**BIOANALYTICAL ANALYSIS:**
Analysis of televancin in plasma and blister fluid was performed using a validated LC/MS/MS method.

| Criterion | Plasma | Blister Fluid | Comments |
|---|---|---|---|
| Concentration range | 0.25 to 100 µg/ml | 0.01 to 5 µg/ml | Satisfactory |
| LLOQ | 0.25 µg/ml | 0.01 µg/ml | Satisfactory |
| Linearity | $R^2 \geq 0.9940$ | $R^2 \geq 0.9984$ | Satisfactory |
| Accuracy | 95.5% to 107.9% | 93.9% to 104.3% | Satisfactory |
| Precision | 3.2% to 8.0% | 2.7% to 5.3% | Satisfactory |
| Specificity | Acceptable | Acceptable | Satisfactory |
| Stability | Freezer -60° to -80°C | Freezer -60° to -80°C | Satisfactory |
| QC range | 0.75 to 80 µg/ml | 0.03 to 18 µg/ml | Satisfactory |

**PHARMACOKINETIC/STATISTICAL ANALYSIS:**
For telavancin plasma or blister fluid concentrations below the limit of quantitation, zero was used for mean calculations. A mean value was not to be reported if more than 50% of the samples had values below the limit of quantitation. Nominal time was used in pharmacokinetic calculations.The pharmacokinetic parameters of telavancin were determined by non-compartmental analysis using WinNonlin Version 4.0.1. The trough (C24 or Cmin) and peak (Cmax) plasma concentration and the time to reach the peak concentration (Tmax) were taken directly from the plasma concentration-time data. Tmax was defined as the time that Cmax was observed. The areas under the plasma concentration versus time curve from time zero to 24 hours (AUC0-24) after dosing were calculated by the linear trapezoidal rule. The terminal elimination rate constant ($\lambda z$) was determined by linear regression of the natural logarithms of plasma concentrations versus time during the terminal phase. The terminal-phase elimination half-life (t1/2) was calculated as $\ln(2)/\lambda z$. The telavancin clearance (CL) was calculated as dose/AUC0-24. The area under the first moment curve (AUMC0-24) was calculated using the trapezoidal rule. The mean residence time (MRT) of telavancin was calculated as AUMC0-24/AUC0-24. The volume of distribution at the steady state Vss was calculated as CL*MRT.

**RESULTS:**
Eight of the nine subjects received all three doses of telavancin and were evaluable for the PK analyses. The mean obsereved noncompartmental PK parameters of telavancin for both plasma and blister fluid are listed in Table 1.

Table 1. Mean (±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) |
|---|---|---|
| $C_{max}$ (µg/mL) | 84.8 ± 5.3 | 16.0 ± 2.0 |
| $T_{max}$ (hr) | 1.0 ± 0.0 | 9.3 ± 2.4 |
| $AUC_{0-24}$ (µg.hr/mL) | 604 ± 83 | 241 ± 33 |
| $C_{24}$ on Day 3 (µg/mL) | 4.92 ± 1.58 | 3.90 ± 1.24 |
| $T_{1/2}$ (hr) | 6.26 ± 0.78 | 6.91 ± 0.53[1] |
| $CL_{ss}$ (mL/hr/kg) | 12.6 ± 2.1 | ND |
| $V_{ss}$ (mL/kg) | 105 ± 16 | ND |
| MRT (hr) | 8.37 ± 1.03 | ND |
| | SBF/Plasma Ratios | |
| $C_{max}$ | 0.189 ± 0.030 | |
| AUC | 0.403 ± 0.058 | |
| $C_{24}$ (Day 3) | 0.816 ± 0.182 | |

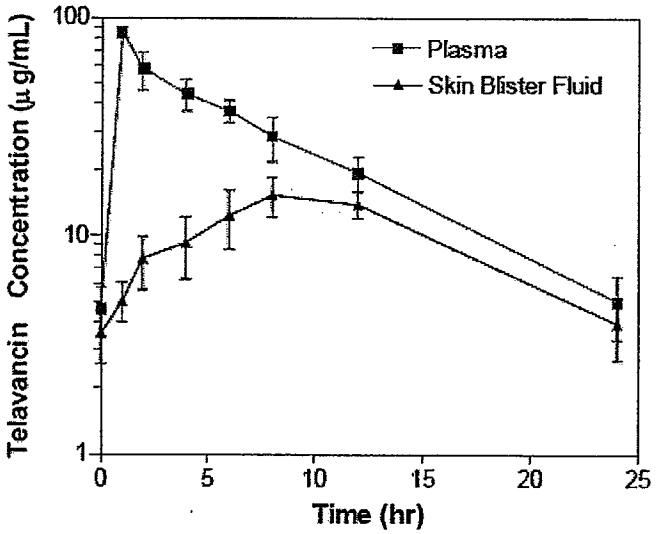
[1] n=5

* The maximum MIC for recent clinical isolates of *Staphylococcus aureus*, including methicillin-resistant strains, is 0.25 µg/mL and the $MIC_{90}$ for such strains of *S. aureus* (0.5 µg/mL).

ND: Not determined

Mean plasma and blister fluid concentration-time profiles for subjects receiving a one-hour infusion of 7.5mg/kg are shown in Figure 1.

Figure 1. Semi-Log Plot of Mean ±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




After the administration of telavancin, individual subject's telavancin levels in blister fluid rose slowly to reach Tmax at 6 to 12 hrs after dosing and declined at a rate similar to that of plasma concentrations (Figure 1.).

Reviewer Note: It would be expected that the concentration-time curve of telavancin in skin blister fluid would show an overlap at some point when the drug accumulates in the tissue and has a higher concentration than that found in the plasma, but this did not occur with the subjects in this study.

Similar mean T1/2 values (6.3 vs 6.9 hrs) were observed for telavancin in plasma and blister fluid (Table 1.) The Tmax value in plasma occurred at the end of the infusion and the maximal value in skin blister fluid was observed, on average, approximately 9 hr after the start of the infusion. The mean ± SD trough telavancin concentration in skin blister fluid was 3.90 ± 1.24 μg/mL. The mean ± SD ratio of AUC for skin blister fluid to AUC for plasma was 0.403 ± 0.058. The mean (± SD) Cmax values of telavancin in plasma and skin blister fluid were 84.8 ± 5.3 and 16.0 ± 2.0 μg/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 *Staphylococcus aureus* (0.5 μg/mL) including methicillin-resistant strains, by at least 4-fold. This product is approximately 90% protein bound. This would suggest that the concentrations of unbound drug in the blister fluid would reach exceed the MIC90 to an even greater extent, which is beneficial. Table 2. shows the mean (±SD) trough concentrations of telavancin in plasma and skin blister fluid and their ratios. The data shows a mean increase during multiple dosing suggesting minimal accumulation.

Table 2. Trough Concentrations of Telavancin in Plasma and Skin Blister Fluid Following Intravenous Administration to Healthy Subjects at a Dose of 7.5mg/kg via a 60-minute Infusion for 3 days

| Parameter | Plasma* (μg/mL) | Skin Blister Fluid* (μg/mL) | SBF/Plasma Ratio |
|---|---|---|---|
| N | 8 | 8 | 8 |
| Day 3, pre-dose | 4.61 ± 1.17 | 3.55 ± 0.95 | 0.787 ± 0.176 |
| Day 3, 24 hr post-initiation of 3rd infusion ($C_{24}$) | 4.92 ± 1.58 | 3.90 ± 1.24 | 0.816 ± 0.182 |

The maximum MIC for recent clinical isolates of *S. aureus*, including methicillin-resistant strains, is 0.25 μg/mL and the $MIC_{90}$ for such strains of *S. aureus* (0.5 μg/mL).)

Values are presented as mean ± SD

**CONCLUSIONS:**

In this study, mean (±SD) maximum concentration of telavancin in human inflammatory blister fluid, 16.0 ± 2.0 μg/mL, is achieved approximately 9 hours after the start of the last infusion. Mean blister fluid AUC values after the third day of daily 7.5 mg/kg intravenous infusions are 40 ± 6% of corresponding plasma AUC values. Respectively, mean plasma and blister fluid concentrations of telavancin 24 hours after the third dose were 4.92 ± 1.58 and 3.90 ± 1.24μg/mL. These concentrations of telavancin resulted in bactericidal activity in serum and blister fluid as measured by an ex vivo assay. Concentrations of telavancin in skin blister fluid following intravenous administration at 7.5 mg/kg every 24 hours for three consecutive days reflect those in plasma and, in healthy subjects, appear adequate for the treatment of infections due to *S. aureus* strains. In interpreting the findings of this study, it should be noted that the dose of telavancin evaluated in this study was 7.5 mg/kg (the dose used in Phase 2), whereas the recommended dose of telavancin subsequently evaluated in Phase 3 for patients with complicated skin and skin structure infections was 10 mg/kg.

*4.1.3. Intrinsic Factors*

**I6424-102a**
**Pharmacokinetics of Intravenous Televancin in Elederly Male and Female Subjects**

Date(s): 07FEB2002 to 11APR2002

Clinical Sites:

b(4)

**OBJECTIVES:**
To assess the pharmacokinetics, safety, and tolerability of televancin in elderly male and female subjects following intravenous administration. Gender effects will be assessed by comparison of pharmacokinetics in male vs. female subjects. Potential determinants of pharmacokinetic behavior such as renal function (creatininbe clearance) and body-mass index will be explored.

