the clinical studies.

Table 11. Summary of Post-Drug changes from Baseline in QTcF Interval (QT Corrected Using Fridericia's Correction Formula)-All Efficacy and Safety Studies in cSSSI

	Studies 0017, 0018, 202b		Studies 0017, 0018, 202b		All Efficacy and Safety	
	Original Protocol and 202a		Post-Amendment		Studies in cSSSI	
	TLV 7.5 mg/kg (N=192)	Vanc ¹ (N=189)	TLV 10 mg/kg (N=1029)	Vanc ¹ (N=1033)	TLV (N=1221)	Vanc ¹ (N=1222)
Post-Drug Average² Change, msec						
N	189	183	971	979	1160	1162
Mean	11.6	3.8	9.4	2.8	9.8	3.0
Standard Deviation	15.6	14.8	17.4	15.9	17.1	15.7
Minimum	C)
Median	12.0	5.0	9.0	2.7	9.7	3.0
Maximum	C)
Post-Drug Maximum³ Change, msec						
N	189	183	971	979	1160	1162
Mean	20.6	12.4	15.9	8.4	16.7	9.0
Standard Deviation	17.2	18.0	18.7	16.7	18.5	17.0
Minimum	C)
Median	19.3	12.0	15.3	7.7	16.0	8.3
Maximum	C)
Maximum Post-Drug Value, number (%) by category						
≤450 msec	171 (90)	178 (96)	874 (88)	934 (95)	1045 (89)	1112 (95)
>450-≤480 msec	16 (8)	7 (4)	106 (11)	41 (4)	122 (10)	48 (4)
>480-≤500 msec	2 (1)	0	8 (<1)	9 (<1)	10 (<1)	9 (<1)
>500 msec	0	1 (<1)	1 (<1)	2 (<1)	1 (<1)	3 (<1)
Total	189(100)	186(100)	989(100)	986(100)	1178(100)	1172(100)
Maximum Post-Drug Change, number (%) by category						
≤30 msec	141 (75)	161 (88)	789 (81)	885 (90)	930 (80)	1046 (90)
>30-≤60 msec	46 (24)	21 (11)	168 (17)	89 (9)	214 (18)	110 (9)
>60 msec	2 (1)	1 (<1)	14 (1)	5 (<1)	16 (1)	6 (<1)
Total	189(100)	183(100)	971(100)	979(100)	1160(100)	1162(100)

¹ Includes 27 patients (20 in 202a and 7 in 202b Post-Amendment) who received an antistaphylococcal penicillin instead of vancomycin

Note 1: Three ECGs were to be obtained at each assessment time. Triplicate readings were reduced to a single value at each assessment time by averaging within the triplicate.

Note 2: In 202a and 202b, post-drug ECGs were to be obtained on every third day of study drug and at the end-of-therapy evaluation. In 0017 and 0018, post-drug ECGs were to be obtained once on Day 3, 4 or 5 and at the end-of-therapy evaluation

² Based on all QT measurements from Day 1 on in patients with a Baseline and at least one 1 Post-Baseline value.

³ Based on maximum value of all QT measurements (triplicate averages) from Day 1 on in patients with a Baseline and at least 1 Post-Baseline value.

None of the patients had an absolute maximum QTcF interval >500msec, and two telavancin 10mg/kg patients (0017-38111-0380 and 202b-907-8003) had a maximum change in QTcF interval of >60msec. In

b(4)

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one of these patients (0017-38111-0380) the adverse event of myocardial infarction was considered serious. With the exception of one telavancin 10mg/kg patient (202b-907-8003), no other patients were discontinued from therapy due to a cardiac adverse event.

2.2.4.4. *Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?*

The dosage regimen selected for evaluation in the Phase 3 clinical trials (studies 0017 and 0018) is consistent with the findings from the PK/PD analysis using Monte Carlo simulation suggesting that doses of 750 mg (approximately 10 mg/kg) would result in >99% probability of target attainment for organisms with MICs as high as 2 µg/mL as well as the higher microbiologic eradication rate observed in the Phase 2 clinical trials (202a and 202b) with telavancin 10 mg/kg compared to 7.5 mg/kg.

2.2.5. *What are the PK characteristics of telavancin?*

2.2.5.1. *What are the single and multiple dose PK parameters?*

The pharmacokinetics of telavancin following intravenous administration have been evaluated in eight Phase 1 studies. Single-dose telavancin plasma concentrations in healthy, male subjects are presented in Figure 19. Table 12 summarizes the plasma PK parameters of telavancin for subjects receiving intravenous single dose administration. The pharmacokinetics of telavancin were linear and increased nearly proportional to dose as the dose of telavancin increased from 5 mg/kg to 12.5 mg/kg. Although mean clearance values were higher with doses less than 5 mg/kg compared to doses higher than 5 mg/kg, the observation may be attributable to plasma concentrations near the assay's lower limit of quantitation by 8 hours with the 0.25 mg/kg dose and 24 hrs with the 1 mg/kg dose.

Figure 19. Plasma Concentrations ($\mu\text{g/ml}$) of telavancin Following 120-minute Intravenous Administration. Data are presented as arithmetic mean \pm SD

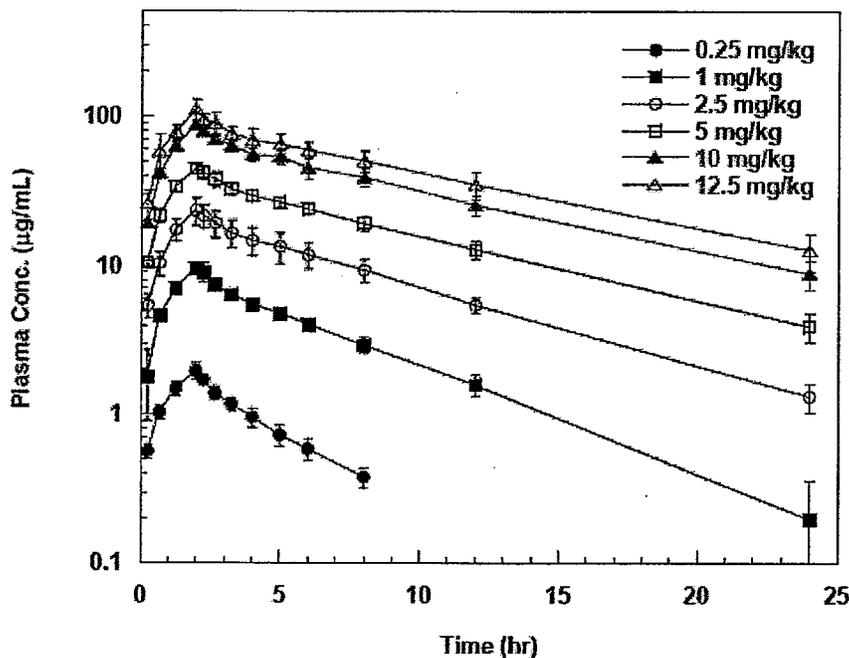


Table 12. Plasma PK Parameters following Intravenous Single-Dose Administration (Values are presented as arithmetic mean \pm SD) (Study I6424-101a)

Duration of Infusion	120 Minute						60 Minute	30 Minute	30 Minute
	0.25 mg/kg	1.0 mg/kg	2.5 mg/kg	5.0 mg/kg	10 mg/kg	12.5 mg/kg	12.5 mg/kg	12.5 mg/kg	15.0 mg/kg
N	6	6	5 ^b	6	5 ^c	6	5 ^d	6	6
C_{max} ($\mu\text{g/mL}$)	1.98 \pm 0.25	9.97 \pm 0.91	23.6 \pm 4.8	44.9 \pm 3.2	87.5 \pm 6.0	111.7 \pm 18.3	114.0 \pm 4.9	153.8 \pm 26.3	178.7 \pm 9.6
AUC_{0-24} ($\mu\text{g}\cdot\text{hr/mL}$)	7.60 \pm 0.91	59.1 \pm 8.8	182.2 \pm 29.7	386.3 \pm 37.8	761.8 \pm 81.2	996 \pm 150	814.9 \pm 77.3	1006 \pm 202	1210.3 \pm 138
$AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{hr/mL}$)	8.92 \pm 1.33 ^a	63.2 \pm 6.4	193.2 \pm 31.0	425.8 \pm 48.8	858.2 \pm 108.6	1143 \pm 195	912.6 \pm 95.4	1136 \pm 241	1430 \pm 202.2
$t_{1/2}$ (hr)	2.9 \pm 0.2 ^a	4.6 \pm 0.5	5.7 \pm 0.6	6.9 \pm 0.6	7.5 \pm 0.6	7.9 \pm 0.9	7.6 \pm 0.3	7.8 \pm 0.6	9.1 \pm 1.0
CL (mL/hr/kg)	28.5 \pm 4.2 ^a	15.9 \pm 1.6	13.2 \pm 2.0	11.9 \pm 1.5	11.8 \pm 1.4	11.3 \pm 2.3	13.8 \pm 1.4	11.4 \pm 2.5	10.7 \pm 1.6
MRT (hr)	3.7 \pm 0.2 ^a	5.9 \pm 0.5	7.5 \pm 0.5	9.0 \pm 0.8	9.8 \pm 0.9	10.5 \pm 1.3	9.8 \pm 0.5	10.2 \pm 0.9	11.8 \pm 1.3
V_{ss} (mL/kg)	104 \pm 17.9 ^a	93.5 \pm 4.8	99.8 \pm 19.3	106.3 \pm 5.3	115.0 \pm 6.3	116.4 \pm 12.5	134.9 \pm 8.5	115.3 \pm 17.7	124.3 \pm 7.8

^a N = 4; 2 subjects had $>20\%$ of the AUC values being extrapolated and were excluded from the mean calculations.

^b One subject with most of the plasma concentrations below limit of the quantitation and were excluded from the mean calculations.

^c One subject had a T_{max} at 4 hr and data was not included in the mean and SD calculations.

^d One subject had no quantifiable concentration in plasma at the end of infusion and data was not included in the mean and SD calculations.

Table 13 summarizes the concentrations of telavancin in plasma samples obtained on Day 1 and Day 7 of the multiple ascending dose part of the study. As shown in the table, the mean half-life of telavancin appears to increase with multiple doses and the clearance appears to decrease slightly. The

mean AUC_{0-∞} following a single dose was similar to the mean AUC_{0-τ} at steady-state for doses ranging from 7.5 to 12.5 mg/kg, supporting that single dose pharmacokinetics are predictive of steady-state pharmacokinetics.

NOTE: The AUC ratio (Day 7/Day 1) in Table 13 for telavancin 15 mg/kg/day should be 0.94 rather than 1.01 as reported by the sponsor. All other pharmacokinetic parameters are correct.

Table 13. Pharmacokinetic Parameters following Intravenous Infusion for 7 Consecutive Days. Arithmetic mean values are presented.

Parameter	7.5 mg/kg/day		12.5 mg/kg/day		15 mg/kg/day	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
N	7	6	6	6	7	4
C _{max} (µg/mL)	90.3	96.7	154.7	151.3	181.4	202.5
AUC _(0-∞) or AUC _{SS} * (µg.hr/mL)	668	700	1013	1033	1239	1165
t _{1/2} (hr)	7.9	8.8	7.3	9.1	7.3	8.8
CL (mL/hr/kg)	12.0	9.0	12.0	10.0	12.0	11.0
MRT (hr)	9.9	11.4	9.7	11.7	9.5	11.3
V _{ss} (mL/kg)	113	105	121	119	117	126
AUC ratio (Day 7/Day 1)	1.05		1.02		1.01	

*AUC_{SS} on Day 7

C_{max}: Maximum plasma concentrations of TD-6424

AUC_{SS}: Steady-state area under the plasma concentration time curve

AUC_(0-∞): Value of AUC extrapolated to infinity

CL: Total body clearance

V_{ss}: Steady-state volume of distribution

MRT: Mean residence time

2.2.5.2. How does the PK of telavancin in healthy volunteers compare to that in patients?

The pharmacokinetics of telavancin in patients with cSSSI were evaluated in two Phase 2 and two Phase 3 clinical trials using a 2-compartment model. In general, the pharmacokinetics of telavancin in healthy subjects were comparable to that observed in patients with cSSSI. Among patients with cSSSI, the clearance of telavancin was 22% higher than healthy subjects and the volume of distribution of the central (V1) and peripheral (V2) compartments were 28% and 26% higher, respectively than the corresponding volumes in healthy subjects.

2.2.5.3. What are the characteristics of drug absorption?

Telavancin for injection is an intravenously administered product.

2.2.5.4. What are the characteristics of drug distribution?

The *in vitro* protein binding of telavancin was evaluated in human, rat, dog, and mouse plasma using equilibrium dialysis over a concentration range of 0.1 to 100 µg/mL (Study 01-6424-PK-14). Over the concentration range studied, the protein binding of telavancin was independent upon concentration tested and ranged from 93.1-94.3%, 93.4-95.6%, 91.5-94.3% and 93.8-96.2% in human, rat, dog, and mouse plasma, respectively.

The steady-state volume of distribution (V_{ss}) of telavancin is approximately 125 to 150 mL/kg (9-10 L for a 70 kg person). Thus, the compound primarily distributes to extracellular water. The sponsor investigated the distribution of telavancin in skin blister fluid (Study 107a) to support the clinical use of telavancin in complicated skin and skin structure infections (cSSSI).

Figure 20 shows a semi-log plot of concentrations of telavancin in plasma and skin blister fluid for subjects receiving a one-hour infusion at a dose of 7.5 mg/kg. After the administration of telavancin, mean values for subject's telavancin levels in blister fluid rose slowly to reach T_{max} at 6 to 12 hrs after dosing and declined at a rate similar to that of plasma concentrations. Table 14 shows the mean non-compartmental PK parameters on Day 3 for telavancin.

Figure 20. Semi-Log Plot of Mean \pm SD Concentrations of Telavancin in Plasma and Skin Blister Fluid in Healthy Subjects Following the Third Intravenous Dose of Telavancin, 7.5 mg/kg Once daily for 3 days

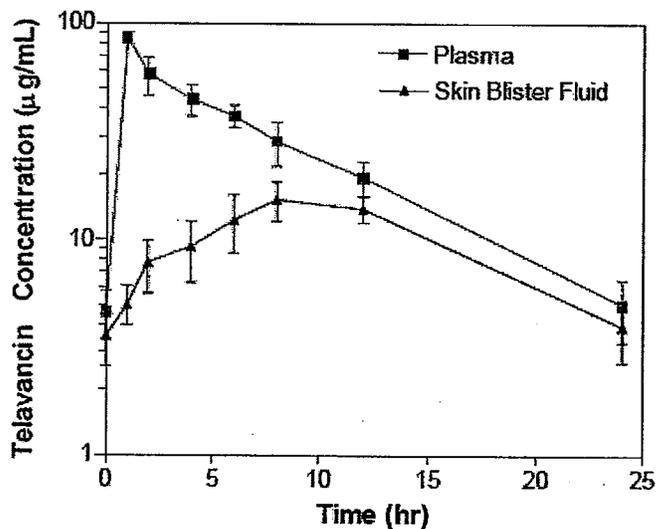


Table 14. Mean (\pm SD) Non-Compartmental Pharmacokinetic Parameters on Day 3 for Telavancin in Plasma and Skin Blister Fluid Following Intravenous Administration to 8 healthy Subjects at a Dose of 7.5 mg/kg via a 60-Minute Infusion Daily for 3 days

Pharmacokinetic Parameters	Plasma* (n=8)	Skin Blister Fluid* (n=8)
C_{max} (μ g/mL)	84.8 \pm 5.3	16.0 \pm 2.0
T_{max} (hr)	1.0 \pm 0.0	9.3 \pm 2.4
AUC ₀₋₂₄ (μ g.hr/mL)	604 \pm 83	241 \pm 33
C_{24} on Day 3 (μ g/mL)	4.92 \pm 1.58	3.90 \pm 1.24
$T_{1/2}$ (hr)	6.26 \pm 0.78	6.91 \pm 0.53 ¹
CL _{ss} (mL/hr/kg)	12.6 \pm 2.1	ND
V _{ss} (mL/kg)	105 \pm 16	ND
MRT (hr)	8.37 \pm 1.03	ND
SBF/Plasma Ratios		
C_{max}	0.189 \pm 0.030	
AUC	0.403 \pm 0.058	
C_{24} (Day 3)	0.816 \pm 0.182	

¹n=5

* The maximum MIC for recent clinical isolates of *Staphylococcus aureus*, including methicillin-resistant strains, is 0.25 μ g/mL and the MIC₉₀ for such strains of *S. aureus* (0.5 μ g/mL).