**FORMULATION:**
Televancin in 5% dextrose injection 250ml.
Batch No. AME001.

**STUDY DESIGN:**
This was a randomized, double-blind, placebo-controlled, gender-stratified study. In each of the two groups, eight subjects were to be randomized to receive a single dose of either placebo (two subjects) or telavancin (six subjects). The dose of telavancin was 12.5 mg/kg infused over 30 minutes. A total of 16 subjects were to be enrolled. Eight elderly (65 years of age or older) male and eight elderly female subjects were to participate. A total of three subjects (two females, one male) were enrolled and treated, before enrollment was suspended. This study hold was due to the findings of prophtombin time (PT) and activated partial thrombin time (aPTT) in two of the three subjects, as well as the findings from a Phase 1 study (I6424-104a) in healthy young subjects of possible prolongation of the QTc interval. Based on extensive in vitro experiments, the abnormal coagulation test results were judged to be due to interactions of telavancin with the reagents used in the coagulation tests rather than an effect on clotting in vivo. Therefore, the protocol was amended to perform a small substudy in four healthy young subjects to examine the effects of telavancin on various coagulation tests following intravenous administration. The results of this substudy are provided in this report.

**PHARMACOKINETIC ASSESSMENTS:**
Blood (5 mL) was collected from the contralateral side to that of drug administration at pre-dose (within 30 minutes prior to dosing), at approximately 5, 10, 20, and 28 minutes post start of infusion as well as 5, 10, 30 minutes and 1, 2, 4, 7, 11, and 23.5 hours post end of infusion. Urine was collected pre-dose as well as over the intervals 0 to 6, 6 to 12 hours, and 12 to 24 hours post start of drug infusion. For pre-dose measurements, subjects were asked to void within 30 minutes prior to dosing. A 10-mL sample was used for urinary protein assessments and the other 10-mL sample was used for pharmacokinetic assessments and further divided into two aliquots and transferred to appropriately labeled tubes and kept frozen at approximately -60 to –80 °C. For the 0 to 6 hour, 6 to 12 hour, and 12 to 24 hour interval collections, subjects were asked to void within 30 minutes prior to the completion of each interval. The volume of the collection was recorded to the nearest 5 mL. A 10ml sample for pharmacokinetic assessment was removed and divided into two aliquots and transferred to appropriately labeled tubes and kept frozen at approximately -60 to -80°C; the remainder of the collection was discarded.

**BIOANALYTICAL ANALYSIS:**
Plasma and urine samples were analyzed at Covance (Indianapolis, IN) using a validated bioanalytical method for televancin with LC-MS/MS detection.

**AMI-6424**

| Criterion | Plasma | Urine | Comments |
|---|---|---|---|
| Concentration range | 0.25 to 100 µg/ml | 0.25 to 100 µg/ml | Satisfactory |
| LLOQ | 0.25 µg/ml | 0.25 µg/ml | Satisfactory |
| Linearity | $R^2 \geq 0.9997$ | $R^2 \geq 0.9955$ | Satisfactory |
| Accuracy | 94.1% to 98.7% | 95.1% to 107.7% | Satisfactory |
| Precision | NA* | 1.1% to 7.0% | Satisfactory |
| Specificity | Acceptable | Acceptable | Satisfactory |
| Stability | Freezer -60° to -80°C | Freezer -60° to -80°C | Satisfactory |
| QC range | 0.75 to 400 µg/ml | 0.75 to 400 µg/ml | Satisfactory |

NA=Not available
*Reviewer Note: Inter-assay precision was not calculated for human plasma due to insignificant amount of values (n=1 or 2).

**PHARMACOKINETIC ANALYSIS:**
Pharmacokinetic parameter values were estimated using WinNonlin pharmacokinetic software (v3.2). A non-compartmental model was used to generate parameter estimates. The following pharmacokinetic parameter estimates were calculated:
• Cmax(obs) was determined by direct inspection of the plasma drug concentration versus time data point values.
• Tmax(obs) was determined by direct inspection of the plasma drug concentration versus time data point values.
• AUC(0-t) (where t=time of the last sample on the pharmacokinetic profile in which quantifiable drug was detected) was estimated using trapezoidal calculation.
• k (terminal slope) was estimated by ln-linear regression analysis of the terminal part of the curve.
• t1/2 (terminal half life) was estimated as t1/2=(ln2)/k.
AUC(0-∞) was calculated by extrapolation of the terminal slope from t to infinity, thus:
AUC(0-∞) = AUC (0-t) + (Ct/k),
where Ct = plasma drug concentration at time t.
CL (plasma clearance) was estimated using the formula:
CL = Dose / AUC(0-∞).
MRT was estimated using the formula:
MRT = AUMC(0-∞) / AUC(0-∞),
where AUMC(0-∞) is defined as the area under the Ct * t curve.

**RESULTS:**
**Changes in planned Study:**
A total of 16 subjects (eight elderly males and eight elderly females) were to be enrolled. A total of three subjects (two females, one male) were enrolled and treated before enrollment was suspended. This study hold was due to the findings of elevated coagulation tests (PT/aPTT) in two of the three subjects (both of these subjects were on telavancin), as well as the findings from a Phase 1 study in healthy young subjects of possible prolongation of the QTc interval. Based on extensive in vitro experiments, the abnormal coagulation test results were judged to be due to interactions of telavancin with the reagents used in the tests rather than to an effect on clotting in vivo. Therefore, the protocol was amended to enroll four

healthy young subjects to examine the effects of telavancin on various coagulation tests following intravenous administration. Table 1 shows the disposition of study subjects.

**Table 1. Disposition of study subjects**

| | Telavancin (N=2) | Placebo (N=1) |
|---|---|---|
| No. of Subjects | n | n |
| Screened | 2 | 1 |
| Randomized | 2 | 1 |
| Complete Study | 2 | 1 |
| Discontinued Prematurely | 0 | 0 |

**Protocol Deviation:**
One female subject (No. 200) had body mass index (31.3) exceeding the protocol threshold of 30.0. However, the sponsor granted an exception to allow enrollment.

Table 2 shows the demographics and baseline characteristics of the study subjects

**Table 2. Demographics**

| | Subject Number | | |
|---|---|---|---|
| | 200 | 201 | 400 |
| Study Medication | Telavancin | Placebo | Telavancin |
| Gender | F | F | M |
| Age (years) | 71 | 75 | 69 |
| Weight (kg) | 73.2 | 75.4 | 80.3 |
| Height (cm) | 153 | 160 | 163 |

There were no clinically significant changes in laboratory findings except for coagulation parameters. Table 3 shows the coagulation parameters.

**Table 3. Coagulation Parameters**

| Study Medication | Subject Number and Treatment | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 200 Telavancin | | | 201 Placebo | | | 400 Telavancin | | |
| Sample Times | aPTT (sec) | PT (sec) | INR | aPTT (sec) | PT (sec) | INR | aPTT (sec) | PT (sec) | INR |
| Pre-Infusion | 24.9 | 9.6 | 0.89 | 26.9 | 10.0 | 0.92 | 24.2 | 10.3 | 0.95 |
| 5 minutes | **44.3** | **62.0** | **6.05** | 27.5 | 10.7 | 0.99 | **43.7** | **76.1** | **7.47** |
| 30 minutes | **35.0** | **45.3** | **4.38** | 29.3 | 10.5 | 0.97 | **34.8** | **44.1** | **4.26** |
| | | | | | | | **32.2** | **30.4** | **2.90** |
| 2 hours | 30.9 | **28.7** | **2.74** | 27.8 | 10.5 | 0.97 | **38.7** | **15.2** | **1.42** |
| 7 hours | 28.1 | **14.6** | **1.36** | 26.7 | 10.4 | 0.96 | 24.5 | 11.0 | 1.02 |
| 23.5 hours | 24.7 | 10.4 | 0.96 | 26.9 | 10.6 | 0.98 | 24.5 | 11.0 | 1.02 |

Abnormal values are bolded in print
Normal ranges: APTT, 20.4-31.4 sec; PT, 9.4-13.5 sec; INR, 0.82-1.17

**Pharmacokinetic Evaluation:**

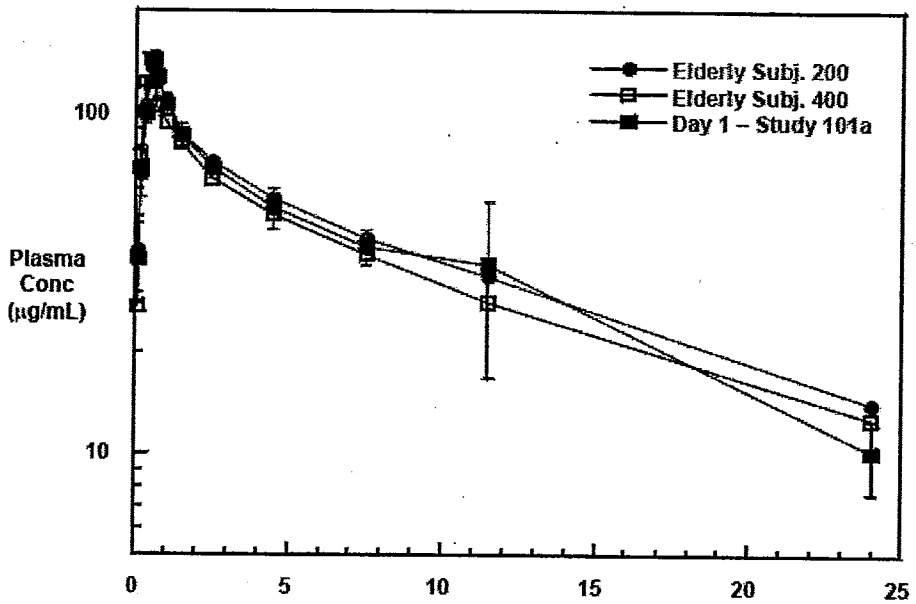
The table and figure below provide the pharmacokinetic parameters for the two elderly subjects who received telavancin 12.5 mg/kg. The individual subject's data are compared to the mean data derived from the young healthy male subjects in the earlier Phase 1 study (I6424-101a), who received 12.5 mg/kg over 30 minutes. The data displayed below are those generated after the first dose in Study 101a. The pharmacokinetic parameters are similar between these two elderly individuals and the mean data from young males.