ND: Not determined

Similar mean $t_{1/2}$ values (6.3 vs. 6.9 hrs) were observed for telavancin in plasma and blister fluid (Table 14). The T_{max} value in plasma occurred at the end of the infusion and the maximal value in skin blister fluid was observed, on average, approximately 9hr after the start of the infusion. The mean \pm SD trough, on day 3, telavancin concentration in skin blister fluid was 3.90 \pm 1.24 μ g/mL. The mean \pm SD ratio of AUC₀₋₂₄ for skin blister fluid to AUC₀₋₂₄ for plasma was 0.403 \pm 0.058. The mean (\pm SD) C_{max} values of telavancin in plasma and skin blister fluid were 84.8 \pm 5.3 and 16.0 \pm 2.0 μ g/mL, respectively. At every time point throughout the 24-hour dosing interval in each of the 8 subjects, the total concentration of telavancin in the skin blister fluid exceeded the MIC₉₀ for *S. aureus* (0.5 μ g/mL) including methicillin-resistant strains, by at least 4-fold. Although telavancin is approximately 90% protein bound, unbound concentrations of telavancin in skin blister fluid following the administration of 10 mg/kg should exceed the MIC₉₀ of *S. aureus* for most of the dosing interval.

2.2.5.5. Does the mass balance study suggest renal or hepatic as the major route of elimination?

A mass balance study for telavancin (0027) demonstrated renal as the major route of elimination. Total radioactivity was eliminated primarily in the urine, accounting for a mean of 76.3% (range C) of the administered dose by the end of the collection period (216 hrs post-dose), with approximately 73.2% of the administered dose eliminated in the urine by 48 hrs post dose. Excretion via feces accounted for a mean of 0.7% (range C) of the administered dose by the end of the collection period (216 hours). Total radioactivity recovered in urine and feces accounted for a mean of 77% (range C) () of the administered dose.

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Figure 21 shows the telavancin concentration-time curve in plasma based on total radioactivity and LC/MS/MS and whole blood based on total radioactivity. Table 15 shows the PK parameters in plasma and whole blood in these subjects.

Figure 21. Semi-log Plot of Mean \pm SD Plasma and Whole Blood Concentrations of [14 C]-telavancin Following I.V. Administration to Healthy Subjects at a Dose of 10 mg/kg

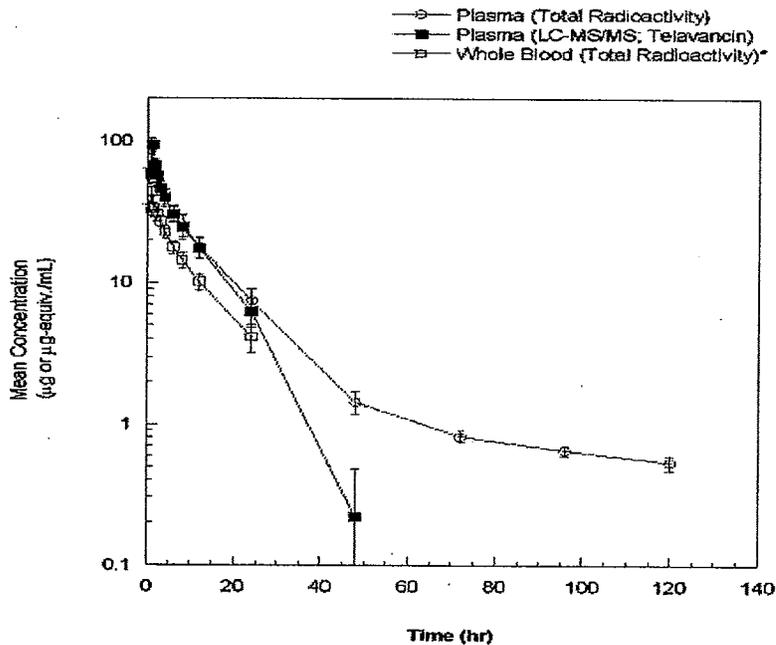


Table 15. Non-compartmental Pharmacokinetic Parameters in Plasma and Whole Blood Following I.V. Administration of [14 C]-telavancin to Healthy Subjects at a Dose of 10 mg/kg (mean \pm SD)

Biological Matrix	Plasma	Plasma	Whole Blood
Analysis	LC-MS/MS (Telavancin)	Total Radioactivity	Total Radioactivity
Number of subjects	6	6	6
C_{max} (μ g or μ g-equiv./mL)	93.6 \pm 10.2	89.6 \pm 11.8	43.7 \pm 7.0
T_{max} (h)	1.00 \pm 0.00	1.00 \pm 0.00	1.00 \pm 0.00
$AUC_{(0-4)}$ (μ g or μ g-equiv. h/mL)	620 \pm 125	764 \pm 119	371 \pm 67
$AUC_{(0-\infty)}$ (μ g or μ g-equiv. h/mL)	649 \pm 103	827 \pm 120	396 \pm 56
Elimination $T_{1/2}$ (h)	7.08 \pm 0.50	94.2 \pm 17.8	9.89 \pm 1.21
Cl (mL/h/kg)	15.7 \pm 2.5	12.3 \pm 1.8	25.7 \pm 3.8
V_{ss} (mL/kg)	150 \pm 19	478 \pm 102	301 \pm 28
Cl _r (mL/h/kg)	9.00 \pm 1.32	NA	NA
% excreted as telavancin (0-48 h)	82.3 \pm 7.4	NA	NA

NA: Not applicable

NOTE: In Table 15, the % excreted as telavancin (0-48h) represents the mean percent of telavancin that was excreted in the urine. Thus, of the amount of drug recovered in the urine, 82.3 \pm 7.4% was excreted as telavancin or parent.

The concentrations of telavancin in plasma based on total radioactivity following administration of [¹⁴C]-telavancin accounted for greater than 95% of the total radioactivity in plasma for up to 12 hours post-dose. The parent molecule, telavancin, accounted for 83% of the total radioactivity in plasma at 24 hours post-dose. At 48 hours post-dose, the concentration of telavancin in plasma was above the LLOQ (0.25 µg/mL) in only three subjects and accounted for 21.8% to 33.3% of the total radioactivity in plasma.

The sponsor has not provide an explanation why the telavancin half-life in plasma based on total radioactivity is considerably longer than the mean half-life in plasma based on LC/MS/MS or whole blood base don total radioactivity. It is plausible that the formation of a metabolite with an elimination half-life longer than telavancin may be contributing to the retained radioactivity in plasma. Although the sponsor has not determined the elimination half-life of AMI-11352 due to limited blood samples and assay sensitivity, the reviewer estimates that the elimination half-life of AMI-11352 is longer than telavancin and may range from 25 to 83 hours based on data from six healthy subjects (Study 103a).

2.2.5.6. *What are the characteristics of drug metabolism?*

In vitro assays demonstrated that none of the following CYP450 isoforms metabolized telavancin in human liver microsomes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, and CYP4A11. Thus, the clearance of telavancin is not expected to be altered by inhibitors of these enzymes.

The primary metabolite of telavancin is the hydroxylated metabolite AMI-11352, which has about one-tenth of the microbiological activity of telavancin. In plasma, the AUC of AMI-11352 is approximately 1-3% of the AUC of telavancin. The metabolic pathway to AMI-11352 and two additional minor hydroxylated metabolites is unknown.

2.2.5.7. *What are the characteristics of drug excretion?*

The primary route of elimination of telavancin is through renal excretion. In a mass balance study (0027), approximately 76% of the administered dose was recovered from urine based on total radioactivity and <1% of the dose was recovered from feces (collected for up to nine days). Among the radioactivity recovered in urine, approximately 47-68% of the dose was excreted as unchanged telavancin and 6-11% of the dose was excreted as AMI-11352. Almost 82% of drug excreted in urine is excreted as unchanged telavancin.

2.2.5.8. *Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?*

The linearity of the pharmacokinetics of TD-6424 were examined (Study I6424-101a) among subjects who received 120-minute infusions of 1 mg/kg to 12.5 mg/kg. Six subjects who received 0.25 mg/kg infusions were excluded from this analysis because of nonquantifiable plasma concentrations after 8 hours. The data shows that as the dosage of the product increases the AUC and C_{max} values also increase proportionally, exhibiting linearity of this drug product. Figure 22 and Figure 23 display the dose linearity analysis for C_{max} and AUC, respectively. Both figures exhibit approximate linear pharmacokinetics in healthy volunteers following single-dose administration.

Figure 22. Dose Linearity Analysis for C_{max} Values

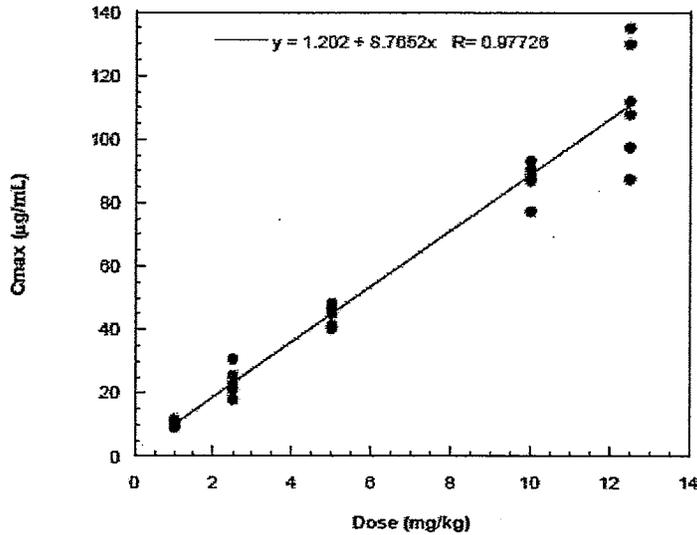


Figure 23. Dose Linearity Analysis for AUC Values

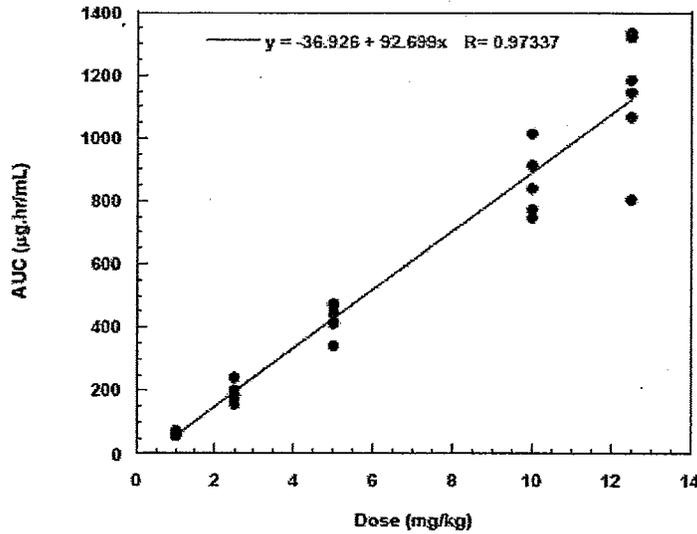


Table 16 indicates that dose-proportional increases in C_{max} values were observed (for 2.5, 5, 10, and 12.5 mg/kg doses: 2.4-, 4.5-, 8.8- and 11 times increase in respect to 1 mg/kg, respectively). The ratio of C_{max}/dose was fairly consistent, averaging 9 µg/mL to 10 µg/mL. Based on dose-normalized AUC_(0-∞) normalized to 1 mg/kg, the AUC_(0-∞) values at 2.5, 5, 10, and 12.5 mg/kg were 22%, 35%, 36%, and 45% higher, respectively, than expected from dose-proportional increase.

Table 16. Dose Proportion Analysis

Parameter	1 mg/kg	2.5 mg/kg	5 mg/kg	10 mg/kg	12.5 mg/kg
C _{max} (µg/mL)	9.97 ± 0.91	23.6 ± 4.8	44.9 ± 3.2	87.5 ± 6.0	111.7 ± 18.3
Ratio		2.4	4.5	8.8	11
C _{max} /dose	9.97 ± 0.91	9.45 ± 1.94	8.97 ± 0.65	8.75 ± 0.60	8.93 ± 1.46
AUC _(0-∞) /dose	63.2 ± 6.3	77.3 ± 12.4	85.2 ± 9.8	85.8 ± 10.9	91.4 ± 15.6
Ratio		22%	35%	36%	45%

2.2.5.9. *How do PK parameters change with time following chronic dosing?*

The pharmacokinetics of telavancin were evaluated following daily dosing for seven days. The PK results show a trend for a modest increase in the elimination half-life and a modest decrease in the plasma clearance (Table 13) following administration of 7.5, 10, and 12.5 mg/kg. However, the AUC_{0-∞} values estimated on day 1 were similar to the AUC_{0-τ} values estimated on day 7. Thus, the pharmacokinetics of telavancin following a single dose were able to predict the pharmacokinetics of telavancin at steady-state.

2.2.5.10. *What is the inter- and intra-subject variability in volunteers and patients, and what are the major causes of variability?*

Table 17 (pop-PK-Phase 1, 2 and 3 studies) shows the PK parameters inter-individual and intra-individual results. The inter-individual coefficient of variation for CL parameter was approximately 27% and for volume at steady state (V₁ +V₂) was approximately 35%. The intra-individual results were low at 16.4%. There appeared to be minimal variability in the inter-individual and intra-individual values.

Table 17. Final Model Estimated PK Parameters

Pharmacokinetic Parameter	Median Value	Interindividual CV (RSE)
CL (L/h)	1.15	27.15 (16.1)
V ₁ (L)	5.65	41.11 (25.0)
Q (L/h)	6.91	20.57 (178.5)
V ₂ (L)	6.59	30.03 (25.9)
Residual Error Parameters	Estimate (RSE)	Intraindividual Error
Additive	1.09 (65.4)	1.044 µg/mL
Proportional	0.0269 (13.8)	16.4 (%CV)

2.3. Intrinsic Factors

2.3.1. *What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?*

The only intrinsic factor that appears to significantly influence exposure and/or response is renal impairment (see 2.3.2.5) Dose adjustment is warranted in patients with severe renal impairment, but not for other intrinsic covariates.

2.3.2. *Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.*

2.3.2.1. *Elderly*

The sponsor conducted Study I6424-105a to evaluate the effect of gender on the pharmacokinetics of telavancin in healthy elderly subjects aged 65 years of age or older. The mean creatinine clearance of elderly subjects was 66.3 mL/min (range c) mL/min). The sponsor has not performed a formal study to compare the pharmacokinetics in healthy young and elderly subjects. Thus, the reviewer compared the plasma concentrations and pharmacokinetic parameters from healthy elderly subjects in study I6424-105a to the plasma concentrations and pharmacokinetic parameters from healthy young subjects in Study I6424-108a since this study was conducted with the same dose for telavancin of 10 mg/kg.

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Study 108a evaluated the penetration of telavancin into pulmonary epithelial lining fluid (ELF) and alveolar macrophages (AM). Twenty healthy males and females (age 18-50 years) were enrolled in this multiple dose study. Each subject received a daily 1-hour infusion of 10 mg/kg telavancin on 3 consecutive days. Plasma samples were collected from each subject on day 3 up to 24 hours after the third telavancin infusion.

In this analysis, individual plasma concentrations following a single dose of telavancin in healthy elderly subjects (Study I6424-105a) were corrected for accumulation using each individual's elimination rate constant prior to comparing plasma concentrations following three daily doses in healthy young subjects (Study I6424-108a). The mean PK values for this analysis are shown in Table 18. The mean concentration-time profiles are shown in Figure 24. In general, the mean plasma concentration-time profiles from young subjects were similar to elderly subjects.

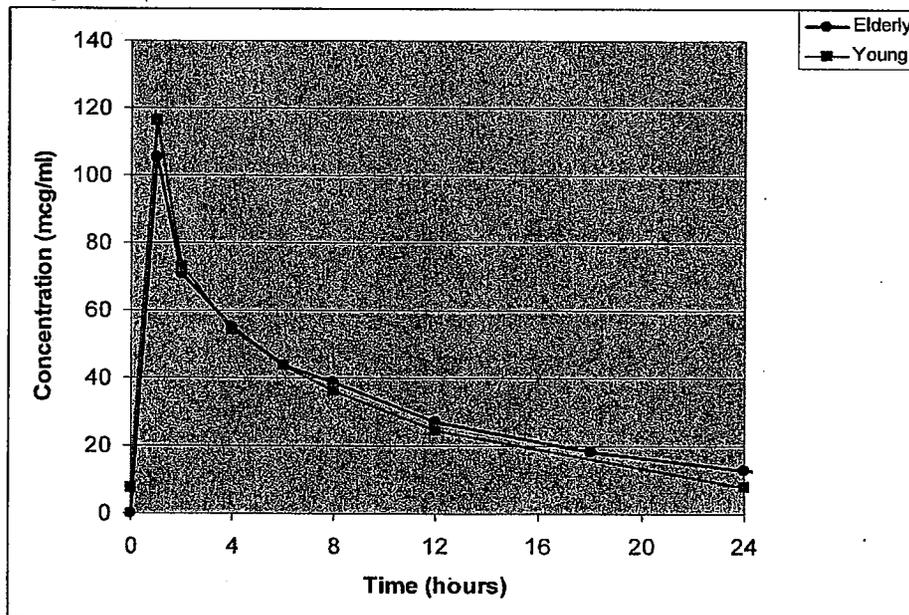
The mean C_{max} was higher in young subjects compared to elderly subjects and may be related to a modestly lower V_{SS} in young subjects. As predicted based on the relationship between plasma clearance and creatinine clearance (see 2.3.2.5 Renal Impairment), the mean CL_T was lower in elderly subjects compared to young subjects. However, the mean $AUC_{0-\tau}$ in young subjects after three doses was similar to the $AUC_{0-\infty}$ in elderly subjects after a single dose.

Table 18. Mean (CV%) PK parameters from Study I6424-108a (young) and Study I6424-105a (elderly)

Parameters	Healthy Young (Study I624-108a)	Healthy Elderly (Study I624-103a)
N	20	16
Age (yrs)	30.2 (20%)	70.7 (8%)
Weight (kg)	72.5 (19%)	71.9 (12%)
C_{max} ($\mu\text{g/mL}$) ¹	116.3 (26%)	87.7 (11%)
AUC_{0-t} ($\mu\text{g}\cdot\text{hr/mL}$)	784.5 (14%) ²	NA
$AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{hr/mL}$)	NA	828.4 (11%) ³
CL_T (mL/hr/kg)	13.0 (15%)	12.2 (12%)
CL_T (mL/min)	15.5 (18%)	14.6 (15%)
V_{ss} (mL/kg)	122 (18%)	156 (7%)
$t_{1/2}$ (hrs)	7.4 (14%)	9.3 (14%)

1- C_{max} obtained after the third dose in healthy young subjects and after the first dose in healthy elderly subjects; 2- AUC_{0-t} estimated after the third dose in young subjects; 3- $AUC_{0-\infty}$ estimated after the first dose in elderly subjects.

Figure 24. Plasma concentration time curve for Subjects in Study I6424-105a compared to subjects in Study I6424-108a.



2.3.2.2. Pediatric Patients

The sponsor has requested a deferral for pediatric studies. The suggested deferred date for submission of studies is not known at this time.

2.3.2.3. Gender

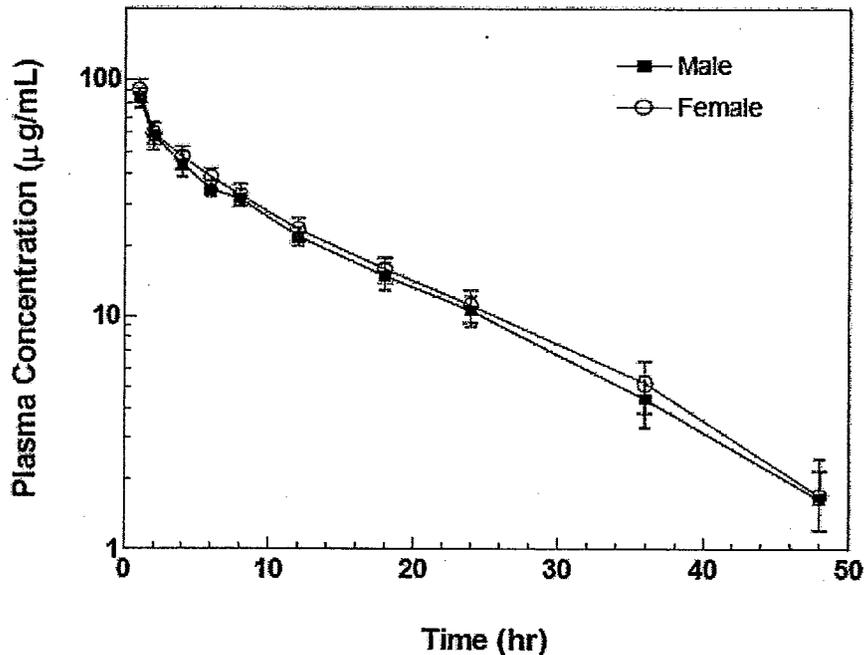
Study I6424-105a was a study conducted in elderly (65 years or older) male and female subjects. All subjects received a single infusion of telavancin 10 mg/kg over 60-minutes. Table 19 shows the mean PK parameters for the subjects in this study.

Table 19. Mean \pm SD Pharmacokinetic Parameters for Telavancin in Plasma Following Intravenous Administration to Elderly Subjects at 10 mg/kg via a 60-minute infusion (Study I6424-105a)

Parameter	Male (n=8)	Female (n=8)	Overall (n=16)
C_{max} (μ g/ml)	84.7 \pm 8.2	90.8 \pm 10.7	87.7 \pm 9.7
AUC ₀₋₂₄ (μ g.hr/ml)	653 \pm 51	693 \pm 64	673 \pm 59
AUC ₀₋₄₈ (μ g.hr/ml)	780 \pm 75	831 \pm 90	805 \pm 84
AUC _{0-∞} (μ g.hr/ml)	803 \pm 87	854 \pm 96	829 \pm 92
$T_{1/2}$ (hr)	9.0 \pm 1.6	9.5 \pm 0.9	9.3 \pm 1.3
CL (ml/hr/kg)	12.6 \pm 1.4	11.8 \pm 1.4	12.2 \pm 1.3
MRT (hr)	12.8 \pm 1.6	12.9 \pm 1.1	12.9 \pm 1.3
V_{ss} (ml/kg)	160 \pm 11	152 \pm 12	156 \pm 12
CL_r (ml/hr/kg)	2.7 \pm 0.9 ^a	3.3 \pm 0.7	3.0 \pm 0.8 ^b

The mean half-life was approximately 9 hours in both males and females. The mean plasma clearance value was approximately 12 mL/hr/kg in both males and females. The steady-state volume of distribution and C_{max} values were comparable in males and females. The mean (\pm SD) telavancin plasma concentration versus time profiles in male and female subjects are shown in Figure 25. Following a single intravenous dose, telavancin plasma concentrations were measurable for approximately the same amount of time in both elderly males and females. Telavancin plasma concentrations declined in an apparent bi-exponential manner. At each time point following the infusion, no sex-related differences were observed in the telavancin plasma concentration vs. time profiles.

Figure 25. Semi-log Plot of Mean \pm SD Telavancin Plasma Concentration-Time Profiles Following Intravenous Administration to elderly Subjects at 10 mg/kg via a 60 minute Infusion



Gender did not have a clinically meaningful impact on the PK of telavancin in phase 1 studies.

2.3.2.4. Race

The effect of race on the pharmacokinetics of telavancin has not been defined.

2.3.2.5. Renal Impairment

The effect of renal impairment on the pharmacokinetics of telavancin was evaluated in 28 subjects with differing degrees of renal function (Study 116424-103a). The mean plasma concentration-time profiles following administration of a single 7.5 mg/kg dose of telavancin is shown in Figure 26. Subjects with ESRD were dosed beginning approximately 3 hours before hemodialysis. In each group, the concentration of telavancin decreased in a log linear manner, indicating first order disposition processes. After a single IV dose, plasma levels remained measurable for the longest interval in the groups with $CL_{cr} < 30$ mL/min. The mean pharmacokinetics parameters of telavancin in subjects with normal renal function and varying degrees of renal impairment are shown in Table 20.

The mean C_{max} was similar among subjects with normal renal function and mild, moderate or severe renal impairment although it was lowest in subjects with ESRD immediately following hemodialysis. The mean V_{SS} was modestly higher among subjects with mild and moderate renal impairment compared to subjects with normal renal function, suggesting renal function had little effect on the distribution of telavancin after IV administration.

The mean clearance was 11% and 19% lower in subjects with mild and moderate renal impairment, respectively compared to normal renal function but 55% lower in subjects with severe renal impairment.

Among subjects with end-stage renal disease (ESRD) who received hemodialysis immediately following administration of telavancin, the mean plasma clearance was 40% lower than subjects with normal renal function. The mean AUC_{0-∞} increased 13%, 29%, 119%, and 79% in subjects with mild, moderate, severe, and ESRD, respectively, compared to subjects with normal renal function.

Figure 26. Semi-log Plot of mean Plasma Concentrations of Telavancin after a 1-hour Intravenous Infusion to Subjects With and Without Renal Dysfunction (Study I6424-103a)

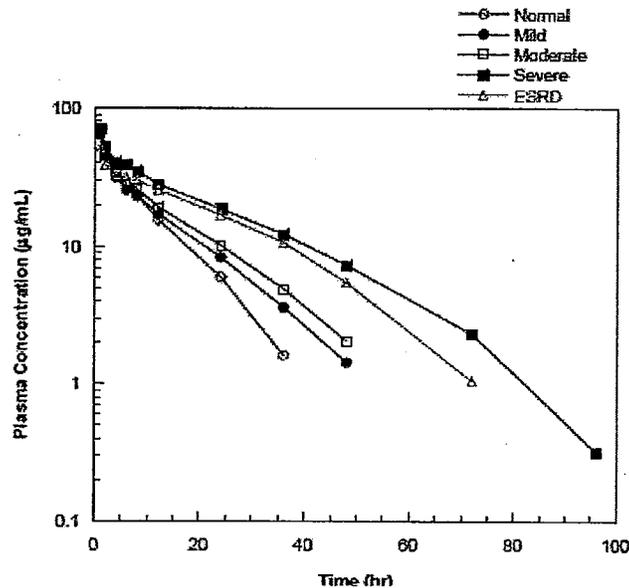


Table 20. Non-Compartmental Mean (\pm SD) Pharmacokinetic Parameters of Telavancin in Subjects With and Without Renal Dysfunction (Study I6424-103a)

Renal Conditions	Normal (n=6)	Mild (n=6)	Moderate (n=6)	Severe (n=4)	ESRD (n=6)
Protein Binding (%)	86.5 \pm 1.3	87.5 \pm 1.0	87.8 \pm 1.1	86.7 \pm 1.2	87.6 \pm 1.0
C _{max} (µg/ml)	70.6 \pm 11.2	65.9 \pm 2.7	65.8 \pm 12.1	71.8 \pm 7.1	52.1 \pm 10.1
T _{1/2} (hr)	6.90 \pm 0.60	9.61 \pm 2.93	10.6 \pm 2.4	14.5 \pm 1.3	11.8 \pm 2.8
AUC ₀₋₄₈ (µg.hr/ml)	554 \pm 92	608 \pm 81	683 \pm 169	1060 \pm 70	898 \pm 264
AUC _{0-∞} (µg.hr/ml)	560 \pm 93	633 \pm 101	721 \pm 200	1220 \pm 120	1010 \pm 341
Cl (ml/hr/kg)	13.7 \pm 2.1	12.1 \pm 1.9	11.1 \pm 3.3	6.18 \pm 0.63	8.18 \pm 2.65
MRT (hr)	9.6 \pm 0.7	13.3 \pm 3.3	14.7 \pm 3.3	22.3 \pm 2.8	20.1 \pm 3.7
V _{ss} (ml/kg)	131 \pm 2.1	157 \pm 19	156 \pm 24	136 \pm 10	157 \pm 27
Cl _r (ml/hr/kg) ^a	102 \pm 17	96.9 \pm 10.7	90.2 \pm 22.3	46.6 \pm 6.2	66.9 \pm 24.8
Cl _{r,0-48} (ml/hr/kg)	5.48 \pm 0.67	2.89 \pm 1.32	3.66 \pm 1.34	1.80 \pm 0.30	NA

Based on the measurement of telavancin concentration in the dialysate fluid collected over the hemodialysis session, an average of 5.9% of the dose was removed. The clearance of

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telavancin based on dialysis flow rate, dialysate and arterial concentrations of drug entering the dialyzer, indicated that telavancin clearance during dialysis was low, averaging 4.5 ml/min (range 2.5 - 6.5), compared with plasma clearance of 14 ml/hr/kg in normal subjects (16 ml/min for a 70 kg person). The primary route of elimination of telavancin is via the kidneys. Accordingly, the pharmacokinetic disposition of telavancin was influenced in a graded fashion by the degree of renal impairment. The relationship between creatinine clearance and plasma clearance is shown in Figure 27.

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Figure 27. Relationship between creatinine clearance and plasma clearance
 $(CL = 6.81 + 0.119 * CL_{CR}, R^2 = 0.763)$

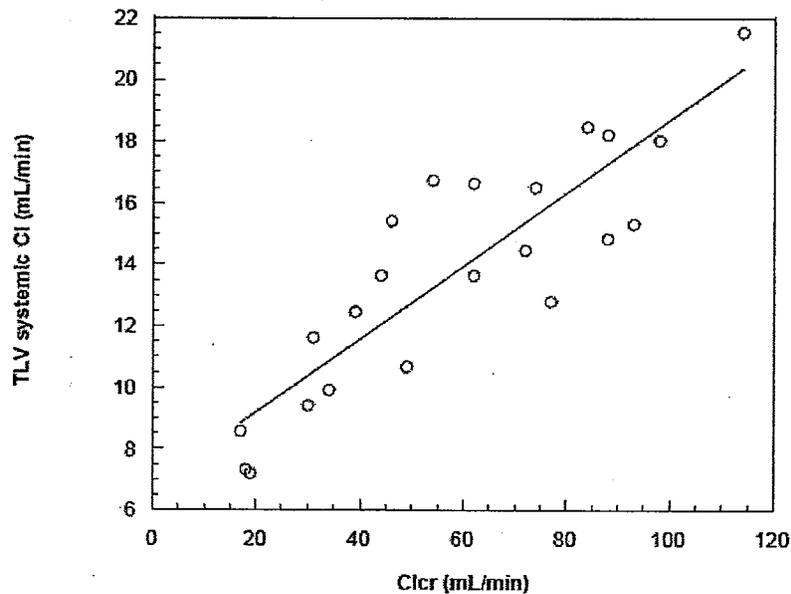


Table 21 shows the sponsor's proposed dosing changes based upon renal function. The reviewer evaluated the sponsor's proposed dosage regimens for patients with renal impairment by fitting individual concentration-time profiles from subjects with normal renal function and mild, moderate, and severe renal impairment to a two-compartment pharmacokinetic model (WinNonlin Professional, Version 4.0, Pharsight Corp., Mountain View CA) with zero-order infusion and first-order elimination. Plasma concentrations were simulated to compare individual and mean concentration-time profiles from subjects with normal renal function (n=6) and mild (n=6), moderate (n=6), and severe (n=4) renal impairment receiving the following dosage regimens: normal renal function and mild renal impairment (10 mg/kg q24h); moderate renal impairment (7.5 mg/kg q24h); and severe renal impairment (10 mg/kg q48h and 7.5 mg/kg q48h). The mean plasma concentration-time profiles are shown in Figure 28. The mean pharmacokinetic parameters based on simulated plasma concentrations for each regimen are shown in Table 22.

Table 21. Sponsor's Recommended Dosage Adjustment in Adult Patients with Renal Impairment

Creatinine clearance* (ml/min)	Telavancin Dose and Dosage Interval
>50	10 mg/kg every 24 hours
30-50	7.5 mg/kg every 24 hours
<30	10 mg/kg every 48 hours

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* As measured using the Cockcroft-Gault formula

Figure 28. Mean simulated plasma concentration-time profiles for subjects with normal renal function and mild, moderate, and severe renal impairment

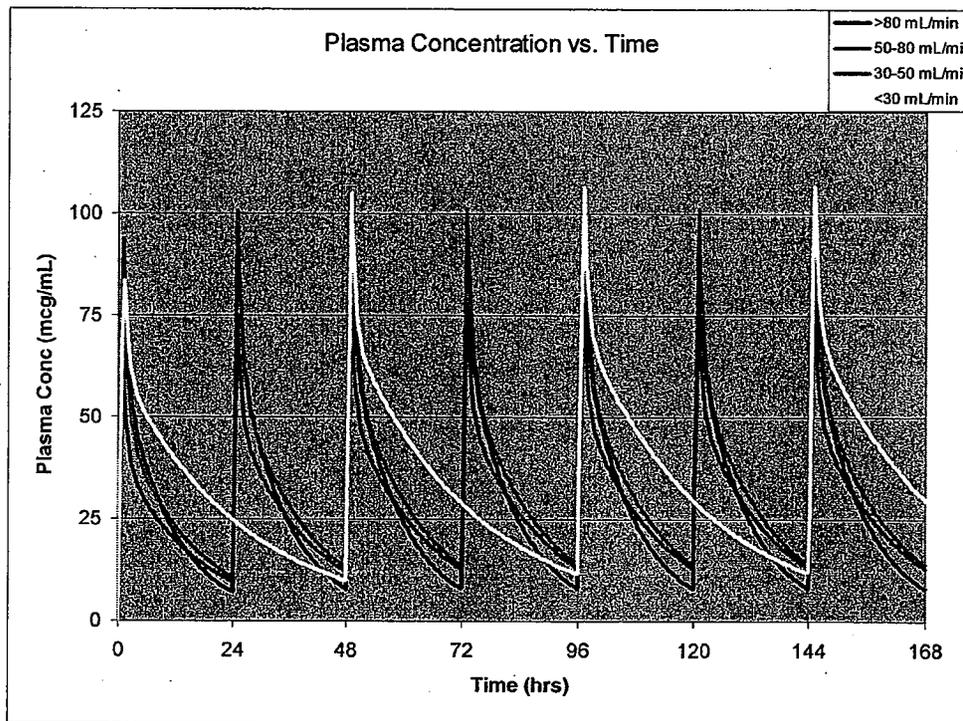


Table 22. Mean (range) pharmacokinetic parameters on day 7 based on simulated plasma concentrations

Dosage Regimen	AUC _{0-τ} (μg*hr/mL)	C _{max} (μg/mL)	C ₂₄ (μg/mL)	C ₄₈ (μg/mL)
Normal renal function (CL_{CR} ≥80 mL/min)				
10 mg/kg q24h	720	101.3	7.9	NA
Mild renal impairment (CL_{CR} 50 - <80 mL/min)				
10 mg/kg q24h	832	100.8	13.8	NA
Moderate renal impairment (CL_{CR} 30 - <50 mL/min)				
7.5 mg/kg q24h	712	78.1	13.0	NA
Severe renal impairment (CL_{CR} <30 mL/min)				
10 mg/kg q48h	1661	106.8	29.6	11.9 (7.9 – 14.0)
7.5 mg/kg q48h	1246	80.2	22.2	8.9 (5.9 – 10.5)

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Although the estimated mean C_{max} value for subjects with moderate renal impairment receiving 7.5 mg/kg q24h was lower than all other groups, the mean AUC₀₋₂₄ was similar to that estimated for subjects with normal renal function and the anticipated unbound plasma concentrations (assuming a protein binding of 87%) will remain above a MIC of 1 μg/mL. The estimated mean C_{max} in subjects with severe renal impairment receiving 10 mg/kg q48h will be comparable to that estimated for subjects with normal renal function and mild renal impairment and the anticipated unbound plasma concentrations will remain above a MIC of 1 μg/mL for all or most of the 48-hour dosing interval. Thus, the results of the pharmacokinetic analysis support the sponsor's proposed dosage adjustment for patients with moderate and severe renal impairment.