**Table 4. Noncompartmental Pharmacokinetic parameters for telavancin in Plasma Following Intravenous Administration to healthy Subjects at 12.5 mg/kg via a 30-Minute Infusion**

| Study protocol | I6424-102a | | I6424-101a |
|---|---|---|---|
| N | 1 | 1 | 6 |
| Age (yr) | 69 | 71 | 19-27 |
| Gender | Male | Female | Male |
| CLcr (ml/min)* | 85 | 60 | 114 ± 14 |
| Cmax (µg/ml) | 123.0 | 146.0 | 154.7 ± 24.0 |
| AUC (0-t)(µg.hr/ml) | 845.5 | 957.6 | 910.4 ± 99.0 |
| AUC (0-∞)( µg.hr/ml) | 1024.3 | 1157.5 | 1013.0 ± 118.1 |
| T½ (hr) | 10.0 | 9.9 | 7.3 ± 1.2 |
| CL (ml/hr/kg) | 12.2 | 10.8 | 12 ± 2 |
| MRT (hr) | 12.8 | 12.8 | 9.7 ± 1.4 |
| Vss (ml/kg) | 157 | 139 | 121 ± 14 |
| Urinary recovery (% of dose over 0-24 hr) | 49.6 | 45.1 | 61.0 ± 15.8 |

* Measured for 102a subjects, Cockcroft-Gault estimate for 101a subjects

**Figure 1. Concentrations of Televancin in Plasma Following Intravenous Infusion to healthy Subjects at 12.5 mg/kg**




The plasma concentration vs. time curves displayed in the figure above are for each of the two elderly subjects from Study 102a who received telavancin at a dose of 12.5 mg/kg IV over 30 minutes, and the curve derived from the mean data following the first dose (Day 1) in Study 101a in healthy young male subjects, who received 12.5 mg/kg of telavancin IV over 30 minutes. As can be seen, the curves for the elderly subjects and the mean data from Study 101a are similar.

**CONCLUSIONS:**

Three elderly subjects were dosed in Protocol I6424-102a. Two of the three subjects were found to have transient elevations in PT and aPTT. The blind was broken for the three subjects; the two subjects with transient elevations had received active study medication. The elevations were believed to be due to assay interference. While this hypothesis was investigated further, elderly subject dosing was suspended. No other clinically significant changes in vital signs, physical examinations, audiometry, electrocardiograms or laboratory data (except the coagulation parameters) were observed. No clinical evidence of bleeding was found. The only adverse events reported to be associated with telavancin were mild flushing and constipation. The pharmacokinetic disposition of telavancin in the two elderly subjects appeared to be similar to that observed in healthy young male subjects. However, further evaluation is needed to assesss the impact of age on the PK of telavancin.

**SUBSTUDY 102a:**

**OBJECTIVE:**

To confirm in a substudy in healthy young adults, that the transient elevations in prothrombin time (PT) and activated partial thromboplastin time (aPTT) observed in the elderly subjects treated under the main protocol were due to assay interference by televancin.

**STUDY DESIGN:**

Four male subjects (age 24-38 years, height 78.5-87.0 kg) were enrolled in a randomized, double blind, placebo-controlled, crossover study. In the first treatment period, four subjects were randomized to receive a single dose of either placebo (two subjects) or telavancin 7.5 mg/kg (two subjects). After a washout period of approximately 48 hours, the four subjects were crossed over so that the two subjects

who had previously received placebo received telavancin at a dose of 15 mg/kg and that the two subjects who had previously received telavancin would receive placebo.

**BLOOD SAMPLE COLLECTIONS:**

Blood (5 mL) was collected from the contralateral side to that of drug administration at pre-dose and 5 minutes post end of infusion into sodium heparin glass tubes and centrifuged. The collected plasma divided into two aliquots and transferred to appropriately labeled tubes and kept frozen at approximately -60 to -80°C.

**COAGULATION PARAMETERS:**

Hematology, clinical chemistry and coagulation parameters (INR, PT, aPTT) were performed at screening, at admission, 5 minutes and 23.5 hours post end of drug infusion in each treatment period, and at the post-study visit. Whole blood activated clotting time (ACT) and bleeding time were performed prior to each dosing (within 24 hours of dosing) and 5 minutes post end of infusion in each treatment period. The bleeding time was to be performed after other procedures that were to be completed 5 minutes post end of infusion. The two bleeding time assessments (prior to and 5 minutes post end of infusion) for each dose must have been performed by the same person. If the whole blood ACT or bleeding time was prolonged at the 5 minutes post end of infusion time point, the test was to be repeated.

**RESULTS:**

Values for PT and aPTT were transiently elevated following infusion of either the 7.5 or 15 mg/kg dose. Additionally, ACT prolongation was also seen following the higher dose of TD-6424. Bleeding times remained within the normal range. No changes were observed following infusion of the placebo. Table 5 shows the results of the coagulation tests.

**Table 5. Coagulation Parameters**

| Subject | Parameter | Treatment Period 1 | | | Treatment Period 2 | | | Repeat Testing |
|---|---|---|---|---|---|---|---|---|
| | | Pre-infusion | 5 min post-infusion | 23.5 hr post-infusion | Pre-Dose | 5 min post-infusion | 23.5 hr post-infusion | |
| 600[a] | Platelets (x10$^9$/L) | | | | | | | |
| | ACT | | | | | | | |
| | Bleeding Time | | | | | | | |
| | aPTT | | | | | | | |
| | PT | | | | | | | |
| | INR | | | | | | | |
| 601[a] | Platelets (x10$^9$/L) | | | | | | | |
| | ACT | | | | | | | |
| | Bleeding Time | | | | | | | |
| | aPTT | | | | | | | |
| | PT | | | | | | | |
| | INR | | | | | | | |
| 602[b] | Platelets (x10$^9$/L) | | | | | | | |
| | ACT | | | | | | | |
| | Bleeding Time | | | | | | | |
| | aPTT | | | | | | | |
| | PT | | | | | | | |
| | INR | | | | | | | |
| 603[b] | Platelets (x10$^9$/L) | | | | | | | |
| | ACT | | | | | | | |
| | Bleeding Time | | | | | | | |
| | aPTT | | | | | | | |
| | PT | | | | | | | |
| | INR | | | | | | | |

b(4)

a Period 1: Placebo; Period 2: Telavancin 15 mg/kg
b Period 1: Telavancin 7.5 mg/kg; Period 2: Placebo
ND = not done
NR = not recordable
*Time after Dose 2
Abnormal values are shaded

| Normal Ranges: | |
|---|---|
| Platelets (x10$^9$/L) | 127 – 304 x10$^9$/L |
| ACT (sec) | 98 – 142 sec |
| Bleeding Time (min) | < 10 minutes |
| aPTT (sec) | 20.4 – 31.4 sec |
| PT (sec) | 9.4 – 13.5 sec |
| INR | 0.82 – 1.17 |

**CONCLUSIONS:**

In this substudy all four young, healthy, male subjects experienced transient elevations in PT and aPTT following doses of 7.5 mg/kg or 15 mg/kg of telavancin. Bleeding times remained in the normal range and ACT values were somewhat elevated following the 15 mg/kg dose. The sponsor suggests that the findings from extensive in vitro studies support the hypothesis that the observed prolongations in the PT, aPTT and ACT are due to the interaction of telavancin with the reagents used in those in vitro tests. However, there is inconclusive data in this study. Several values for the INR comparing treatment period one and treatment period two are missing at the 5 minute post-infusion collection as can be seen from Table 5. Therefore I cannot concur with the sponsors conclusion.

**I6424-105a**

**Safety and Pharmacokinetics of IV ARBELIC™ (Telavancin for Injection) in Elderly Male and Female Subjects**

Date(s): 20JUL2003 to 18OCT2003

Clinical Sites:

b(4)

**OBJECTIVES:**

To assess the safety (including the effect on the QTc) and tolerability of telavancin, and to assess the effect of sex on the pharmacokinetic disposition of telavancin following intravenous administration in elderly male versus female subjects. Potential determinants of pharmacokinetic behavior such as renal function (creatinine clearance) were to be explored.

**FORMULATION:**

Telavancin in 250 mL 5% dextrose injection intravenous over 60 minutes, Batch No. AME006

**STUDY DESIGN:**

Open label, single-dose, sex-stratified study in subjects 65 years of age or older. All subjects received a single infusion of telavancin 10 mg/kg via a 60-minute intravenous infusion. Subjects were stratified based on sex to one of two panels consisting of eight elderly male or eight elderly female subjects. Each subject participated in one treatment period lasting 3 nights and 4 days (Days 0 to 3). Subjects were discharged from the clinic following the 48-hour post-infusion protocol specified examinations and returned for a follow-up visit 5 to 7 days post-dose.

**PHARMACOKINETIC ASSESSMENTS:**

Blood samples (5 mL) were to be collected from the contralateral side to that of drug administration into sodium heparin glass tubes at pre-dose, 1, 2, 4, 6, 8, 12, 18, 24, 36 and 48 hours post initiation of the infusion. Samples were to be maintained chilled in an ice bath until plasma was harvested.
Urine samples for pharmacokinetics were to be collected pre-infusion, and cumulative urine collections were to be obtained following the start of the infusion on Day 1 and continuing into Day 2 for the periods 0 - 6, 6 - 12, 12 - 24, 24 - 36, and 36 - 48 hours after the start of the infusion.

**BIOANALYTICAL ANALYSIS:**

Concentrations of TD-6424 (also known as AMI-6424 and telavancin, and formerly known as ARBELIC™), AMI-11352 and AMI-999 in human plasma and urine were determined using HPLC with MS/MS.

**TD-6424**

| Criterion | Plasma | Urine | Comments |
|---|---|---|---|
| Concentration range | 0.25 to 100 µg/ml | 0.25 to 100 µg/ml | Satisfactory |
| LLOQ | 0.25 µg/ml | 0.25 µg/ml | Satisfactory |
| Linearity | $R^2 \geq 0.9944$ | $R^2 \geq 0.9952$ | Satisfactory |
| Accuracy | 88.5% to 103.2% | 91.2% to 104.3% | Satisfactory |
| Precision | 4.4% to 5.8% | 10.0% to 11.9% | Satisfactory |
| Specificity | Acceptable | Acceptable | Satisfactory |
| Stability | Freezer -60° to -80°C | Freezer -60° to -80°C | Satisfactory |
| QC range | 0.75 to 400 µg/ml | 0.75 to 400 µg/ml | Satisfactory |

**AMI-11352**

| Criterion | Plasma | Urine | Comments |
|---|---|---|---|
| Concentration range | 0.25 to 100 µg/ml | 0.25 to 100 µg/ml | Satisfactory |
| LLOQ | 0.25 µg/ml | 0.25 µg/ml | Satisfactory |
| Linearity | $R^2 \geq 0.9965$ | $R^2 \geq 0.9970$ | Satisfactory |
| Accuracy | 95.5% to 98.4% | 98.1% to 102.8% | Satisfactory |
| Precision | 6.0% to 7.0% | 10.2% to 21.1% | Satisfactory |
| Specificity | Acceptable | Acceptable | Satisfactory |
| Stability | Freezer -60° to -80°C | Freezer -60° to -80°C | Satisfactory |
| QC range | 0.75 to 400 µg/ml | 0.75 to 400 µg/ml | Satisfactory |

**AMI-999**

| Criterion | Plasma | Urine | Comments |
|---|---|---|---|
| Concentration range | 0.25 to 100 µg/ml | 0.25 to 100 µg/ml | Satisfactory |
| LLOQ | 0.25 µg/ml | 0.25 µg/ml | Satisfactory |
| Linearity | $R^2 \geq 0.9940$ | $R^2 \geq 0.9971$ | Satisfactory |
| Accuracy | 96.5% to 102.9% | 97.7% to 104.8% | Satisfactory |
| Precision | 4.2% to 7.4% | 3.1% to 16.7% | Satisfactory |
| Specificity | Acceptable | Acceptable | Satisfactory |
| Stability | Freezer -60° to -80°C | Freezer -60° to -80°C | Satisfactory |
| QC range | 0.75 to 400 µg/ml | 0.75 to 400 µg/ml | Satisfactory |

**PHARMACOKINETIC/STATISTICAL ANALYSIS:**

Nominal time was used in pharmacokinetic calculations. Individual subject plasma concentration versus time plots were prepared using Prism, version 4.03 (GraphPad Software, San Diego, CA). The pharmacokinetic parameters of telavancin, AMI-11352 and AMI-999 were determined by non-compartmental analysis (Model 202 for constant infusion) using WinNonlin,version 4.0.1 (Pharsight, Mountain View, CA). The peak plasma concentration (Cmax) and the time to reach the peak concentration (Tmax) were taken directly from the plasma concentration-time data. Tmax was defined as the time that Cmax was reached. The areas under the plasma concentration versus time curve from time zero to 24 hours (AUC0-24) after dosing were calculated by the linear trapezoidal rule. The (AUC0-t) areas under the plasma concentration versus time curve from time zero to the last measurable concentration ($C_{lm}$) were calculated by the linear trapezoidal rule. The terminal elimination rate constant ($\lambda z$) was determined by linear regression of the natural logarithms of plasma concentrations versus time during the terminal phase. The
terminal-phase elimination half-life (t1/2) was calculated as $\ln(2)/\lambda z$. The areas under the plasma concentration versus time curve from the last measurable concentration ($C_{lm}$) to infinite time (AUCt-∞) were calculated as $C_{lm}/\lambda z$. The areas under the plasma concentration versus time curve from time 0 hours to infinite time (AUC0-∞) were calculated as AUC0-t + AUCt-∞. The telavancin clearance (CL) was calculated as dose/AUC0-∞. The area under the first moment curve (AUMC) was calculated using the trapezoidal rule. The mean residence time (MRT) of telavancin was calculated as AUMC/AUC. The volume of distribution at the steady state was calculated as CL*MRT. For AMI-11352 and AMI-999, only Tmax, Cmax, and AUC0-48 are reported here. The total amount of telavancin excreted unchanged in urine (Ae) was estimated as:

$$\sum_{0}^{t} U_t * Cu_t$$

where Ut and Cut are the urine volume and telavancin concentration in urine, respectively, for time t (48 hours). The corresponding renal clearance (CLr) was calculated as Ae/AUC0-48. For the metabolites for which incomplete recovery may have occurred, the corresponding renal clearances (CLr) were estimated as:

$$(\sum_{0}^{72} U_i * Cu_i) / (\int_{0}^{t} C * dt)$$

where t is 48 hours.

**RESULTS:**

**Changes in Planned Study:**

The original protocol for this study was issued on 23 April 2003. An amendment to the original protocol was issued on 20 June 2003. Amendment 1 included the following changes:

1. Added the requirement to obtain seven plasma samples for PT/aPTT/INR at time points coinciding with the following pharmacokinetic sampling times: pre-infusion, and 1, 4, 8, 12, 18 and 24 hours relative to the start of the infusion. Previous in vitro studies demonstrated that telavancin interfered with the PT and aPTT assays at concentrations greater than 20 μg/mL. Therefore, this amendment to the protocol was designed to validate the in vitro findings in subjects receiving telavancin.
2. Added the requirement to include an additional plasma pharmacokinetic sampling time point at 18 hours relative to the start of the infusion. This was done to generate an 18-hour sample for plasma concentrations to match the 18-hour coagulation sample.

**Study Population:**

Sixteen subjects, eight males and eight females, were enrolled into the study and received study drug. All subjects completed the study. Overall, the male and female groups were well-matched in terms of age and race but the males, on average, weighed more than the females. All subjects were White. Both males and females had a mean age of 71 years. The males ranged in age from 65 to 83 years, two being ≥ 75 years of age. The females ranged in age from 66 to 78 years, three being ≥ 75 years of age. Thus, all subjects were greater than 65 years old and the median age was 69 years in males and 68.5 years in females. The mean weight was 76 kg for males and 68 kg for females.

**Pharmacokinetics:**

Table 1 shows the mean (±SD) non-compartmental pharmacokinetic parameters for telavancin in elderly male and female subjects.