The pharmacokinetics of telavancin have not been evaluated in subjects with ESRD receiving hemodialysis prior to drug administration. In addition, the clearance among subjects with ESRD was greater than expected based on the percent of the dose of telavancin removed via hemodialysis (i.e., 5.9%). Thus, the pharmacokinetic data support the sponsor's proposed dosage adjustment for patients with ESRD

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2.3.2.6. Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of telavancin (study 0016) after the administration of a single 10mg/kg intravenous infusion was assessed. Figure 29 shows the concentration time profile of normal vs. hepatically impaired subjects. Figure 30 shows a plot of mean clearance values for the normal and moderately impaired hepatic function groups. Table 23 shows the mean observed noncompartmental pharmacokinetic parameters of telavancin for both normal subjects and subjects with moderate hepatic impairment.

Figure 29. Plot of Mean \pm SD Plasma Clearance for Telavancin Following Intravenous Administration to Subjects with Normal or Moderately Impaired Hepatic Function at a Dose of 10mg/kg (Study 0016)

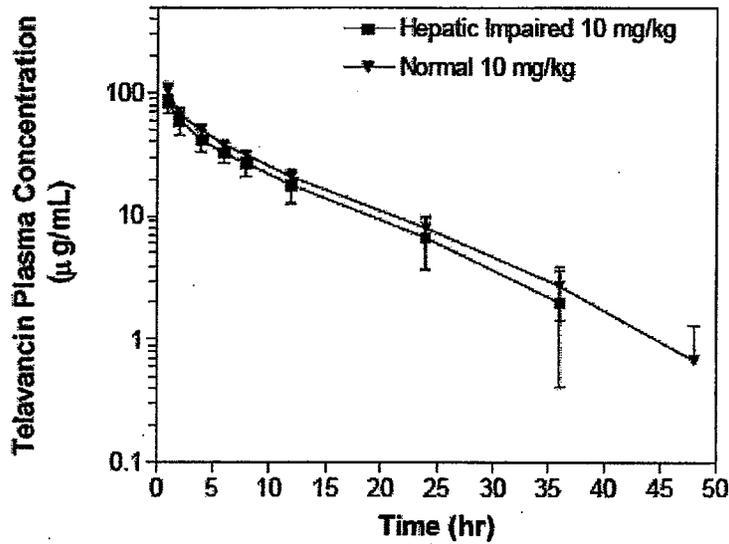


Figure 30. Total body clearance for Telavancin Following Intravenous Administration to Subjects with Normal or Moderately Impaired Hepatic Function at a Dose of 10mg/kg.

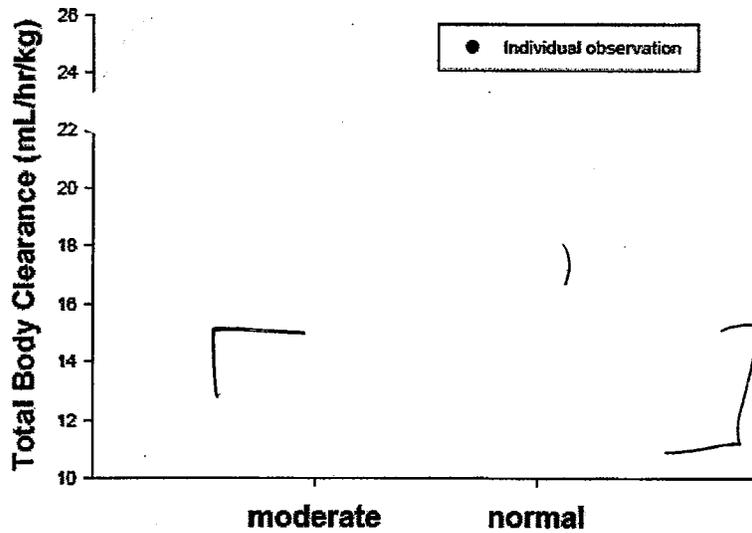


Table 23. Mean (\pm SD) Telavancin Pharmacokinetic Parameters for Subjects with Normal or Moderately Impaired Hepatic Function after Receiving Telavancin 10mg/kg (Study 0016)

Hepatic Function	Normal (n=8)	Moderately Impaired (n=8)	Moderately Impaired (n=6)*
C_{max} (μ g/ml)	105 \pm 12	82.8 \pm 13.7	88.1 \pm 11.3
T_{max} (hr)	1.0 \pm 0.0	1.0 \pm 0.0	1.0 \pm 0.0
$AUC_{(0-\infty)}$ (μ g·hr/ml)	789 \pm 69	660 \pm 159	736 \pm 86.4
Elimination $T_{1/2}$ (hr)	7.3 \pm 1.3	7.2 \pm 2.1	7.96 \pm 1.89
Cl (ml/hr/kg)	12.8 \pm 1.1	16.1 \pm 4.6	13.7 \pm 1.49
V_{ss} (ml/kg)	125 \pm 17	148 \pm 31	141.5 \pm 32.7
MRT(hr)	9.9 \pm 1.6	9.6 \pm 2.4	10.33 \pm 2.19
% Unbound	11.4 \pm 1.0	12.6 \pm 1.9	12.1 \pm 1.54
Cl_{fb} (ml/hr/kg)	113 \pm 13	129 \pm 35	115.6 \pm 23.7

*Mean pharmacokinetic parameters excluding subjects 38103-0104 and 38103-0107

The mean clearance was 26% higher and $AUC_{0-\infty}$ 16% lower in subjects with moderate hepatic impairment compared subjects with normal hepatic function. However, when subjects 38103-0104 and 38103-0107 (representing the two outliers) were excluded from the analysis, the mean clearance was only 8% higher and $AUC_{0-\infty}$ 7% lower in subjects with moderate hepatic impairment compared subjects with normal hepatic function (Figure 27). The reviewer was unable to identify any characteristics of the two subjects that could explain their higher clearance values. Thus, the lower mean AUC value among all patients with hepatic impairment may not be entirely related to the presence of hepatic impairment. In general, the mean pharmacokinetic parameters for telavancin in normal subjects and subjects with moderate hepatic impairment are similar following a 10 mg/kg infusion of telavancin and no dosage adjustment is recommended.

2.4. Extrinsic Factors

2.4.1. What extrinsic factors influence dose-exposure and/or response, and what is the impact of any differences in exposure on response?

No studies were conducted with telavancin regarding extrinsic factors such as herbal products, smoking, and alcohol.

2.4.2. Drug-Drug Interactions

2.4.2.1. Is there any in vitro basis to suspect in vivo drug-drug interactions?

In vitro studies in human liver microsomes indicated that telavancin exhibited weak inhibitory effects on the activity of major CYP 450 enzymes in human liver microsomes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 with concentrations of telavancin ranging from 0.1 to 100 μ M.

2.4.2.2. Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Telavancin is not a substrate of CYP enzymes. In vitro assays demonstrated that none of the following CYP450 isoforms metabolized telavancin in human liver microsomes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, and CYP4A11.

2.4.2.3. *Is the drug an inhibitor and/or inducer of CYP enzymes?*

An *in vitro* study was conducted to evaluate the potential for telavancin to inhibit the human cytochrome P450 enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5 in human liver microsomes (Study 05-6424-PK-31).

Incubation of telavancin in human liver microsomes at concentrations ranging from 0.1 to 100 μM resulted in inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 (as measured by both testosterone 6 β -hydroxylation and midazolam 1'-hydroxylation) with IC_{50} values of 40 μM , 89 μM , 54 μM , 35 μM , 25 μM , and 14 μM , respectively. At a concentration of 10 μM , little or no inhibition was observed for telavancin on the activity of CYP1A2, CYP2C9, CYP2C19 and CYP2D6. However, 10 μM telavancin had an effect on the activity of CYP3A4/5 (as measured by both testosterone 6 β -hydroxylation and midazolam 1'-hydroxylation) with approximately 20-40% decrease in enzyme activity. The *in vivo* concentration of telavancin is 66.1 μM and the IC_{50} for CYP3A4/5 is 14 μM . Thus the ratio is greater than 0.1 which would require an *in vivo* evaluation. These results support the study design of a drug-drug interaction study with telavancin and midazolam in healthy volunteers.

The induction potential of telavancin was not evaluated.

2.4.2.4. *Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?*

In vitro studies investigating telavancin as a substrate or inhibitor of P-gp were not conducted

2.4.2.5. *Are there other metabolic/transporter pathways that may be important?*

Not evaluated.

2.4.2.6. *What other co-medications are likely to be administered to the target patient population?*

The target patient populations for cSSSI range from mild to moderately healthy patients to patients with significant co-morbidities. Thus, telavancin hydrochloride may be used with a wide variety of co-medications from different drug classes for many different indications. Other intravenous antibiotics that are renally excreted were investigated in drug-drug interaction studies with telavancin (see Section 2.4.2.7).

2.4.2.7. *Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?*

2.4.2.8.

The sponsor conducted two studies with telavancin to determine *in vivo* drug-drug interactions

2.4.2.8.1. Midazolam

The sponsor conducted Study 0032, which was a Phase I, randomized, double-blind, placebo-controlled, crossover study to assess the effects of telavancin on the pharmacokinetic disposition of midazolam, a well-characterized probe substrate for CYP3A4. The rationale for this study was that IC_{50} of telavancin for CYP3A4/5 was lower than for the other CYPs, that is, 25 μM (44 $\mu\text{g}/\text{mL}$) for testosterone-6 β -

hydroxylation and $14 \mu\text{M}$ ($25 \mu\text{g/mL}$) for midazolam-1'-hydroxylation, which are lower than the C_{max} for telavancin following administration of 10 mg/kg . A total of 16 subjects were enrolled in this open, randomized, crossover study. Study treatments were telavancin 10 mg/kg and placebo as daily one-hour infusions for 7 days. On the seventh day of each treatment, immediately following the telavancin/placebo infusion, each subject received a single 1-minute infusion of 1 mg IV midazolam. Plasma concentrations of midazolam, 1'-hydroxy-midazolam, telavancin, the telavancin metabolite, AMI-11352, and AMI-999, were measured. Following a single IV dose, plasma concentrations of midazolam and 1'-hydroxy-midazolam with and without coadministration of telavancin declined in similar bi-exponential manners and the plasma concentration versus time curves were nearly superimposable. The noncompartmental PK parameters for midazolam and 1'-hydroxy-midazolam with and without telavancin were similar. These observations suggest that telavancin has no clinically significant effect on the PK disposition of midazolam and its major metabolite, 1'-hydroxy-midazolam. No dosage adjustment is recommended. Figure 31 shows the mean plasma concentrations of the drugs in this study. Table 24 shows the mean PK parameters in the study.

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Figure 31. Semi-log Plot of Mean Plasma Concentrations of Midazolam and 1'-Hydroxy-Midazolam Following Intravenous Administration of 1 mg Midazolam with and without Coadministration of Telavancin at 10 mg/kg via a 60-minute infusion (Study 0032)

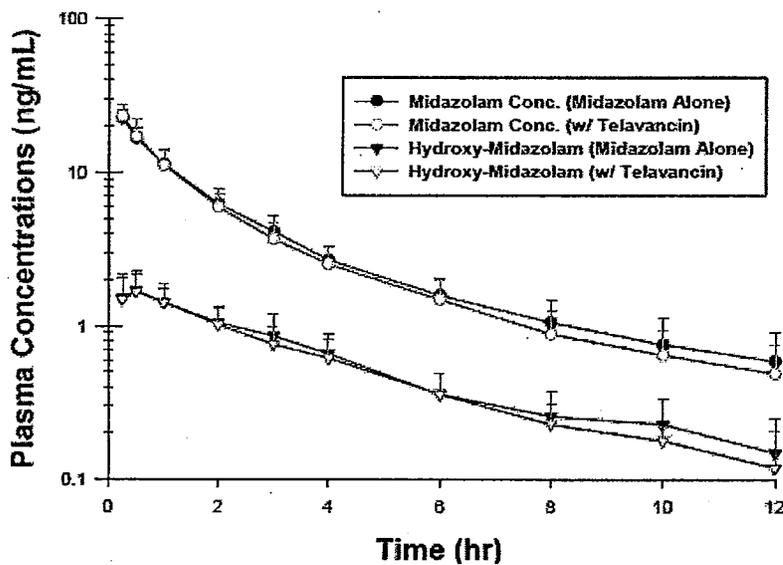


Table 24. Mean (\pm SD) Midazolam and 1'-Hydroxy-Midazolam PK Parameters for Healthy Subjects (N=16) after receiving 1mg intravenous administration of midazolam with and without Telavancin Infusion at 10mg/kg (Study 0032)

PK Parameters	Midazolam		1'-Hydroxy-Midazolam	
	Alone	w/ Telavancin	Alone	w/ Telavancin
T _{max} (hr)	0.266 \pm 0.063	0.266 \pm 0.063	0.484 \pm 0.232	0.422 \pm 0.120
C _{max} (ng/mL)	22.6 \pm 2.9	23.5 \pm 4.7	1.75 \pm 0.44	1.77 \pm 0.57
AUC ₀₋₄ (ng.hr/mL)	45.1 \pm 9.6	42.7 \pm 10.4	6.81 \pm 1.86	6.49 \pm 1.85
AUC _{0-∞} (ng.hr/mL)	46.8 \pm 9.7	44.3 \pm 10.3	8.07 \pm 2.30	7.46 \pm 2.08
T _{1/2} (hr)	4.08 \pm 1.48	3.88 \pm 1.46	4.36 \pm 2.12	4.10 \pm 1.90
CL (L/hr)	22.5 \pm 6.2	23.8 \pm 5.7	NA	NA
V _{ss} (L)	85.9 \pm 23.9	84.4 \pm 24.3	NA	NA
MRT (hr)	4.01 \pm 1.42	3.67 \pm 1.16	NA	NA
	Midazolam with Telavancin/Midazolam Alone			
C _{max} Ratio ^a	1.04 \pm 0.18		1.04 \pm 0.41	
AUC ₀₋₄ Ratio ^a	0.949 \pm 0.084		0.968 \pm 0.213	
AUC _{0-∞} Ratio ^a	0.948 \pm 0.085		0.944 \pm 0.202	

NA=Not applicable

Table 25 summarizes the mean (N=16) observed noncompartmental pharmacokinetic parameters for telavancin and its accompanying analytes. Mean C_{max} and AUC₀₋₂₄ values were much lower for AMI-11352 and AMI-999 than for telavancin. The ratios of AMI-11352 and AMI-999 to telavancin for mean AUC₀₋₂₄ values were approximately 0.008 and 0.029, respectively.

Table 25. Mean (\pm SD) Telavancin, AMI-11352, and AMI-999 Following Administration of Telavancin at 10 mg/kg via a 60-Minute Intravenous Infusion with 1 mg Midazolam Intravenous Push

PK Parameters	Telavancin	AMI-11352	AMI-999
T _{max} (hr)	1.25 \pm 0.00	3.04 \pm 0.69	1.27 \pm 0.06
C _{max} (μ g/ml)	97.0 \pm 13.6	0.379 \pm 0.161	1.73 \pm 0.51
C ₂₄ (μ g/ml) ^a	9.09 \pm 3.42	0.266 \pm 0.163	0.618 \pm 0.257
AUC ₀₋₂₄ (μ g-hr/ml)	774 \pm 143	6.49 \pm 3.50	23.2 \pm 7.5
t _{1/2} (hr)	8.86 \pm 1.48	NA	NA
Cl (ml/hr/kg)	13.3 \pm 2.1	NA	NA
C _{max} Ratio Analyte/Telavancin	-	0.00400 \pm 0.00175	0.0176 \pm 0.00333
AUC ₀₋₂₄ Ratio Analyte/Telavancin	-	0.00840 \pm 0.00459	0.0294 \pm 0.0042

^aC₂₄ is the concentration 24 hours after completion of the telavancin infusion.

NA=Not applicable

2.4.2.8.2. Aztreonam and Piperacillin-Tazobactam

The sponsor conducted Study 0035 to investigate the influence of aztreonam and the influence of piperacillin/tazobactam on the PK of telavancin in healthy subjects, and vice-versa. A total of 26 subjects were enrolled: 14 in Part 1 and 12 in Part 2. Study treatments in Part 1 were telavancin 10 mg/kg alone (TLV), aztreonam 2 gm alone (Az), and the combination of telavancin 10 mg/kg and aztreonam 2 gm (TLV+Az) on 3 separate treatment days (Study Days 1, 8, and 15). Study treatments in Part 2 were telavancin 10 mg/kg alone (TLV), piperacillin/tazobactam 4.5 gm alone (Pip/Taz), and the combination of telavancin 10 mg/kg and piperacillin/tazobactam 4.5 gm (TLV+Pip/Taz) on 3 separate treatment days (Study Days 1, 8, and 15). Within each part, a washout period of at least 7 days separated each period. Plasma concentrations of aztreonam or piperacillin/tazobactam and telavancin were measured. Measurements of urine drug concentrations to meet the objectives in characterizing the potential for interaction between telavancin and the other drugs and/or to further characterize the pharmacokinetic profile of telavancin were also conducted. The telavancin metabolite, AMI-11352, and C AMI-999, were also measured in plasma and urine. Results from each equivalence analysis are summarized in Table 26 with respect to plasma concentrations. The 90% confidence intervals (CIs) within each of the 5 comparisons met the hypothesis criterion of (0.70, 1.43) that was specified in the protocol.

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Table 26. Summary of Equivalence Analyses (Study 0035)

Parameter	Test to Reference Geometric Mean Ratios	90% Confidence Interval
Aztreonam with Telavancin versus Aztreonam Alone		
C _{max}	1.13	0.989, 1.28
AUC _{0-t}	1.09	0.942, 1.25
AUC _{0-∞}	1.08	0.941, 1.25
Telavancin with Aztreonam versus Telavancin Alone		
C _{max}	1.09	0.991, 1.19
AUC _{0-t}	1.05	0.968, 1.14
AUC _{0-∞}	1.05	0.965, 1.15
Piperacillin with Telavancin versus Piperacillin/Tazobactam alone		
C _{max}	0.990	0.910, 1.08
AUC _{0-t}	1.06	0.979, 1.15
AUC _{0-∞}	1.06	0.979, 1.15

Parameter	Test to Reference Geometric Mean Ratios	90% Confidence Interval
Tazobactam with Telavancin versus Piperacillin/Tazobactam Alone		
C_{max}	0.968	0.885, 1.06
AUC_{0-4}	1.01	0.903, 1.13
$AUC_{0-\infty}$	1.01	0.902, 1.13
Telavancin with Piperacillin/Tazobactam versus Telavancin Alone		
C_{max}	0.940	0.847, 1.04
AUC_{0-4}	0.996	0.900, 1.10
$AUC_{0-\infty}$	0.995	0.892, 1.11

Study results from Part 1 demonstrated that coadministration of aztreonam with telavancin did not alter the pharmacokinetics of aztreonam to a clinically significant degree or vice versa. Similarly, study results from Part 2 demonstrated that coadministration of piperacillin or tazobactam with telavancin did not alter the pharmacokinetics of either to a clinically significant degree or vice versa. No dosage adjustment is recommended.

2.4.2.9. *Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?*

There is no known mechanistic basis for pharmacodynamic drug-drug interactions for telavancin.

2.4.2.10. *Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?*

There are no unresolved questions related to telavancin.

2.4.3. *What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?*

None.

2.5. General Biopharmaceutics

2.5.1. *Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?*

Not applicable

2.5.2. *What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?*

Telavancin hydrochloride is an intravenous injectable product.

2.5.3. *What is the effect of food on the bioavailability (BA) of faropenem from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?*

Not applicable.

2.5.4. *How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?*

Not applicable.

2.5.5. *What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?*

Not applicable.

2.6. Analytical Section

2.6.1. *How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?*

Telavancin was measured by LC/MS/MS in the phase 1 studies. AMI-11352, the primary metabolite of telavancin (has one-tenth of the microbiological activity of telavancin) and AMI-999, C) were also measured using LC/MS/MS.

b(4)

2.6.2. *For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?*

Total telavancin concentrations were measured in all Phase 1 clinical pharmacology studies.

2.6.3. *What bioanalytical methods are used to assess concentrations?*

All the methods used to quantitate telavancin, its major metabolite AMI-11352, and C) AMI-999 in all matrices used liquid chromatography coupled with a tandem mass spectrometry detection (LC/MS/MS) system.

b(4)

2.6.3.1. *What is the range of the standard curve? What curve fitting techniques are used?*

Calibration curves for TD-6424, AMI-11352, and AMI-999 in human plasma and urine ranged from 0.250 to 100 µg/ml and were generated using a weighted (1/concentration²) linear least squares regression.).

2.6.3.2. *What are the lower and upper limits of quantification (LLOQ/ULOQ)?*

In general, for telavancin the lower limit of the various assays was 0.25µg/ml and the upper limits ranged from 100 to 200 µg/ml in plasma. For the metabolite AMI-11352 the lower limits ranged between 0.25 to 2.95 µg/ml and the upper limits ranged from 100 to 118 µg/ml in plasma. In urine, the lower limits ranged between 1.0 to 0.25µg/ml and the upper limits ranged from 0.25 to 1000µg/ml for telavancin; the lower and upper limits of quantification were 0.25 to 100 µg/ml for the metabolite.

2.6.3.3. What are the accuracy, precision, and selectivity at these limits?

The accuracy ranged from () and the precision ranged from (). For further information see individual study reviews in section 4.1.

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2.6.3.4. What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Telavancin was found to be stable in plasma following three freeze-thaw cycles and long-term stability at -60° to -80°C.

2.6.3.5. What is the QC sample plan?

Control of the quality of the analytical assay was performed with spiked QC samples, which were prepared in drug-free biological matrix. The QC samples were diluted to the same extent as the most highly diluted sample, and were included at least at every order of magnitude utilized for dilutions. The results of the unknowns from the daily runs were only accepted if the QCs met predefined acceptance criteria.

24 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio-1

4. APPENDICES

4.1. Individual Study Reviews

4.1.1. Bioanalytical Methods

4.1.2. General Pharmacokinetics

0027

A Phase I Study to Investigate the Disposition, Metabolism and Excretion of [¹⁴C]-telavancin Following Single Intravenous Administration to Healthy Volunteers.

Date(s): 22 September 2005 to 15 October 2005

Clinical sites:

Clinical Phase:

C

Analytical sites:

Analytical Phase (Total Radioactivity and Metabolite Samples) C

Analytical Phase (Parent Investigational Medicinal Product [IMP] Plasma Samples): Covance Laboratories, Inc., Madison, WI 53704, USA

b(4)

OBJECTIVES:

Primary:

The primary objective of the study was to define the disposition and excretion kinetics of the investigational medical product (IMP) in man following intravenous (i.v.) administration, and to investigate the nature of the metabolites present in plasma, urine and feces.

Secondary:

The secondary objective of the study was to assess the tolerability of the IMP.

FORMULATION:

The test product was [¹⁴C]-telavancin, given at a dose of 10 mg/kg as an I.V. infusion over 1 h (approximately 0.68 μCi/kg). The batch number is 181097-002.

STUDY DESIGN:

This study was an open-label, nonrandomized, single-dose study conducted on six, healthy, male subjects aged 30 to 55 years with a body weight of 50 to 100kg and a body mass index (BMI) of 18 to 29 kg/m² (or body weight/BMI outside these ranges which was not considered to be clinical significant). Subjects were screened in the 21 days before dosing and were admitted to the clinical unit on Day -1. At approximately 06:30 hrs (2hrs before dosing) each subject received a light breakfast consisting of 1 slice of unbuttered toast with jam, 1 glass of orange juice and 1 cup of decaffeinated tea or coffee. At approximately 08:00hrs each subject was required to drink approximately 240ml of water. The subject was then to empty his bladder immediately before dose administration. At approximately 08:30hrs a single i.v. infusion of 10 mg/kg of [¹⁴C]-telavancin was administered over 1 h on Day 1. Subjects were to remain in the clinical unit until 216 h after dosing but could have been discharged after 168 h if >90% of the dose was recovered and/or <1% of the dose was excreted in a 24 h period. During this time blood, urine and fecal samples were taken at regular intervals. The subjects were to collect samples of urine

and/or feces for an extended period (either within the clinical unit or at home) if recovery of radioactivity was incomplete at the end of the planned collection period (216 h after dosing). Physical examination, 12-lead and continuous electrocardiogram (ECG), vital signs and laboratory evaluations were performed at specified times during the study. All adverse events (AEs), whether volunteered spontaneously by the subject, or discovered as a result of general questioning, physical examination or laboratory tests were recorded from the time of dose administration on Day 1 until study discharge.

SAMPLING PROCEDURES:

Whole Blood and Plasma Samples

Whole blood samples (12ml) were collected from the arm not used for the investigational medical product infusion during the course of the study immediately before dosing (0 hrs) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours after dosing. Also 192 and 216 hrs if required. From these samples, t=0 was the time of initiation of the I.V. infusion.

Plasma

Approximately 10 mL of the 12 mL blood sample was placed into a 10 mL sodium heparin tube. After centrifugation at 1500 G for 10 minutes at approximately 4°C, the separated plasma was transferred to 3 polypropylene tubes. One plasma sample (0.5 mL) was to be used for possible future metabolite profiling (see also Section 9.4.2.1.2). One sample (0.5 mL) was transferred frozen on dry ice to Covance Laboratories, Inc for parent drug analysis. The remaining plasma sample was used for total radioactivity analysis. All plasma samples were stored at approximately -20°C until analyzed.

Whole Blood

The remaining 2 mL of blood was placed into a 2 mL sodium heparin tube and was stored at approximately 4°C until used for total radioactivity analysis.

Metabolite Profiling Sampling

A separate 30 mL blood sample was collected at the following times: Immediately before dosing (0 hrs, *i.e.* predose) and at 1, 12, 24 and 48 hr after dosing. Each sample was placed into 3 x 10 mL sodium heparin tubes. After centrifugation at 1500 G for 10 minutes at approximately 4°C the separated plasma was transferred into 2 polypropylene tubes and stored at approximately -20°C until analyzed.

Urine Samples

Urine was collected in polyethylene containers at the following times: Predose, 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hrs after dosing. For these samples, t=0 was the time of initiation of the i.v. infusion. Subjects were to remain in the clinical unit until 216 h after dosing but could have been discharged after 168 hr if >90% of the dose was recovered and/or <1% of the dose was excreted in a 24 hr period. Urine was collected at 168-192 and 192-216 hr after dosing if required.

Feces Samples

Fecal samples were collected during the course of the study at the following times: Predose, 0-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hr after dosing. For these samples, t=0 was the time of initiation of the i.v. infusion. Subjects were to remain in the clinical unit until 216 hr after dosing but could have been discharged after 168 h if >90% of the dose was recovered and/or <1% of the dose was excreted in a 24 hr period. Feces were collected at 168-192 and 192-216 hrs after dosing if required.

ASSAY METHODOLOGY

Telavancin, AMI-11352 (a known metabolite) and AMI-999 () concentrations were assayed in plasma at Covance (Indianapolis, IN) using a validated bioanalytical method with LC-MS/MS detection.

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Telavancin

Criterion	Plasma	Comments
Concentration range	0.25 to 100µg/ml	Satisfactory
LLOQ	0.25µg/ml	Satisfactory
Linearity	$R^2 \geq 0.9985$	Satisfactory
Accuracy	97.9% to 106.6%	Satisfactory
Precision	2.0% to 6.2%	Satisfactory
Specificity	Acceptable	Satisfactory
Stability	Freezer -60° to -80°C	Satisfactory
QC range	0.75 to 80.0 µg/ml	Satisfactory

AMI-11352

Criterion	Plasma	Comments
Concentration range	0.295 to 118µg/ml	Satisfactory
LLOQ	0.295µg/ml	Satisfactory
Linearity	$R^2 \geq 0.9986$	Satisfactory
Accuracy	100.1% to 104%	Satisfactory
Precision	3.0% to 7.4%	Satisfactory
Specificity	Acceptable	Satisfactory
Stability	Freezer -60° to -80°C	Satisfactory
QC range	0.75 to 80.0 µg/ml	Satisfactory

AMI-999

Criterion	Plasma	Comments
Concentration range	0.25 to 100µg/ml	Satisfactory
LLOQ	0.25µg/ml	Satisfactory
Linearity	$R^2 \geq 0.9965$	Satisfactory
Accuracy	94.6% to 103.5%	Satisfactory
Precision	4.5% to 9.3%	Satisfactory
Specificity	Acceptable	Satisfactory
Stability	Freezer -60° to -80°C	Satisfactory
QC range	0.75 to 80.0 µg/ml	Satisfactory

DATA ANALYSIS

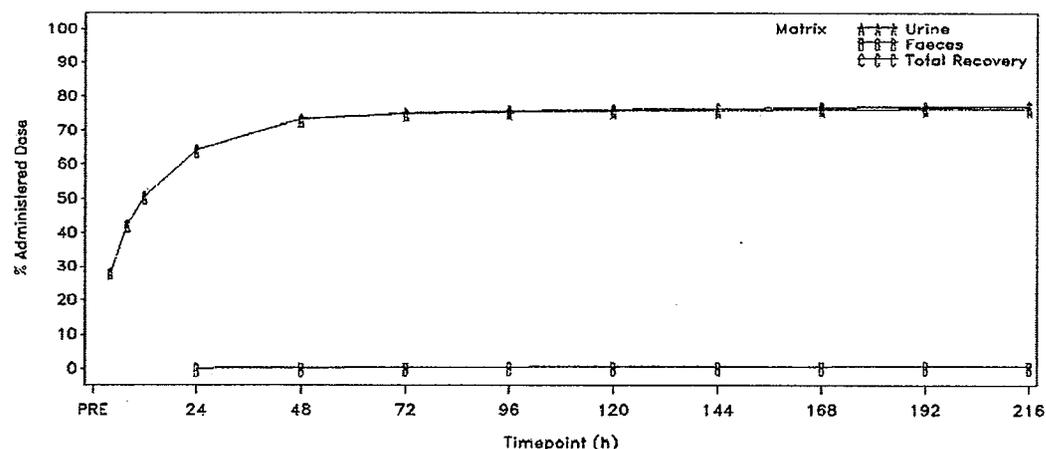
The pharmacokinetic analysis of total radioactivity concentrations was conducted using a non-compartmental approach to generate parameter estimates using WinNonlin model 202 (constant infusion administration). The terminal elimination phase was identified by regression analysis within WinNonlin, using at least 3 data points in each plasma concentration vs. time profile. The peak (C_{max}) plasma concentration and the time to reach the peak concentration (T_{max}) were taken directly from the plasma concentration-time data. T_{max} was defined as the time that C_{max} was observed. The area under the plasma concentration versus time curve from time zero to the last measurable concentration (C_{last}), $AUC_{(0-t)}$, was calculated by the linear trapezoidal rule. The terminal elimination rate constant (λ_z) was determined by linear regression of the natural logarithms of plasma concentrations versus time during the terminal phase. The terminal phase elimination half-life ($t_{1/2}$) was calculated as $\ln(2)/\lambda_z$. The areas under the plasma

concentration versus time curve from time 0 hours to infinite time, $AUC_{(0-\infty)} + C_{last}/\lambda_z$. The televancin clearance (Cl) was calculated as $dose/AUC_{(0-\infty)}$. The area under the first moment curve (AUMC) was calculated using the trapezoidal rule. The mean residence time (MRT) of televancin was calculated as $AUMC/AUC_{(0-\infty)}$. The volume of distribution at the steady state (V_{ss}) was calculated as $Cl \cdot MRT$. The cumulative amount of televancin excreted over 0-48 hour time periods was calculated based on % dose recovered as televancin over 0-48 hour time periods x mg of televancin dosed. The % excreted as televancin in urine over 48 hour time periods was calculated based on % dose recovered as televancin/ % total dose recovered in urine based on total radioactivity over 0-48 hour X 100%. The renal clearance (Cl_r) for televancin was calculated as amount of televancin excreted in urine over 0-48 hr/ $AUC_{(0-48)}$.