Table 1. Mean ±SD Non-compartmental Pharmacokinetic Parameters for Telavancin in Plasma Following Intravenous Administration to Elderly Subjects at 10mg/kg via a 60-minute infusion (Study I6424-105a)

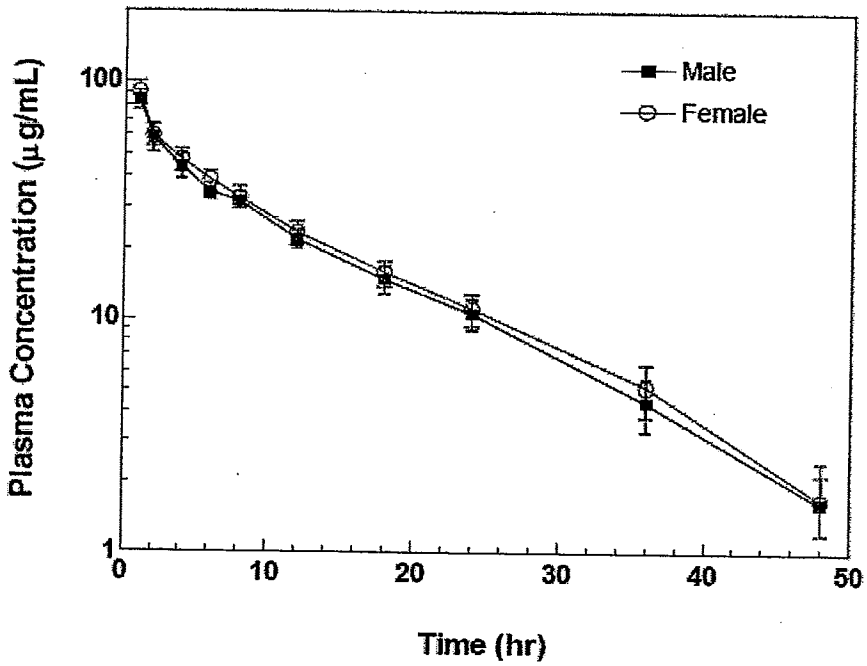
| Parameter | Male (n=8) | Female (n=8) | Overall (n=16) |
|---|---|---|---|
| $C_{max}$ (μg/ml) | 84.7 ± 8.2 | 90.8 ± 10.7 | 87.7 ± 9.7 |
| $AUC_{0-24}$ (μg.hr/ml) | 653 ± 51 | 693 ± 64 | 673 ± 59 |
| $AUC_{0-48}$ (μg.hr/ml) | 780 ±75 | 831 ± 90 | 805 ± 84 |
| $AUC_{0-\infty}$ (μg.hr/ml) | 803 ±87 | 854 ± 96 | 829 ± 92 |
| $T_{½}$ (hr) | 9.0 ± 1.6 | 9.5 ± 0.9 | 9.3 ± 1.3 |
| CL (ml/hr/kg) | 12.6 ± 1.4 | 11.8 ± 1.4 | 12.2 ± 1.3 |
| MRT (hr) | 12.8 ± 1.6 | 12.9 ± 1.1 | 12.9 ± 1.3 |
| $V_{ss}$ (ml/kg) | 160 ± 11 | 152 ± 12 | 156 ± 12 |
| $CL_r$ (ml/hr/kg) | 2.7 ± 0.9[a] | 3.3 ± 0.7 | 3.0 ± 0.8[b] |

[a]N=7, [b]N=15

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 Cmax values was comparable in males and females. There were no sex-related differences in the disposition of telavancin in the elderly. The mean (±SD) telavancin plasma concentration versus time profiles in male and female subjects are shown in Figure 1.

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




AMI-11352 (metabolite) and AMI-999 ( ) were measured in plasma for 48 hours after dosing with telavancin. The non-compartmental pharmacokinetic parameters of AMI-11352 and AMI-999 are summarized in Table 2. Similar results were observed in male and female subjects for each analyte. The mean Tmax values of AMI-11352 and AMI-999 were approximately 19 hours and 1 hour, respectively.

b(4)

Table 2. Mean ±SD Non-compartmental Pharmacokinetic Parameters for AMI-11352 and AMI-999 in plasma Following Intravenous Administration of Telavancin to Elderly Subjects at 10mg/kg via a 60-minute infusion.

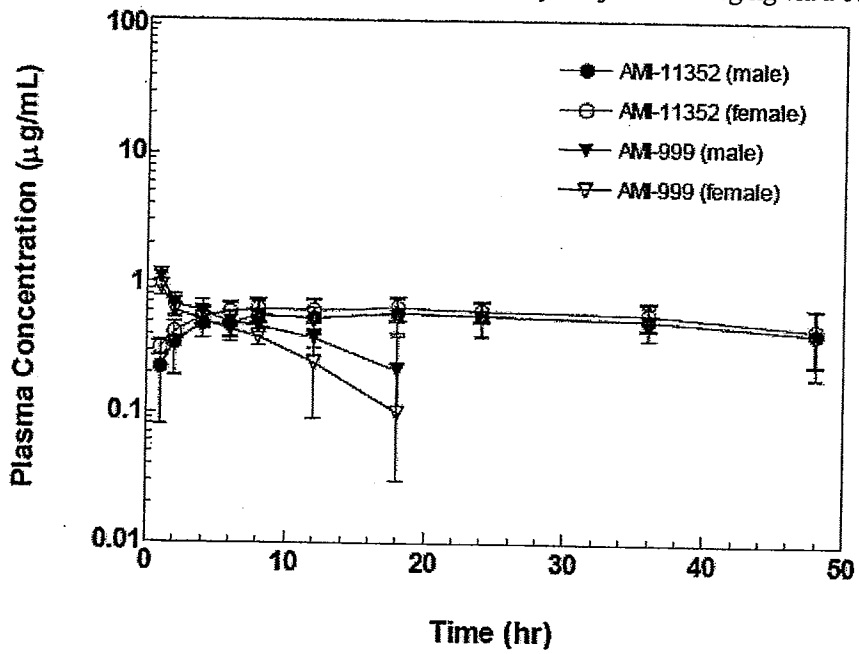
| Analyte | AMI-11352 | | | AMI-999 | | |
|---|---|---|---|---|---|---|
| Sex | Male | Female | Total | Male | Female | Total |
| N | 8 | 8 | 16 | 8 | 8 | 16 |
| $C_{max}$ (µg/ml) | 0.602 ± 0.180 | 0.661 ± 0.121 | 0.632 ± 0.151 | 1.08 ± 0.18 | 0.909 ± 0.143 | 0.994 ± 0.179 |
| $T_{max}$ (hr) | 18.5 ± 12.3 | 19.0 ± 9.5 | 18.8 ± 10.6 | 1.00 ± 0.00 | 1.00 ± 0.00 | 1.00 ± 0.00 |
| $AUC_{0-48}$ (µg·hr/ml) | 24.2 ± 7.0 | 27.2 ± 5.9 | 25.7 ± 6.5 | 12.0 ± 4.2 | 8.01 ± 3.00 | 10.0 ± 4.1 |
| $Cl_r$ (ml/hr/kg) | 23.4 ± 9.0[a] | 28.0 ± 7.5 | 25.8 ± 8.3[b] | 1.47 ± 0.79[a] | 1.03 ± 0.76 | 1.23 ± 0.78[b] |
| $C_{max}$ ratio (analyte/telavancin) | 0.007 ± 0.002 | 0.007 ± 0.001 | 0.007 ± 0.002 | 0.013 ± 0.001 | 0.010 ± 0.001 | 0.011 ± 0.002 |
| AUC ratio (analyte/telavancin) | 0.031 ± 0.008 | 0.033 ± 0.005 | 0.032 ± 0.006 | 0.015 ± 0.004 | 0.009 ± 0.003 | 0.012 ± 0.005 |

[a]n=7, [b]n=15

Figure 2 illustrates the mean (± SD) plasma concentrations of the major metabolite, AMI-11352, and [redacted] (AMI-999) over time following intravenous administration of telavancin. The mean profiles of AMI-11352 were above the lower limit of quantitation for the entire 48-hour period of sample collection. Plasma concentrations of AMI-999 were below limits of detection (on average) by 18 hours after dosing. However, concentrations of each of these moieties were similar in male and female elderly subjects.

b(4)

Figure 2. Mean ±SD Plasma Concentration-Time Profiles of AMI-11352 andAMI-999 Following Intravenous Administration of Telavancin to Elderly Subjects at 10mg/kg via a 60-minute Infusion



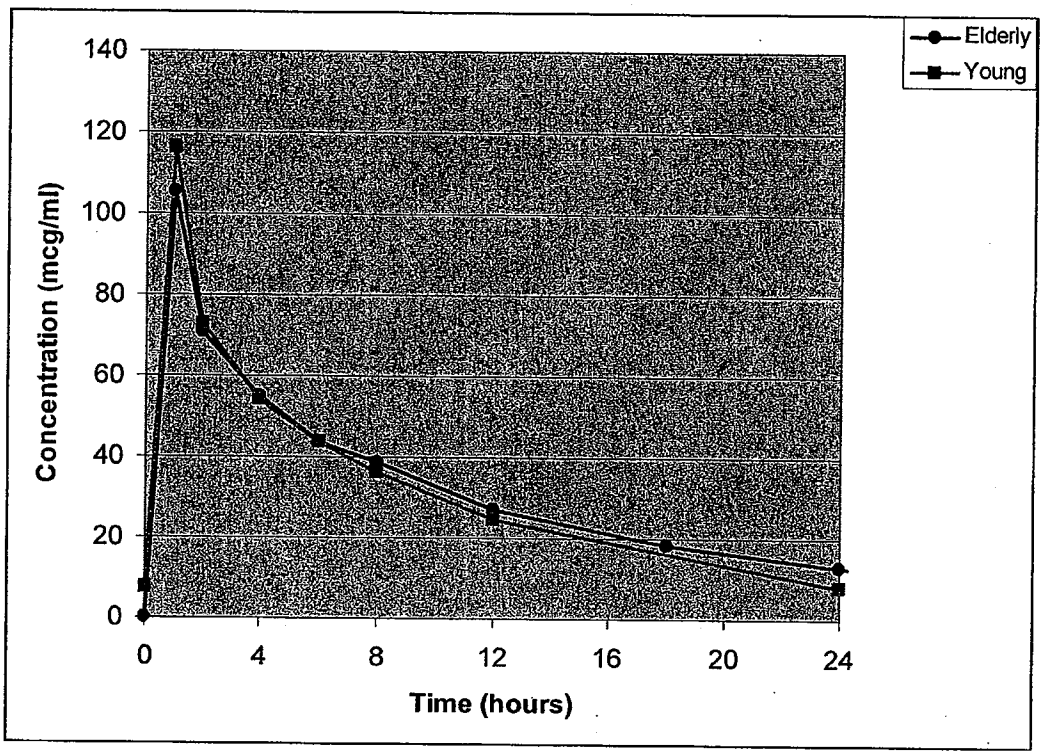
There were no apparent differences in urinary recovery of telavancin and AMI-11352 between elderly male and female subjects, but small differences in mean values were observed for AMI- 999 (Table 3). The mean percentage of the telavancin dose excreted in urine as telavancin, AMI-11352, and AMI-999 within 48 hours were 21.6, 5.70 and 0.19%, respectively, in elderly male subjects, while the corresponding values observed in elderly female subjects were 27.0, 7.36 and 0.08%. The mean total percentage of the telavancin dose measured in urine was 27.5 and 34.4%, respectively, for elderly male and elderly female subjects. The mean renal clearances of telavancin, AMI-11352, and AMI-999 were 2.7, 23.4 and 1.47 mL/hr/kg, respectively, in elderly male subjects, and the corresponding values observed in elderly female subjects were similar, 3.3, 28.0 and 1.03 mL/hr/k(Table 1 and 2).