RESULTS

Six male subjects were enrolled and completed the study. The average age was 44.8 (± 6) years, height was 172.7 (± 7.4) cm, weight was 69.47 (± 10.93) kg, and BMI 23.3 (± 3.23) kg/m^2 . Each subject received a single dose of 10 mg/kg [^{14}C]-televancin. The total dose administered to each subject was between 579.43 and 851.90 mg of [^{14}C]-televancin. All subjects were resident in the clinical unit until 216 hrs after dosing. Total radioactivity recovery ranged from 71.2 to 82.4% of the administered dose at the end of the collection period (216 hrs post-dose). Recovery in all subjects occurred primarily 72 hrs after dosing, ranging from 69.5 to 81% of the administered dose during this time. All subjects had fecal excretion <1% of the administered dose during each 24hr collection period after 72hrs and the amount excreted decreased with time (mean 0.7% at 96 hrs post-dose and 0.1% at 216hrs post-dose). The dose was not quantitatively recovered by the end of the collection period (71 to 82%), and the remainder of the dose could not be determined. Figure 1 shows the cumulative excretion of total radioactivity.

Figure 1. Cumulative Excretion of Total Radioactivity in Urine and Feces: Mean PK Values

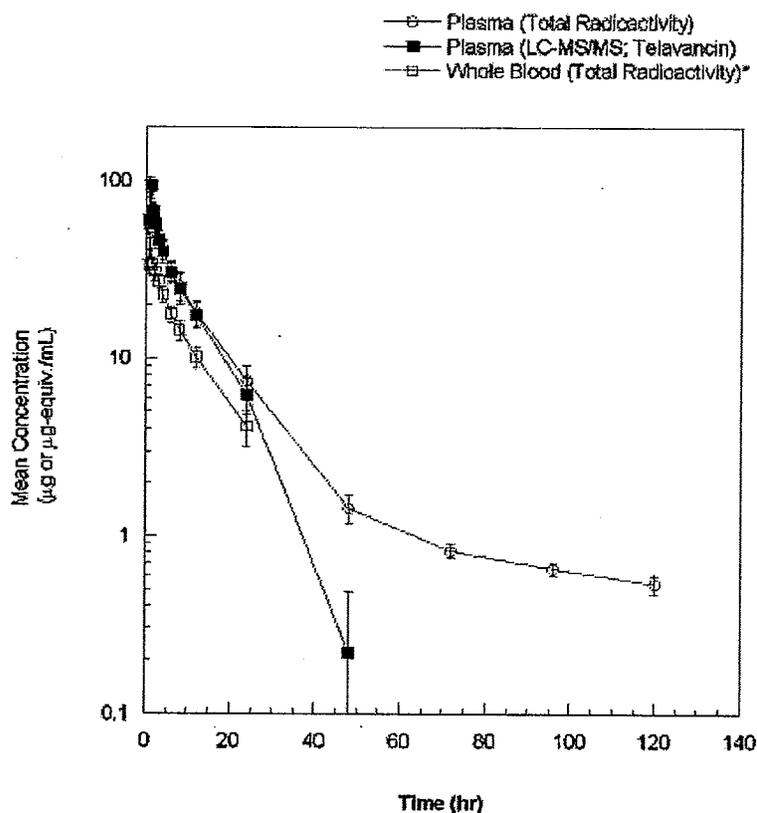


Total radioactivity was eliminated primarily in the urine, accounting for a mean of 76.3% (range 70.8 to 81.9%) of the administered dose by the end of the collection period (216 hrs post-dose), with approximately 73.2% of the administered dose eliminated in the urine by 48 hrs post dose. Excretion via feces accounted for a mean of 0.7% (range 0.4 to 0.9%) of the administered dose by the end of the collection period. Total radioactivity recovered in urine and feces accounted for a mean of 77% (range 71.2 to 82.4%) of the administered dose by the end of the collection period (216 hrs post-dose).

Note: Based upon the mean data (range 71.2 to 82.4%) of total radioactivity recovered, the information in this study appears acceptable.

Concentrations based as total radioactivity in whole blood were lower than that observed in plasma. The mean whole blood to plasma radioactivity ratios ranged from 0.489 to 0.603 for up to 24 hrs post-dose, suggesting a low degree of red blood cell partitioning for [¹⁴C]-televancin. These data are consistent with the plasma protein binding of televancin (~90%) and large molecular weight (1755.6). The mean ±SD plasma concentrations of televancin (based on LC-MS/MS analysis) and total radioactivity in plasma and whole blood as televancin is shown in Figure 2.

Figure 2. Semi-log Plot of Mean ± SD Plasma and Whole Blood Concentrations of [¹⁴C]-televancin Following I.V. Administration to Healthy Subjects at a Dose of 10 mg/kg



The mean ±SD non-compartmental PK parameters of televancin from plasma (based on LC-MS/MS analysis), as well as total radioactivity in plasma and whole blood as televancin equivalents are summarized in Table 1. At 48 hours three subjects were below the LLOQ and the sponsor used a value of zero in calculating a mean concentration. Thus, the average plasma concentration at time 48 hours appears as 0.221 µg/ml. If the average is recalculated, with the three subjects out of six that had measurable values, the average is approximately 0.441 µg/ml. This accounts for the wide separation of mean concentrations in Figure 2.

Table 1. Non-compartmental Pharmacokinetic Parameters in Plasma and Whole Blood Following I.V. Administration of [¹⁴C]-telavancin to Healthy Subjects at a Dose of 10 mg/kg (mean ± SD)

Biological Matrix	Plasma	Plasma	Whole Blood
Analysis	LC-MS/MS (Telavancin)	Total Radioactivity	Total Radioactivity
Number of subjects	6	6	6
C _{max} (µg or µg-equiv./mL)	93.6 ± 10.2	89.6 ± 11.8	43.7 ± 7.0
T _{max} (h)	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
AUC _(0-t) (µg or µg-equiv. h/mL)	620 ± 125	764 ± 119	371 ± 67
AUC _(0-∞) (µg or µg-equiv. h/mL)	649 ± 103	827 ± 120	396 ± 56
Elimination T _{1/2} (h)	7.08 ± 0.50	94.2 ± 17.8	9.89 ± 1.21
Cl (mL/h/kg)	15.7 ± 2.5	12.3 ± 1.8	25.7 ± 3.8
V _{ss} (mL/kg)	150 ± 19	478 ± 102	301 ± 28
Cl _r (mL/h/kg)	9.00 ± 1.32	NA	NA
% excreted as telavancin (0-48 h)	82.3 ± 7.4	NA	NA

NA: Not applicable

Reviewer Note: In Table 1, the percent excreted as telavancin (0-48h) actually represents the percent of drug excreted in the urine that was recovered as telavancin. Thus, of the amount recovered in the urine, 82.3 ± 7.4% was excreted as telavancin or parent.

Mean estimates of C_{max}, AUC_(0-t), and AUC_(0-∞) for total radioactivity in plasma were greater than those observed in whole blood following I.V. infusion of [¹⁴C]-telavancin. Whole blood to plasma systemic exposure ratios based on C_{max}, AUC_(0-t), and AUC_(0-∞) were 0.48-0.49 (a value similar to 1- hematocrit) following I.V. infusion of [¹⁴C]-telavancin, indicating a low degree of red blood cell partitioning for [¹⁴C]-telavancin. Estimates of elimination half-life for total radioactivity were, on average appreciably longer in plasma compared to whole blood, reflecting assay sensitivity differences for [¹⁴C]-telavancin in plasma and whole blood. This long terminal half-life may reflect the efflux of [¹⁴C]-telavancin from tissue.

The concentrations of telavancin in plasma following I.V. administration of [¹⁴C]-telavancin accounted for greater than 95% of the total radioactivity in plasma for up to 12 h post-dose. The parent molecule, telavancin, accounted for 83% and 13% of total radioactivity in the plasma at 24 and 48 hrs post-dose, respectively. These data are consistent with low systemic exposures of AMI-11352 (metabolite) in the plasma based on the AUC_(0-t) ratios of AMI-11352 versus telavancin (ranged from 0.0105 to 0.0307). Plasma concentrations of AMI-999. (), were low with AUC_(0-t) ratios of SMI-999 versus telavancin ranging from 0.00987 to 0.0174. The sponsor didn't provide an explanation why the half-life in plasma is much longer. The formation of a metabolite or distribution to a deep compartment may be possible explanations.

b(4)

CONCLUSIONS

Urinary excretion is the major route of clearance for [¹⁴C]-telavancin in humans. The mean cumulative urinary recovery for the 0-216 hrs interval was 76.3% and ranged from 70.8% to 81.9%. Fecal excretion accounted for less than 1% of the administered dose. The concentrations of telavancin in plasma following I.V. administration of [¹⁴C]-telavancin accounted for greater than 95% of the total radioactivity

in plasma for up to 12 hrs post-dose. The parent molecule, telavancin, accounted for 83% and 13% of the total radioactivity in the plasma at 24 and 48 hrs post-dose respectively. Whole blood to plasma systemic exposure ratios (based on C_{max} , $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$) were 0.48-0.49 following I.V. administration of [^{14}C]-telavancin, indicating a low degree of red blood cell partitioning for [^{14}C]-telavancin.

I6424-101a

Tolerability of Ascending Doses of Intravenous TD-6424 in Healthy Volunteers

Date(s): 12OCT2001 to 25JAN2002

Clinical Sites:

(b)(4)

OBJECTIVES:

To assess the safety and tolerability, pharmacokinetics, and the serum inhibitory and bacterial titers of TD-6424 following intravenous administration.

FORMULATION:

TD-6424 is a sterile, () colorless to slightly colored solution for intravenous administration. Each single-use vial is supplied as either a frozen solution containing 25 mL of formulated TD-6424 at pH 4.7 or a lyophilized powder that should be reconstituted with 24 mL of 5% Dextrose Injection (D5W) prior to intravenous administration. Each mL of formulated solution contains 10 mg TD-6424, 100 mg hydroxypropyl-β-cyclodextrin (HP-β-CD), sugar (35 mg dextrose monohydrate for frozen or 12.5 mg mannitol for lyophilized), and either sodium hydroxide or hydrochloric acid for pH adjustment. TD-6424 is packaged in 30 mL clear glass vials with siliconized rubber stoppers and sealed with flip-top aluminum seals. Placebo is a sterile, () colorless solution for intravenous administration. Each mL of formulated placebo solution contains 100 mg HP-β-CD, sugar (35 mg dextrose monohydrate for frozen or 12.5 mg mannitol for lyophilized), and either sodium hydroxide or hydrochloric acid for pH adjustment. Each single-use vial is supplied as either a frozen solution containing 25 mL of formulated placebo or a lyophilized powder that should be reconstituted with 24 mL of D5W prior to intravenous administration. The test product, TD-6424, was administered as an I.V. infusion of 0.25, 1, 2.5, 5, 10, 12.5 and 15 mg/kg over various infusion rates of 120, 60 and 30 minutes depending upon the part of the study. The infusion volume was 250ml and the batch numbers were AMB001 and AME001. Table 1 shows the test product, dose, mode of administration, batch number.

b(4)

Table 1. Test Product, Dose, Mode of Administration, and Batch Number

Test Products	Doses (mg/kg)	Batch Numbers
TD-6424 (active)	Single doses: 0.25, 1, 2.5, 5, 10, 12.5, 15, Multiple doses: 7.5, 12.5, 15	AMB, AME001
Placebo	Vehicles containing excipients at the same concentration as active	AMC01, AMD001

STUDY DESIGN:

This was a 2-part, randomized, double-blind, placebo-controlled study with ascending doses of TD-6424 or of placebo administered by intravenous infusion. Forty healthy normal males or surgically sterilized females (excluding replacement subjects), 18–50 years old, were to be enrolled in this study. The mean(SD) age of subjects was 25.3(4.7) years, mean weight was 80.47(10.1) kg, and height was 181(7.9) cm. A total of 16 subjects were to be enrolled in Part I of the study with an alternating panel design (i.e., 8 subjects participating in each of 2 panels, A or B). Each subject was to participate in only one panel, consisting of four treatment periods at ascending dose levels. In each treatment period, 2 subjects were to receive placebo and 6 subjects TD-6424. The protocol

provided for the recruitment of another panel (panel C) of 8 subjects in Part I of the study depending on the safety, tolerability, and available pharmacokinetic data from panels A and B. Each subject in panel C could participate in up to four treatment periods. The dose level(s) of TD-6424 for panel C were to be selected following agreement between Theravance, Inc.'s Medical Monitor and the Principal Investigator. Part I was to begin with the first treatment period of panel A. The doses of TD-6424, along with the infusion durations, are shown in Table 2.

Table 2. Doses of TD-6424 or Placebo with Infusion Duration: Part I

Treatment Period	Panel	Dose of Study Drug (mg/kg)	Infusion Duration (min)	Subjects Randomized to TD-6424 (N)	Subjects Randomized to Placebo (N)
1	A	0.25	120	6	2
2	B	1.0	120	6	2
3	A	2.5	120	6	2
4	B	5.0	120	6	2
5	A	10.0	120	6	2
6	B	12.5	120	6	2
7	A	12.5	60	6	2
8	B	12.5	30	6	2
9	C	15.0	30	6	2

A washout interval of 1 week between 2 treatment periods was planned for all subjects. Data were to be reviewed following each treatment period and dose advancements were to be made following agreement between Theravance, Inc.'s Medical Monitor and the Principal Investigator.

Part II was to commence following the completion of Part I. There were three panels in Part II (panels D, E, and F). In each panel, 8 subjects were to be randomized to receive either placebo (2 subjects) or TD-6424 (6 subjects). Each subject was to participate in only one panel. The three doses of TD-6424 administered during the three panels were to be selected by Theravance, Inc.'s

Medical Monitor and the Principal Investigator following the completion of Part I. The highest dose administered in Part II was not to be higher than a dose found to be safe and tolerable in Part I. The infusion duration for Part II was the shortest infusion duration to be found safe and tolerable in Part I. In Part II, study medication was to be administered once daily for a duration of 7 Days. As in Part I, data were to be reviewed following each panel in Part II and dose advancements were to be made following agreement between Theravance, Inc.'s Medical Monitor and the Principal Investigator.

PHARMACOKINETIC ASSESMENTS

In Part I of the study for infusions of 120 minutes duration, blood (5ml) was collected at pre-dose, and approximately 15 min, 40 min, 1 h 15 min, and 1 h 58 min after the start of infusion as well as 15 min, 40 min, 1 h 15 min, 2 h, 3 h, 4 h, 6 h, 10 h, and 24 h, after the end of infusion. In Part I for infusions of 60 minutes duration, blood (5ml) was collected at pre-dose, and approximately 10 min, 20 min, 40 min, and 58 min after the start of infusion as well as 10 min, 20 min, 40 min, 1 h 15 min, 2 h 15 min, 4 h, 7 h, 11 h, and 24 h after the end of infusion. In Part I for infusions of 30 minutes duration, blood (5ml) was collected at pre-dose, and approximately 5 min, 10 min, 20 min, and 28 min after the start of infusion as well as 5 min, 10 min, 30 min, 1 h, 2 h, 4 h, 7 h, 11 h, and 24 h after the end of infusion. In Part II, blood (5ml) was collected at pre-dose, and approximately 5 min, 10 min, 20 min, and 28 min after the start of infusion as well as 5 min, 10 min, 30 min, 1 h, 2 h, 4 h, 7 h, and 11 h after the end of infusion of the first and last dose. Blood samples (5ml) were also collected pre-dose for the second through sixth doses as

well as 24 h and 48 h after the end of infusion of the last dose. Urine was collected in each treatment period of Part I at pre-dose and 0–6 hours, 6–12 hours, and 12–24 hours after the start of drug infusion. In Part II, urine was collected prior to the first dose as well as over the intervals of 0–6 hours, 6–12 hours, and 12–24 hours after start of infusion of the last dose (i.e., the seventh dose). Saliva samples (5ml) were collected prior to the first and last doses as well as at the end of the dosing infusion and 4 hrs after the end of infusion of the first and last doses. Before a saliva sample was collected, the mouth was rinsed four times with water.

BIOANALYTICAL ANALYSIS:

Analysis of telavancin in plasma and urine was performed using a fully validated assay. Concentrations of telavancin were determined by LC-MS/MS.

Criterion	Plasma	Urine	Comments
Concentration range	0.25 to 200 µg/ml	1.0 to 1000 µg/ml	Satisfactory
LLOQ	0.25 µg/ml	1.0 µg/ml	Satisfactory
Linearity	$R^2 \geq 0.98469$	$R^2 \geq 0.99103$	Satisfactory
Accuracy	93.3% to 102.4%	98% to 105.8%	Satisfactory
Precision	4.2% to 8.8%	6.2% to 8.3%	Satisfactory
Specificity	Acceptable	Acceptable	Satisfactory
Stability	RT	RT	Satisfactory
QC range	0.6 to 180 µg/ml	3 to 750 µg/ml	Satisfactory

RT= room temperature

PHARMACOKINETICS/STATISTICAL ANALYSIS:

Pharmacokinetic parameter values were estimated using WinNonlin® pharmacokinetic software. A noncompartmental model was used to generate parameter estimates, provided there were sufficient data to permit calculations. The following pharmacokinetic parameter estimates were calculated: the maximum observed concentration (C_{max}) was determined by direct inspection of the plasma drug concentration versus time data point values, time to maximum observed concentration (T_{max}), observed was determined by direct inspection of the plasma drug concentration versus time data point values, the area under the curve to time ($AUC_{(0-t)}$) where t=time of the last sample on the pharmacokinetic profile in which quantifiable drug was detected and estimated using trapezoidal calculation.

If sufficient elimination phase data points were available, the following parameter estimates were also to be calculated: The terminal slope, k, was estimated by ln linear regression analysis of the terminal part of the curve. The terminal half life, $t_{1/2}$, was estimated as $t_{1/2} = (\ln 2)/k$. The area under the curve to infinity, $AUC_{(0-\infty)}$, was calculated after single dosing by extrapolation of the terminal slope from t to infinity, thus $AUC_{(0-\infty)} = AUC_{(0-t)} + (C_t/k)$ where C_t = plasma drug concentration at time t. Plasma clearance (CL) was estimated using the formula, $CL = Dose / AUC_{(0-\infty)}$. Mean residence time (MRT) was estimated using the formula: $MRT = (AUMC_{(0-\infty)}) / AUC_{(0-\infty)}$ where $AUMC_{(0-\infty)}$ is defined as the area under the $C_t * t$ curve. Similar parameters were estimated under steady state conditions investigated in Part II; the calculation (except for k) being restricted to a 24-hour dosing interval and without extrapolation of the AUC to infinity.

Summary statistics (i.e., mean, standard deviation, median, minimum, maximum, and n) are presented for all pharmacokinetic parameters by treatment group.

Dose proportionality of AMI 6424 was investigated statistically based on ln transformed $AUC_{(0-\infty)}$ for infusions of 120 minutes duration investigated in Part I of the study. The statistical analysis investigated a mixed effects model with a continuous (regression) effect of the logarithm of the dose, a fixed effect for the subject group and a random effect of subject within group. In addition, the $AUC_{(0-\infty)}$ derived after dosing of 25 mg/kg within 120 min, 60 min, or 30 min was compared using an analysis of variance of

$\ln(AUC_{(0-\infty)})$ in dependency of a fixed effect for the infusion duration. $AUC_{(0-\infty)}$ and AUC_{SS} derived in course of Part II of the trial will be compared between dose groups by analysis of variance after logarithmic preresultion and dose adjustment (using the highest dose as standard). The AUC_{SS} will be subjected to explorative statistical analyses in order to identify factors that might influence the bioavailability. After single dosing, the $AUC_{(0-\infty)}$ will be evaluated if this parameter can be estimated with sufficient reliability for at least 40 of the 48 profiles determined in Part I. Otherwise $AUC_{(0-t)}$ will be used. At steady state conditions in Part II, $AUC_{SS}=AUC_{(0-24)}$ will be used. All analyses will be performed after logarithmic preresultion.

Dose proportionality will be investigated separately for data of Part I (120 minutes infusion duration only) and those of Part II (single dosing and steady state). The analysis model will be $\ln(AUC)=\text{intercept}+\text{slope}*\ln(\text{dose})+\text{subject}+\text{error}$ considering fixed subject effects (each subject should provide data for at least two treatments). The influence of the infusion duration will be investigated based on the data of the last three panels in Part I. An analysis of variance (ANOVA) will be calculated with treatment effects only (i.e., ignoring that some subjects might have provided more than one result). In Part II, the steady state AUC will be compared to the single dose AUC with separate tests performed for each panel. The ANOVA model will account for Day and subject effects.

RESULTS:

Changes in Planned Study:

The protocol was amended twice. The first amendment (dated 26 October 2001) added audiologic assessments for subjects participating in Part II of the study and allowed the use of a lyophilized form of the placebo in addition to the frozen drug form. The second amendment (dated 14 November 2001) allowed the use of a lyophilized form of TD-6424 in addition to the frozen drug form, allowed the dosing of 20 mg/kg TD-6424 infused over 30 minutes, added the collection of saliva samples in panels E and F of Part II of the study, allowed subjects to drink fluids once drug infusion was completed, and increased the volume of blood collection from 5 mL to 7 mL for the determination of serum inhibitory and bactericidal titers.

Study Population:

In Part I of the study, a total of 27 subjects, including 3 replacement subjects, were randomized. Three subject panels (panels A, B, and C) were recruited, each consisting of 8 subjects. All subjects in panels A and B participated in four treatment periods, and thus received four different treatments during the study, with the exception of subjects 2, 6, and 13, who terminated early, and their replacements: subjects 102, 106, and 113. A single dose of either TD-6424 or placebo was administered in each period, followed by a washout interval of 1 week. In each treatment period, subjects were randomized to TD-6424 or placebo in a 3:1 ratio, and no subject received placebo more than once during the study.

Subjects in panel A participated in periods 1, 3, 5, and 7, and received TD-6424 0.25, 2.5, and 10 mg/kg infused over 120 minutes; 12.5 mg/kg infused over 60 minutes; or placebo. Subjects in panel B participated in periods 2, 4, 6, and 8, and received TD-6424 1.0, 5, and 12.5 mg/kg infused over 120 minutes; 12.5 mg/kg infused over 30 minutes; or placebo. All 8 subjects in panel C received a single dose of either TD-6424 15 mg/kg or placebo infused over 30 minutes. Table 3 shows subject treatment assignment, study drug dose, and infusion time for each panel and treatment period for Part I of the study.

Table 3. Treatment Assignment: Part I

Treatment Period	Panel	Dose of Study Drug (mg/kg)	Infusion Time (min)	Subjects Receiving Study Drug	Subjects Receiving Placebo
1	A	0.25	120	1, 2, 4, 5, 6, 8	3, 7
2	B	1.0	120	11, 12, 13, 14, 15, 16	9, 10
3	A	2.5	120	1, 2, 3, 7, 8, 106	4, 5
4	B	5.0	120	9, 10, 11, 14, 15, 16	12
5	A	10.0	120	1, 3, 4, 5, 7, 8	102, 106
6	B	12.5	120	9, 10, 11, 12, 16, 113	14, 15
7	A	12.5	60	3, 4, 5, 7, 102, 106	1, 8
8	B	12.5	30	9, 10, 12, 14, 15, 113	11, 16
9	C	15.0	30	17, 19, 20, 21, 23, 24	18, 22

Three subjects terminated prematurely from Part I of the study. Subject 2 terminated due to moderate pre-syncope beginning immediately after the start of infusion in treatment period 3; the pre-syncope lasted until the infusion was stopped, approximately 2 minutes later. Subject 13 terminated the study due to tinnitus, which began 9 hours and 10 minutes after the first dose, lasting for 3 hours. Tinnitus was again reported 23 hours later, specifically in the left ear, at which time the subject terminated. The tinnitus had apparently resolved by the time of the post-study physical examination, 7 Days after study withdrawal. Subject 6 terminated due to an abnormal laboratory value. Further investigation revealed that Subject 6 had had the same condition of glycosuria when screened for a prior study. A glucose tolerance test revealed this subject was not diabetic, but had a low renal threshold. Subjects 2, 6, and 13 were subsequently replaced by subjects 102, 106, and 113 in treatment periods 5, 3, and 6, respectively.

In Part II of the study, 27 subjects, including 3 replacement subjects, were enrolled into one of three panels (D, E, or F). Each subject received a 30-minute infusion of study drug or placebo once daily for 7 days. Subjects were randomized in a 3:1 ratio of study drug to placebo at each level. Subjects in panel D received either TD-6424 7.5 mg/kg or placebo; subjects in panel E received either TD-6424 15 mg/kg or placebo; and subjects in panel F received either TD-6424 12.5 mg/kg or placebo. Five subjects terminated the study early, 4 of whom withdrew due to an adverse event. Subject 31 (received TD-6424) withdrew after experiencing mild tinnitus prior to dosing on Day 3, which resolved in 48 hours. Subject 36 (received TD-6424) withdrew 20 minutes after the start of infusion on Day 1 due to mild urticaria, which resolved in approximately 20 hours. Subject 40 (received TD-6424) had mild pruritus following infusion on Day 1; this event resolved within 19 hours. Subject 45 (received placebo) developed a moderate morbilliform rash 3 hours after the second dose, which was ongoing at the post-study physical exam. Subjects 31, 35, and 45 were replaced by subjects 131, 135, and 145, respectively.

Protocol Deviation:

Urinary pharmacokinetics for TD-6424 was only performed during Part II (multiple

dosing) of the study.

Plasma Pharmacokinetics:

Table 4 summarizes the plasma PK parameters of TD-6424 for subjects receiving intravenous single dose administration. The clearance values are similar at the 5 mg/kg to 12.5 mg/kg dosage range, but appear higher at lower dose levels. The product appears to be linear and dose proportional in the therapeutic dose range.

Table 4. Plasma Pharmacokinetic Parameters following Intravenous Single-Dose Administration (Values are presented as arithmetic mean \pm SD)

Duration of Infusion	120 Minute						60 Minute	30 Minute	30 Minute
	0.25 mg/kg	1.0 mg/kg	2.5 mg/kg	5.0 mg/kg	10 mg/kg	12.5 mg/kg	12.5 mg/kg	12.5 mg/kg	15.0 mg/kg
Parameter									
N	6	6	5 ^b	6	5 ^c	6	5 ^d	6	6
C _{max} (µg/mL)	1.98 \pm 0.25	9.97 \pm 0.91	23.6 \pm 4.8	44.9 \pm 3.2	87.5 \pm 6.0	111.7 \pm 18.3	114.0 \pm 4.9	153.8 \pm 26.3	178.7 \pm 9.6
AUC _(0-∞) (µg.hr/mL)	7.60 \pm 0.91	59.1 \pm 8.8	182.2 \pm 29.7	386.3 \pm 37.8	761.8 \pm 81.2	996 \pm 150	814.9 \pm 77.3	1006 \pm 202	1210.3 \pm 138
AUC _(0-t) (µg.hr/mL)	8.92 \pm 1.33 ^a	63.2 \pm 6.4	193.2 \pm 31.0	425.8 \pm 48.8	858.2 \pm 108.6	1143 \pm 195.	912.6 \pm 95.4	1136 \pm 241	1430 \pm 202.2
t _{1/2} (hr)	2.9 \pm 0.2 ^a	4.6 \pm 0.5	5.7 \pm 0.6	6.9 \pm 0.6	7.5 \pm 0.6	7.9 \pm 0.9	7.6 \pm 0.3	7.8 \pm 0.6	9.1 \pm 1.0
CL (mL/hr/kg)	28.5 \pm 4.2 ^a	15.9 \pm 1.6	13.2 \pm 2.0	11.9 \pm 1.5	11.8 \pm 1.4	11.3 \pm 2.3	13.8 \pm 1.4	11.4 \pm 2.5	10.7 \pm 1.6
MRT (hr)	3.7 \pm 0.2 ^a	5.9 \pm 0.5	7.5 \pm 0.5	9.0 \pm 0.8	9.8 \pm 0.9	10.5 \pm 1.3	9.8 \pm 0.5	10.2 \pm 0.9	11.8 \pm 1.3
V _{ss} (mL/kg)	104 \pm 17.9 ^a	93.5 \pm 4.8	99.8 \pm 19.3	106.3 \pm 5.3	115.0 \pm 6.3	116.4 \pm 12.5	134.9 \pm 8.5	115.3 \pm 17.7	124.3 \pm 7.8

^a N = 4; 2 subjects had >20% of the AUC values being extrapolated and were excluded from the mean calculations.

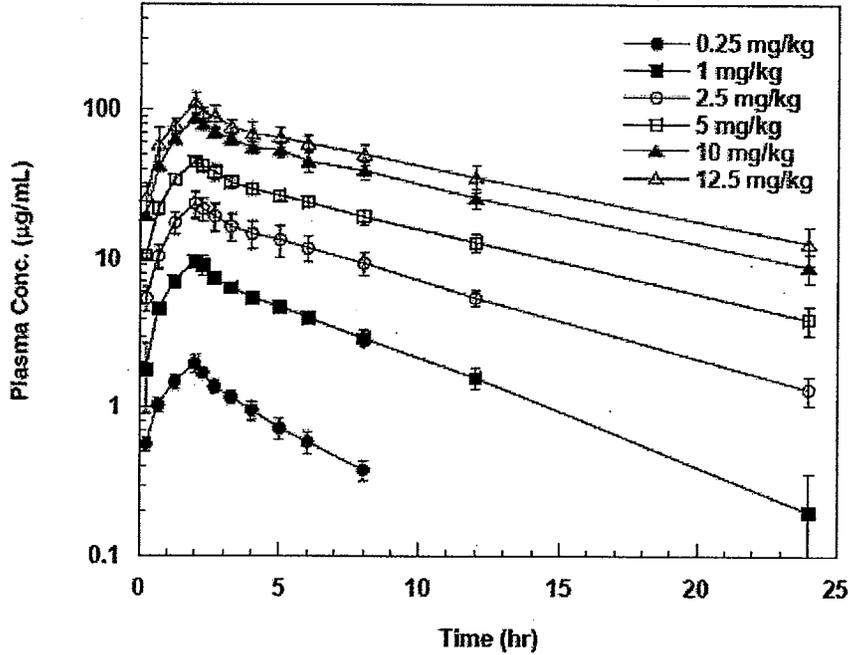
^b One subject with most of the plasma concentrations below limit of the quantitation and were excluded from the mean calculations.

^c One subject had a T_{max} at 4 hr and data was not included in the mean and SD calculations.

^d One subject had no quantifiable concentration in plasma at the end of infusion and data was not included in the mean and SD calculations.

Figure 1 displays the mean plasma concentration \pm SD over time for subjects receiving 120 minute infusions. At the end of infusion, plasma concentrations reached quantifiable levels in all subjects at dose levels and concentrations of TD-6424 in plasma declined in a monoexponential manner with terminal half-lives ranging from 3-8 hours.

Figure 1. Plasma Concentrations ($\mu\text{g/ml}$) of TD-6424 Following 120-minute Intravenous Administration. Data are presented as arithmetic mean \pm SD.



All subjects in the 2.5, 5, 10, and 12.5 mg/kg dose levels displayed quantifiable plasma levels out to 24 hours after dosing. Four out of the 6 subjects in the 1 mg/kg dose group displayed quantifiable plasma concentrations out to 24 hours and 2 subjects out to 12 hours. None of the 6 subjects in the 0.25 mg/kg dose group exhibited quantifiable plasma concentrations after 8 hours.

The linearity of the pharmacokinetics of TD-6424 were examined among subjects who received 120-minute infusions of 1 mg/kg to 12.5 mg/kg. Six subjects who received 0.25 mg/kg infusions were excluded from this analysis because of nonquantifiable plasma concentrations after 8 hours. The data shows that as the dosage of the product increases the AUC and C_{max} values also increase proportionally, exhibiting linearity of this drug product. Figure 2 and Figure 3 display the dose linearity analysis for C_{max} and AUC, respectively. Both figures exhibit approximate linear pharmacokinetics in healthy volunteers following single-dose administration.