Table 3. Mean ±SD Urinary Recoveries (0-48 hours) of Telavancin, AMI-11352 andAMI-999 Following Intravenous Administration of Telavancin to Elderly Subjects at 10mg/kg via a 60 minute Infusion

| | Male (n=8) | Female (n=7) | Overall (n=15) |
|---|---|---|---|
| Cumulative total recovery % dose (0-48 hr) | 27.5 ± 7.1 | 34.4 ± 6.8 | 31.2 ± 7.6 |
| % dose as telavancin | 21.6 ± 6.2 | 27.0 ± 5.9 | 24.5 ± 6.5 |
| % dose as AMI-11352 | 5.70 ± 1.77 | 7.36 ± 1.45 | 6.59 ± 1.77 |
| % dose as AMI-999 | 0.188 ± 0.117 | 0.081 ± 0.054 | 0.131 ± 0.101 |

Reviewer Note: The plasma concentrations for the elderly subjects in this study were compared to the plasma concentrations in Study I6424-108a. The data in this study was single dose and corrected for the accumulation factor of telavancin when compared to the younger patient population in Study I6424-108a. The concentration-time curve is shown in Figure 3. There graphs of the younger subjects and older subjects are almost superimposable. The $C_{max}$ appears to be higher in the young, but this could be due to a slight difference in clearance in the elderly.

Figure 3. Plasma concentration time curve for Subjects in Study I6424-105a compared to subjects in Study I6424-108a.




**Conclusions:**

Following a single intravenous dose, plasma levels of telavancin were measurable for approximately the same amount of time in both elderly males and females. Plasma concentrations of telavancin declined in an apparent bi-exponential manner. At each time point following the infusion, no sex-related differences were observed in the plasma concentration vs. time profiles of telavancin. The mean half-life, plasma clearance, steady-state volume of distribution and Cmax values were all generally comparable in males and females. Further, the pharmacokinetic parameters for AMI-11352, the major metabolite of telavancin, and for AMI-999, ( ) were also comparable in males and females. Therefore, in healthy elderly subjects, there were no sex-related differences in the disposition of telavancin, its major metabolite, nor ( ) There were no apparent differences in urinary recovery of telavancin and AMI-11352, but small differences in mean values were observed for AMI-999 between elderly male and female subjects. The mean renal clearances of telavancin, AMI-11352, and AMI-999 were 2.7, 23.4 and 1.47 mL/hr/kg, respectively, in elderly male subjects, while the corresponding values observed in elderly female subjects were similar, 3.3, 28.0 and 1.03 mL/hr/kg, respectively. No apparent relationships were found in this study between creatinine clearance and renal clearances of telavancin, AMI-11352, and AMI-999. Based upon additional analysis performed by the reviewer the concentration time curves for the young and elderly subjects are almost superimposable. No dosage adjustment is warranted based upon age.

b(4)

**I6424-103a**

**Safety and Pharmacokinetics of Intravenous ARBELIC® (TD-6424 for Injection) in Subjects With Varying Degrees of Renal Function**

Date(s): 14JUL2003 to 11FEB2004

Clincal Sites:

b(4)

**OBJECTIVES:**

The primary objective as to assess the effects of varying degrees of renal function (assessed by creatinine clearance) on the pharmacokinetic disposition of telavancin. The secondary objective was to assess the safety and tolerability of a single intravenous infusion of telavancin in subjects with varying degrees of renal function.

**FORMULATION:**

Telavancin for injection was supplied as a sterile, lyophilized powder. Each vial of telavancin for injection contained 250 mg telavancin, 2.5 g hydroxypropylbetadex, 312.5 mg mannitol, and sodium hydroxide and/or hydrochloric acid used for pH adjustment.
Batch No. AME006

b(4)

**METHODS:**

This study was a single dose, open-label study in male and female adut subjects (≥ 18 years of age) with varying degrees of renal impairment and an age-matched control group of healthy subjects to determine the effect of renal function on the pharmacokinetic disposition of telavancin. Safety and tolerability of telavancin were also assessed. Up to thirty subjects (six subjects per group) were to receive a single intravenous dose of telavancin 7.5 mg/kg infused over 60 minutes. Subjects were to be categorized and grouped by their degree of renal impairment based on calculated creatinine clearance rates (Cockdroft Gault) at baseline as follows:
Group 1: Healthy subjects with no impairment in renal function defined as a calculated creatinine clearance ($CL_{CR}$) > 80 mL/min.
Group 2: Subjects with mildly impaired renal function defined as a calculated $CL_{CR}$ of 51–80 mL/min.
Group 3: Subjects with moderately impaired renal function defined as a calculated $CL_{CR}$ of 30–50 mL/min.
Group 4: Subjects with severely impaired renal function defined as a calculated $CL_{CR}$ < 30 mL/min.
Group 5: Subjects with end-stage renal disease (ESRD) maintained on hemodialysis.

Subjects in Group 5 were to receive the telavancin infusion 2 to 4 hours before commencing hemodialysis.

**PHARMACOKINETIC ASSESSMENTS:**

Blood samples (5 mL) were collected from the contralateral arm to that of drug administration into glass tubes containing sodium heparin at pre-dose and 1, 2, 4, 6, 8, 12, 24, 36, and 48 hours after the start of the infusion for all groups. Blood samples at 72 and 96 hours after the start of the infusion were also collected for Groups 4 and 5. Urine samples were collected pre-infusion and cumulatively over the intervals 0-6 hours, 6-12 hours, 12–24 hours, 24–36 hours, and 36–48 hours relative to the start of the infusion, for Groups 1–4. For subjects with severely impaired renal function (Group 4), urine samples were collected up to 96 hours after iniation of the infusion (48–60 hours, 60-72 hours, 72-84 hours, and 84–96 hours). Plasma samples were also collected during the 4-hour dialysis session for subjects with ESRD (Group 5)

at 0, 60, 120, 180, and 240 minutes following the start of the dialysis procedure. Aliquots of dialysate fluid (10 mL) were collected at 30-minute intervals during dialysis.

**BIOANALYTICAL ANALYSIS:**
Plasma samples were analyzed using a validated bioanalytical method for telavancin, AMI-11352, and AMI-999 with LC-MS/MS detection.

**TD-6424**

| Criterion | Plasma | Urine | Comments |
|---|---|---|---|
| Concentration range | 0.25 to 100 µg/ml | 0.25 to 100 µg/ml | Satisfactory |
| LLOQ | 0.25 µg/ml | 0.25 µg/ml | Satisfactory |
| Linearity | $R^2 \geq 0.9948$ | $R^2 \geq 0.9954$ | Satisfactory |
| Accuracy | 96.2% to 104.9% | 96% to 104% | Satisfactory |
| Precision | 5.0% to 9.1% | 5.6% to 9.4% | Satisfactory |
| Specificity | Acceptable | Acceptable | Satisfactory |
| Stability | Long term at -60°C to -80°C | Long term at -60°C to -80°C | Satisfactory |
| QC range | 0.75 to 80 µg/ml | 0.75 to 400 µg/ml | Satisfactory |

**AMI-11352**

| Criterion | Plasma | Urine | Comments |
|---|---|---|---|
| Concentration range | 0.25 to 100 µg/ml | 0.25 to 100 µg/ml | Satisfactory |
| LLOQ | 0.25 µg/ml | 0.25 µg/ml | Satisfactory |
| Linearity | $R^2 \geq 0.9954$ | $R^2 \geq 0.9964$ | Satisfactory |
| Accuracy | 100.3% to 103.5% | 100% to 103.8% | Satisfactory |
| Precision | 5.3% to 9.2% | 4.4% to 7.7% | Satisfactory |
| Specificity | Acceptable | Acceptable | Satisfactory |
| Stability | Long term at -60°C to -80°C | Long term at -60°C to -80°C | Satisfactory |
| QC range | 0.75 to 80 µg/ml | 0.75 to 400 µg/ml | Satisfactory |

**AMI-999**

| Criterion | Plasma | Urine | Comments |
|---|---|---|---|
| Concentration range | 0.25 to 100 µg/ml | 0.25 to 100 µg/ml | Satisfactory |
| LLOQ | 0.25 µg/ml | 0.25 µg/ml | Satisfactory |
| Linearity | $R^2 \geq 0.9953$ | $R^2 \geq 0.9964$ | Satisfactory |
| Accuracy | 103.7% to 104.8% | 95.3% to 103.5% | Satisfactory |
| Precision | 4.4% to 4.8% | 6.3% to 11.4% | Satisfactory |
| Specificity | Acceptable | Acceptable | Satisfactory |
| Stability | Long term at -60°C to -80°C | Long term at -60°C to -80°C | Satisfactory |
| QC range | 0.75 to 80 µg/ml | 0.75 to 400 µg/ml | Satisfactory |

**TD-6424**

| Criterion | Human Dialysate | Comments |
|---|---|---|
| Concentration range | 0.1 to 25 µg/ml | Satisfactory |
| LLOQ | 0.1 µg/ml | Satisfactory |
| Linearity | $R^2 \geq 0.9995$ | Satisfactory |
| Accuracy | 97.3% to 101.7% | Satisfactory |
| Precision | NA* | Satisfactory |
| Specificity | Acceptable | Satisfactory |
| Stability | Long term at -60°C to -80°C | Satisfactory |
| QC range | 0.3 to 18 µg/ml | Satisfactory |

Not available

*Reviewer Note: Intra-assay precision for TD-6424 in human dialysate was not calculated due to insignificant amount of values (n=1).

**PHARMACOKINETIC/STATISTICAL ANALYSIS:**

For telavancin, AMI-11352, and AMI-999 plasma, urine, or dialysate concentrations below the limit of quantitation, zero was used for mean calculations. Nominal time was used in pharmacokinetic calculations since actual time deviated by less than 5% from the nominal. The pharmacokinetic parameters of telavancin were determined by non-compartmental analysis.

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 areas under the plasma concentration versus time curve from time zero to 24 hours ($AUC_{0-24}$), zero to 48 hours ($AUC_{0-48}$), and zero to the last measurable concentration ($AUC_{0-t}$) were calculated by the linear trapezoidal rule. The terminal elimination rate constant ($\lambda z$) was determined by linear regression of the natural logarithm of plasma concentration versus time during the terminal phase. The terminal-phase elimination half-life ($t_{1/2}$) was calculated as $\ln(2)/\lambda z$. The area under the plasma concentration versus time curve from the last measurable concentration to infinite time ($AUC_{t-\infty}$) was calculated as $Clm/\lambda z$. The area under the plasma concentration versus time curve from time 0 hours to infinite time ($AUC_{0-\infty}$) was calculated as $AUC_{0-t} + AUC_{t-\infty}$. The telavancin clearance (CL) was calculated as dose/$AUC_{0-\infty}$. The volume of distribution at the steady state (Vss) was calculated as CL*MRT. Total body clearance for free telavancin (CLf) was calculated as CL/free fraction.

In subjects with normal renal function and mild and moderate renal impairment, based on the sampling schedule, for AMI-11352 and AMI-999, only $T_{max}$, $C_{max}$, $AUC_{0-48}$, and the corresponding $C_{max}$, and $AUC_{0-48}$ to telavancin ratios are reported here. For subjects with severe renal impairment, in whom sampling extended out to 96 hours, $AUC_{0-96}$, and the corresponding $AUC_{0-96}$ to telavancin ratios are also reported here.

The total amount of telavancin, AMI-11352, and AMI-999 excreted unchanged in urine (Ae) was estimated as

$$\sum_{0}^{t} Ut * Cut$$

where Ut and Cut are the urine volume and reported analyte concentration (including telavancin, AMI-11352 and AMI-999) in urine, respectively, for time t (up to 48 hours).

The corresponding renal clearance values ($CL_R$) were calculated as Ae/$AUC_{0-\infty}$. Individual interval renal clearances ($CL_R$) were also estimated as

$$\left(\sum_{t1}^{t2} U_i * Cu_i\right) / \left(\int_{t1}^{t2} C * dt\right)$$

where t1 and t2 is time of the plasma and urine collection intervals.

**RESULTS:**

**Study Population**

A total of 29 subjects were enrolled, and all subjects received telavancin. Of the 29 subjects, six had normal renal function (mean $CL_{CR}$ 94.2 mL/min; Group 1), seven had mild renal impairment (mean $CL_{CR}$ 66.8 mL/min; Group 2), six had moderate renal impairment (mean $CL_{CR}$ 40.5 mL/min; Group 3), four had severe renal impairment (mean $CL_{CR}$ 21.7 mL/min; Group 4), and six had ESRD requiring hemodialysis (Group 5). Seven subjects with mild renal impairment were enrolled. One subject (001-0011) had the infusion of telavancin discontinued before completion due to an adverse event. Subject 001-0011 developed "red man syndrome" (seen with glycopeptides antibiotics) which was considered severe by the investigator and required discontinuation of the infusion after approximately two-thirds of the dose had been delivered. The subject recovered completely. Subject 001-0111 was enrolled to replace the discontinued subject, for a total of seven subjects in the mild renal impairment group; however, pharmacokinetic data were only evaluated for six subjects in this group.

**Demographics**

The demographics for the 29 subjects enrolled in the study are shown in Table 1. The majority of the subjects (22/29) were male. Fifteen subjects were white and 14 were black. The ratio of whites/blacks varied substantially among the groups, and notably the group with no renal impairment consisted of all white subjects and the group with ESRD consisted of all black subjects. The mean age for all subjects enrolled was 56.8 years; the mean age was highest in the moderate renal impairment group (70.0 years) and lowest in the end-stage renal impairment group (47.3 years). There were no clinically important differences in height, weight, or body mass index among the groups. The differences in creatinine clearance at baseline reflected the varying degrees of renal impairment in each group.

**Table 1. Mean (SD) demographic characteristics**

| Parameter | Renal Function | | | | |
|---|---|---|---|---|---|
| | None (N=6) | Mild (N=7*) | Moderate (N=6) | Severe (N=4) | ESRD (N=6) |
| Sex (M/F) | 5/1 | 4/3 | 5/1 | 3/1 | 5/1 |
| Age (yrs) | 50.5 (9.1) | 58.6 (15.3) | 70.0 (9.2) | 57.5 (12.1) | 47.3 (6.4) |
| Race (White/Black) | 6/0 | 5/2 | 2/4 | 2/2 | 0/6 |
| Weight (kg) | 78.6 (9.8) | 75.6 (14.6) | 68.7 (11.0) | 80.4 (16.8) | 80.6 (23.4) |
| Height (cm) | 174.8 (6.3) | 168.7 (7.4) | 167.8 (10.7) | 172.5 (15.3) | 171.8 (7.1) |
| Body Mass Index ($kg/m^2$) | 25.6 (2.1) | 26.4 (3.6) | 24.5 (3.8) | 26.8 (2.3) | 27.2 (6.9) |
| $CL_{CR}$ (mL/min) | 94.2 (10.9) | 66.8 (8.9) | 40.5 (7.1) | 21.7 (7.2) | NA |

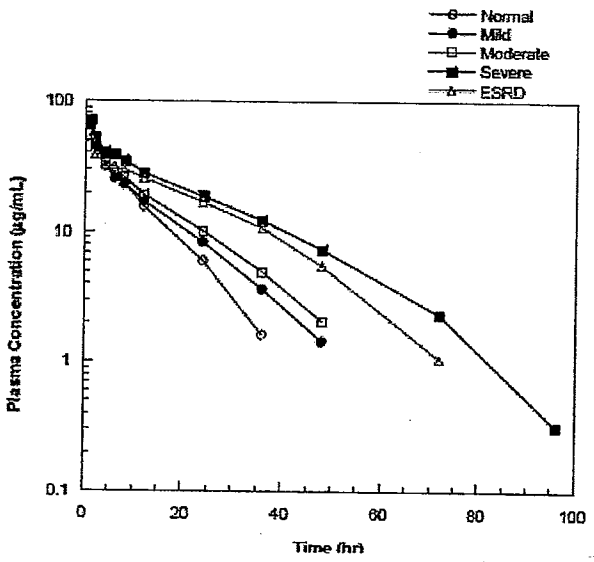
*Pharmacokinetic data were available for 6 subjects in this group; all 7 were included in the safety analysis.

**Plasma Pharmacokinetics**

The mean telavancin plasma concentration-time profiles for each of the five renal function groups are shown inFigure 1. 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 diposition processes. Following administration, plasma concentrations remained above the lower limit of quantiation for the longest interval in the groups with $CL_{CR}$ < 30 mL/min.

**Figure 1. Mena plasma concentration-time profiles of a single dose of telavancin 7.5 mg/kg in subjects with varying degrees of renal impairment**




The mean ± SD pharmacokinetic parameters for telavancin are shown in Table 2. The mean $C_{max}$ and $V_{SS}$ among the study groups were similar, suggesting renal function had minimal effect on the distribution of telavancin after IV administration. The mean plasma clearance was modestly lower in the mildly and moderately impaired groups compared to normal, but approximately 50% lower in the severely impaired and ESRD groups. Relative to subjects with normal renal function, the mean elimination half-life was modestly higher in the mild and moderate groups, but approximately two-times longer in the severe renal impairment and ESRD groups. In the mild, moderate, severe, and ESRD groups, the mean $AUC_{0-\infty}$ increased approximately13%, 29%, 118%, and 79%, respectively compared to subjects with normal renal function. However, there was a larger degree of variability in the $AUC_{0-\infty}$ values for subjects with ESRD compared with healthy subjects (range 639 to 1470 µg·hr/mL). The mean $C_{max}$ tended to be lowest in subjects with ESRD receiving hemodialysis.