Figure 2. Dose Linearity Analysis for C_{max} Values

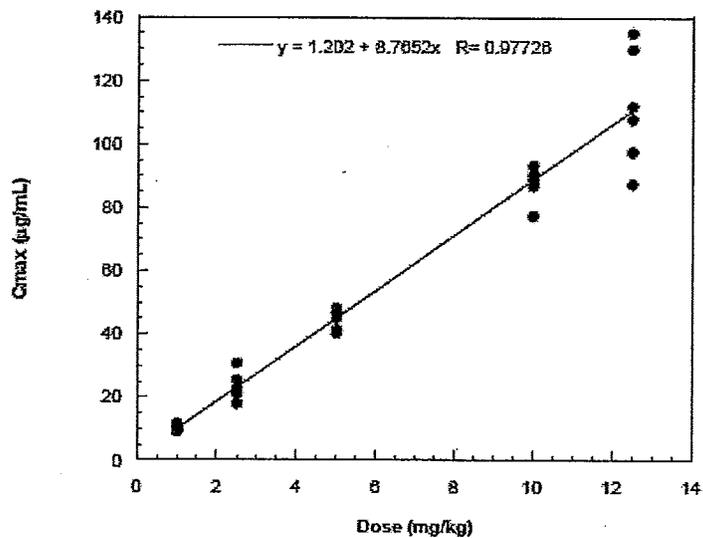


Figure 3. Dose Linearity Analysis for AUC Values

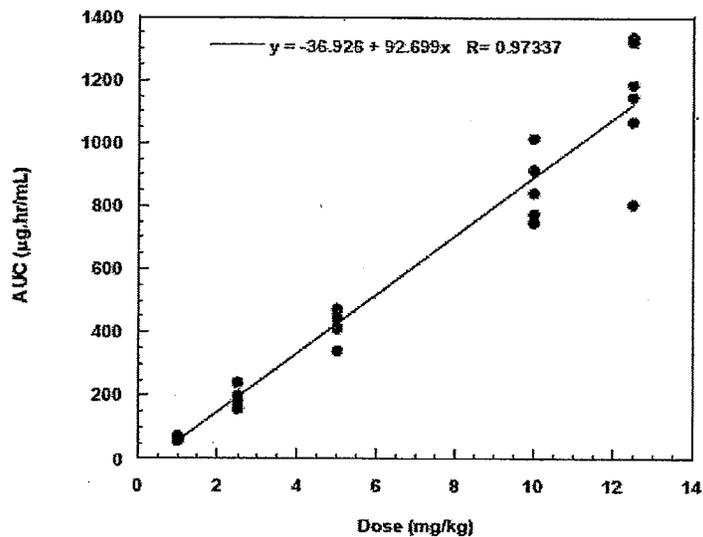


Table 5 indicates that dose-proportional increases in C_{max} values were observed (for 2.5, 5, 10, and 12.5 mg/kg doses: 2.4-, 4.5-, 8.8- and 11 times increase in respect to 1 mg/kg, respectively). The ratio of C_{max}/dose was fairly consistent, averaging 9 µg/mL to 10 µg/mL. Based on dose-normalized AUC_(0-∞) normalized to 1 mg/kg, the AUC_(0-∞) values at 2.5, 5, 10, and 12.5 mg/kg were respectively 22%, 35%, 36%, and 45% more than expected from dose-proportional increase.

Table 5. Dose Proportion Analysis

Parameter	1 mg/kg	2.5 mg/kg	5 mg/kg	10 mg/kg	12.5 mg/kg
C _{max} (µg/mL)	9.97 ± 0.91	23.6 ± 4.8	44.9 ± 3.2	87.5 ± 6.0	111.7 ± 18.3
Ratio		2.4	4.5	8.8	11
C _{max} /dose	9.97 ± 0.91	9.45 ± 1.94	8.97 ± 0.65	8.75 ± 0.60	8.93 ± 1.46
AUC _(0-∞) /dose	63.2 ± 6.3	77.3 ± 12.4	85.2 ± 9.8	85.8 ± 10.9	91.4 ± 15.6
Ratio		22%	35%	36%	45%

Table 6 summarizes the plasma pharmacokinetic parameters following a 120-, 60-, or 30-minute infusion at 12.5 mg/kg. Unexpectedly, the mean AUC value was lower for the 60-minute infusion compared to that observed for the 30- and 120-minute infusions. However, as would be expected, the mean C_{max} value for the 30-minute infusion was higher than that observed for the 60- and 120-minute infusions. In general, the pharmacokinetics of intravenous TD-6424 in healthy volunteers appears to show linear kinetics as evidenced by proportional increases in C_{max} with increases in dose.

Table 6. Plasma Pharmacokinetic Parameters following Intravenous Single-Dose Administration. Values are presented as arithmetic mean ±SD.

Parameter	12.5 mg/kg 120 min	12.5 mg/kg 60 min	12.5 mg/kg 30 min
N	6	5*	6
C _{max} (µg/mL)	111.7 ± 18.3	114.0 ± 4.9	153.8 ± 26.3
AUC ₍₀₋₄₎ (µg.hr/mL)	996 ± 150	814.9 ± 77.3	1006 ± 202
AUC _(0-∞) (µg.hr/mL)	1143 ± 195	912.6 ± 95.4	1136 ± 241
t _{1/2} (hr)	7.9 ± 0.9	7.6 ± 0.3	7.8 ± 0.6
CL (mL/hr/kg)	11.3 ± 2.3	13.8 ± 1.4	11.4 ± 2.5
MRT (hr)	10.5 ± 1.3	9.8 ± 0.5	10.2 ± 0.9
V _{ss} (mL/kg)	116.4 ± 12.5	134.9 ± 8.5	115.3 ± 17.7

* One subject had no quantifiable concentration in plasma at the end of infusion and data was not included in the mean and SD calculations.

Table 7 summarizes the concentrations of TD-6424 in plasma samples obtained on Day 1 and Day 7 of the multiple ascending dose part of the study.

Table 7. Pharmacokinetic Parameters following Intravenous Infusion for 7 Consecutive Days. Arithmetic mean values are presented.

Parameter	7.5 mg/kg/day		12.5 mg/kg/day		15 mg/kg/day	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
N	7	6	6	6	7	4
C _{max} (µg/mL)	90.3	96.7	154.7	151.3	181.4	202.5
AUC _(0-∞) or AUC _{SS} * (µg.hr/mL)	668	700	1013	1033	1239	1165
t _{1/2} (hr)	7.9	8.8	7.3	9.1	7.3	8.8
CL (mL/hr/kg)	12.0	9.0	12.0	10.0	12.0	11.0
MRT (hr)	9.9	11.4	9.7	11.7	9.5	11.3
V _{ss} (mL/kg)	113	105	121	119	117	126
AUC ratio (Day 7/Day 1)	1.05		1.02		1.01	

*AUC_{SS} on Day 7

C_{max}: Maximum plasma concentrations of TD-6424

AUC_{SS}: Steady-state area under the plasma concentration time curve

AUC_(0-∞): Value of AUC extrapolated to infinity

CL: Total body clearance

V_{ss}: Steady-state volume of distribution

MRT: Mean residence time

Figure 4 through Figure 6 display the mean (SD) plasma concentration over time for Days 1 and 7 at the 7.5, 12.5, and 15 mg/kg/day dose levels, respectively. Following the first intravenous infusion of TD-6424, concentrations of TD-6424 in plasma reached quantifiable levels in all subjects at all dose levels. All subjects displayed quantifiable plasma levels out to 24 hours after dosing on both Day 1 and Day 7 at all three dose levels. Elimination phases were estimated in all subjects using data from 4.5 or 7.5 to 24 hours, except one subject in the 12.5 mg/kg/day dose group for which 11.5 to 24 hours data were used. The accumulation based on the accumulation factor $AF=1/(1-e^{-\lambda t})$ was calculated to be 1.145. The accumulation across doses is similar to the predicted accumulation based on this equation.

Figure 4. Concentrations of TD-6424 in Plasma at Days 1 and 7 Following Intravenous Infusion at 7.5mg/kg/day for 7 days. Data are arithmetic mean \pm SD for 7 subjects on Day 1 and 6 subjects for Day 7.

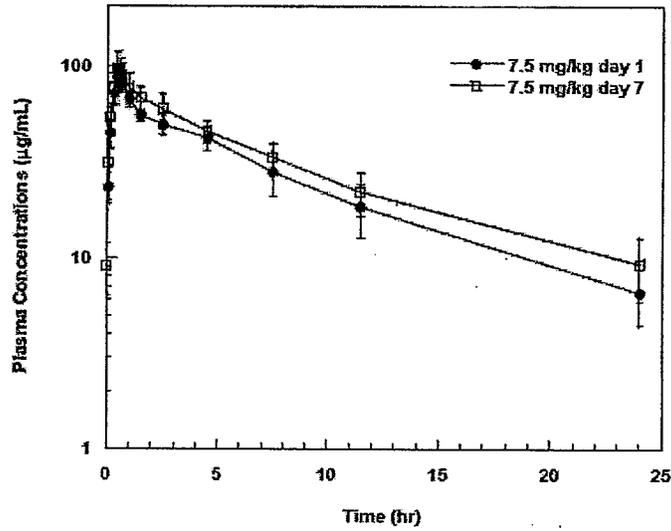


Figure 5. Concentrations of TD-6424 in plasma at Days 1 and 7 Following Intravenous Infusion at 12.5 mg/kg/day for 7 Days. Data are arithmetic mean \pm SD for 6 subjects.

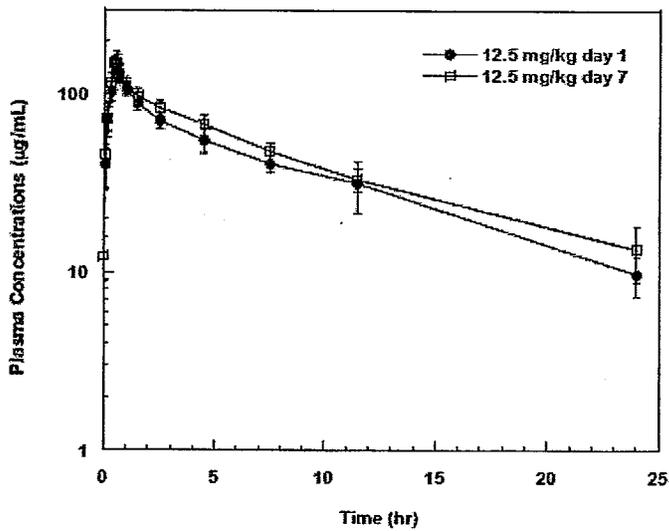
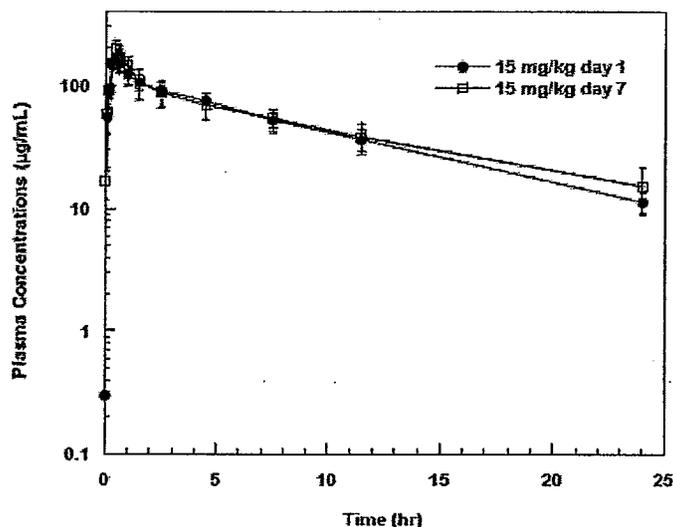


Figure 6. Concentrations of TD-6424 in Plasma at Days 1 and 7 Following Intravenous Infusion at 15 mg/kg/day for 7 Days. Data are arithmetic mean \pm SD for 7 subjects on day 1 and 4 subjects on day 7



The trough plasma concentrations of TD-6424 were also determined for Days 1 through 7; data is summarized in Table 8. It appears that steady state is attained on Day 3-4 and plasma concentrations were not increased further once reaching steady state.

Table 8. Trough Plasma Concentrations of TD-6424 (μ g/ml) for 7 Consecutive Days

Dose	7.5 mg/kg/day		12.5 mg/kg/day		15.0 mg/kg/day	
	Mean	SD	Mean	SD	Mean	SD
Day 1	6.56	2.15	9.78	2.43	11.3	2.12
2	7.44	2.76	12.7	2.98	10.0	7.57
3	6.55	5.25	13.0	4.08	15.4	3.22
4	9.37	3.46	12.7	2.84	15.5	3.42
5	8.83	3.90	13.4	4.34	14.1	5.10
6	9.09	2.74	12.3	3.44	16.7	4.82
7	9.38	3.15	13.5	4.69	15.2	6.15

In summary, the pharmacokinetics of intravenous TD-6424 in healthy subjects was largely independent of dose following seven daily doses at the 7.5, 12.5, and 15 mg/kg dose levels. No significant changes were observed in C_{max} , AUC, and half-lives following repeated administrations of TD-6424 at the 7.5, 12.5, and 15 mg/kg dose levels. The steady state is attained on Day 3-4, based on trough plasma concentration. Based on the AUC values, daily administration of TD-6424 does not result in appreciable accumulation in healthy subjects.

Urinary Pharmacokinetics:

Data for cumulative percentage of the dose excreted in urine based on unchanged TD-6424 are summarized in Table 9. Twenty-four hour urinary recoveries were 68.3%, 61%, and 60% for the 7.5, 12.5, and 15 mg/kg/day dose levels, respectively. These data indicate that renal excretion is the major route of elimination for TD-6424 in humans. It should be noted that significant amounts of TD-6424 were still being excreted in the 12 to 24 hour sampling period, suggesting that additional drug may be excreted beyond 24 hours. Therefore, the values for urinary recovery obtained in this analysis may be underestimates. This is also supported by the approximate 8 hour plasma elimination half-life. Additionally, the recovery of 36% to 40% of the administered dose within 6 hours is consistent with the plasma elimination half-life of approximately 8 hours.

Table 9. Urinary Recovery of TD-6424 Following Intravenous Infusion to Healthy Subjects at 7.5, 12.5, and 15mg/kg/day for 7 Consecutive Days (Arithmetic mean values are presented).

Time Intervals	% Dose Recovered as Unchanged TD-6424		
	7.5 mg/kg/day	12.5 mg/kg/day	15 mg/kg/day
Dose			
N	5	6	6
0-6 hr	39.5	37.6	35.9
6-12 hr	13.6	14.1	13.4
12-24 hr	15.2	9.2	10.8
Total % (cumulative recovery 0-24 hr)	68.3	61.0	60.1

Preliminary results revealed that three hydroxyl metabolites were present in the urine samples at varying concentrations, but in relatively low amounts. The retention time of the hydroxyl metabolite present in the greatest quantity roughly corresponded to the TD-11352 standard (7-OH metabolite, a major metabolite observed in pre-clinical animal models). Two additional hydroxyl metabolites were present at very low amounts. In addition, (TD-999) (TD-6424 des-phosphonate) was also detected in the urine samples at relatively low amounts.

b(4)

CONCLUSIONS:

The pharmacokinetic disposition of intravenous TD-6424 following single doses in healthy volunteers appeared to be largely independent of dose. The Cmax values following single-dose administration of TD-6424 demonstrate approximate dose proportionality. The AUC values were slightly higher than expected, but this finding does not suggest non-linearity. Following multiple dose administration in Part II of the study, the pharmacokinetic disposition of TD-6424 was similar to that following single doses, and no significant accumulation was observed. Renal excretion was found to be the major route of elimination.

I6424-107a

Pharmacokinetics and Tissue Penetration of Telavancin in Healthy Subjects

Date(s): 04APR2004 to 15MAY2004

Clinical Sites:

C

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b(4)

OBJECTIVES:

Primary:

The primary objective of this study was to compare the steady-state pharmacokinetic profiles of telavancin in plasma and blister fluid following infusion of telavancin 7.5 mg/kg administered once daily for 3 days, in healthy male and female subjects.

Secondary:

Safety and tolerability of telavancin was also assessed.

FORMULATION:

Telavancin was supplied as a sterile, [^] / lyophilized powder. Each vial of telavancin for injection contained 250 mg telavancin, 2.5 g hydroxypropylbetadex, 3.125 mg mannitol, and sodium hydroxide and/or hydrochloric acid (for pH adjustment). Each vial of telavancin 250mg was reconstituted with 24ml of 5% dextrose. Following reconstitution, each ml of formulated solution contained approximately 10mg telavancin, 100 mg hydroxypropylbetadex, and 12.5 mg mannitol. The reconstituted solution of telavancin (10mg/ml) was aseptically diluted further in 5% dextrose to an administration volume of 250ml. Telavancin for injection batch no. AME006 was used in this study.

b(4)

STUDY DESIGN:

This was a Phase 1, open-label, single-arm, multiple-dose, single center study to compare blister fluid and plasma concentrations of telavancin when approximate steady-state levels were achieved. A total of nine male and female subjects were enrolled and received at least one dose of telavancin. One of the first 8 subjects enrolled discontinued the study after the first dose of telavancin when it was noted that his hepatic enzymes were abnormal in samples drawn prior to the first dose of telavancin and was replaced, bringing the total back to 8 subjects. Eight of the 9 subjects were male; 7 were Caucasian. The mean age of the 9 subjects was 26.1 years (range: 21-46) and mean body weight was 80.1 kg (range: 60.8-114.3). Subjects received a 1 hour intravenous infusion of 7.5 mg/kg telavancin once daily for 3 consecutive days. A total of 14 cantharidin-induced blisters were produced on each subject. Six blisters were created on each arm of each subject approximately 10 hours after the start of the second infusion on Day 2 and 1 blister was created on each arm of each approximately 10 hours after the start of the third infusion on Day 3.

PHARMACOKINETIC ASSESSMENTS:

Blood samples (5ml) for telavancin concentrations were to be collected pre-infusion on Days 1 and 3, at the end of the infusion on Day 3 and at 1, 3, 5, 7, 11 and 23 hours following completion of the Day 3 infusion. Blister fluid samples (100µl to 200 µl) for telavancin concentrations were to be collected on Day 3 at the same times as the plasma samples. Serum and blister fluid bactericidal and inhibitory concentrations against two bacterial isolates were also to be determined in the 11 hour sample and 23 hour sample after completion of the Day 3 infusion.