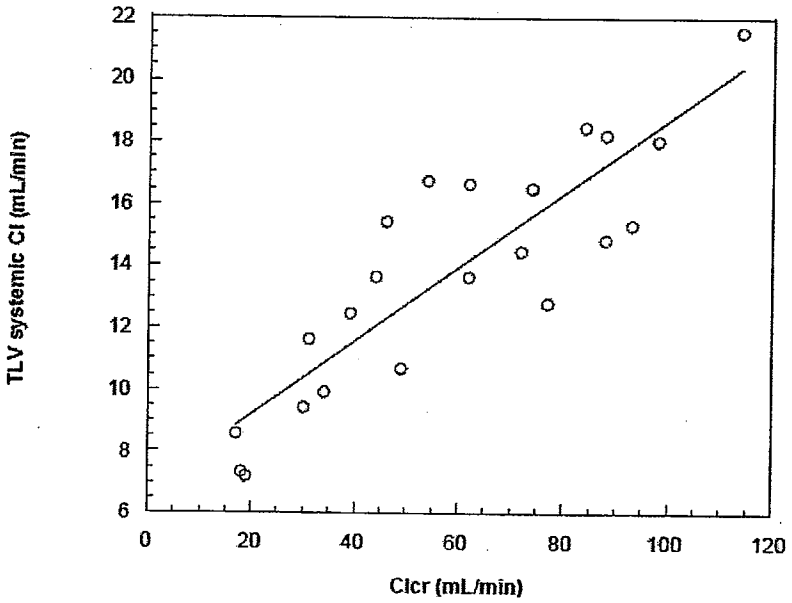
**Table 2. Mean ± SD pharmacokinetic parameters of telavancin in subjects with varying degrees of renal function**

| Parameter | Normal (n=6) | Mild (n=6) | Moderate (n=6) | Severe (n=4) | ESRD (n=6) |
|---|---|---|---|---|---|
| Protein binding (%) | 86.5 ± 1.3 | 87.5 ± 1.0 | 87.8 ± 1.1 | 86.7 ± 1.2 | 87.6 ± 1.0 |
| $C_{max}$ (µg/ml) | 70.6 ± 11.2 | 65.9 ± 2.7 | 65.8 ± 12.1 | 71.8 ± 7.1 | 52.1 ± 10.1 |
| $t_{½}$ (hr) | 6.90 ± 0.60 | 9.61 ± 2.93 | 10.6 ± 2.4 | 14.5 ± 1.3 | 11.8 ± 2.8 |
| $AUC_{0-48}$ (µg.hr/mL) | 554 ± 92 | 608 ± 81 | 683 ± 169 | 1060 ± 70 | 898 ± 264 |
| $AUC_{0-\infty}$ (µg.hr/mL) | 560 ± 93 | 633 ± 101 | 721 ± 200 | 1220 ± 120 | 1010 ± 341 |
| CL (mL/hr/kg) | 13.7 ± 2.1 | 12.1 ± 1.9 | 11.1 ± 3.3 | 6.18 ± 0.63 | 8.18 ± 2.65 |
| MRT (hr) | 9.6 ± 0.7 | 13.3 ± 3.3 | 14.7 ± 3.3 | 22.3 ± 2.8 | 20.1 ± 3.7 |
| $V_{ss}$ (mL/kg) | 131 ± 2.1 | 157 ± 19 | 156 ± 24 | 136 ± 10 | 157 ± 27 |
| $Cl_f$ (mL/hr/kg)[a] | 102 ± 17 | 96.9 ± 10.7 | 90.2 ± 22.3 | 46.6 ± 6.2 | 66.9 ± 24.8 |

| | | | | | |
|---|---|---|---|---|---|
| $CL_R$ (mL/hr/kg) | 5.48 ± 0.67 | 2.89 ± 1.32 | 3.66 ± 1.34 | 1.80 ± 0.30 | NA |

The relationship between $CL_{CR}$ and plasma clearance is shown in Figure 2. In general, individual plasma clearance values were associated with $CL_{CR}$.

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




Plasma protein binding of telavancin was determined via equilibrium dialysis for all subjects using a pre-dose plasma sample. Over a concentration range of 1 to 500 µg/mL, there were no appreciable differences in the degree of protein binding. The average binding of telavancin to plasma proteins was approximately 87% in all renal function groups (mean values were 86.5%, 87.5%, 87.8%, and 87.6% for all subjects with normal, mild renal impairment, moderate renal impairment, severe renal impairment, and ESRD, respectively). Plasma protein binding was determined for Subject 001-011 (86%); however, because Subject 001-011 received only a partial dose, the data were excluded from the mean calculation for plasma protein binding.

The mean ± SD pharmacokinetic parameters of AMI-11352 and AMI-999 are shown in Table 3 and Table 4, respectively. The mean plasma concentrations of telavancin for all groups were approximately 70 µg/mL at peak and greater than 10 µg/mL over the first 48 hours after dosing compared with less than 8 µg/mL at all time points for AMI-11352 and less than 1 µg/mL for AMI-999. Subjects in the moderate, severe, and ESRD groups had $AUC_{0-t}$ values of AMI-11352 3- to 12-times higher compared to subjects with normal and mild renal imparment. The exposure to AMI-999 was approximately 3- to 3.5-times higher in subjects with severe renal impairment and ESRD compared to subjects with normal renal function; however, these moieties represented only a small percentage of the total drug in plasma.

**Table 3. Mean ± SD pharmacokinetic arameters of AMI-11352**

| Parameter | Renal Function | | | | |
|---|---|---|---|---|---|
| | Normal (n=6) | Mild (n=6) | Moderate (n=6) | Severe (n=4) | ESRD (n=6) |
| $C_{max}$ (µg/mL) | 0.482 ± 0.086 | 0.748 ± 0.291 | 1.09 ± 0.47 | 2.70 ± 0.97 | 6.80 ± 0.99 |
| $T_{max}$ (hr) | 12.7 ± 8.9 | 29.3 ± 13.8 | 31.3 ± 15.7 | 51.0 ± 15.1 | 64.0 ± 12.4 |
| $AUC_{0-48}$ (µg.hr/mL) | 17.2 ± 4.9 | 27.9 ± 12.1 | 42.9 ± 18.6 | 89.0 ± 33.0 | 177 ± 24 |
| $CL_R$ (mL/hr/kg) | 50.6 ± 9.9 | 22.7 ± 11.3 | 24.0 ± 7.7 | 9.53 ± 2.61 | NA |
| (AMI-11352/telavancin Ratio) | | | | | |
| $C_{max}$ Ratio | 0.00692 ± 0.00138 | 0.0113 ± 0.0042 | 0.0169 ± 0.0069 | 0.0388 ± 0.0171 | 0.136 ± 0.039 |
| $AUC_{0-48}$ Ratio | 0.0308 ± 0.0062 | 0.0455 ± 0.0176 | 0.0624 ± 0.0196 | 0.0857 ± 0.0371 | 0.215 ± 0.079 |

**Table 4. Mean ± SD pharmacokinetic parameters of AMI-999**

| Parameter | Renal Function | | | | |
|---|---|---|---|---|---|
| | Normal (n=6) | Mild (n=6) | Moderate (n=6) | Severe (n=4) | ESRD (n=6) |
| $C_{max}$ (µg/mL) | 0.729 ± 0.159 | 0.882 ± 0.436 | 0.712 ± 0.210 | 0.648 ± 0.107 | 0.504 ± 0.181 |
| $T_{max}$ (hr) | 1.0 ± 0.0 | 1.0 ± 0.0 | 1.0 ± 0.0 | 1.0 ± 0.0 | 5.2 ± 4.8 |
| $AUC_{0-48}$ (µg.hr/mL) | 4.01 ± 1.31 | 7.32 ± 6.79 | 4.64 ± 1.93 | 11.7 ± 6.0 | 12.7 ± 8.4 |
| $t_{½}$ (hr) | 11.0 ± 4.4 | 12.0[a] | 11.0 ± 2.0[b] | 49.8 ± 9.2[b] | 41.1 ± 25.4[c] |
| $CL_R$ (mL/hr/kg) | 8.42 ± 1.27 | 2.62 ± 2.73 | 3.22 ± 2.25 | 0.558 ± 0.714 | NA |
| AMI-999/telavancin Ratio | | | | | |
| $C_{max}$ Ratio | 0.010 ± 0.001 | 0.013 ± 0.006 | 0.011 ± 0.003 | 0.009 ± 0.001 | 0.009 ± 0.002 |
| $AUC_{(0-48)}$ Ratio | 0.007 ± 0.002 | 0.011 ± 0.009 | 0.007 ± 0.003 | 0.011 ± 0.005 | 0.013 ± 0.005 |

[a]n=2, [b]n=3, [c]n=4

**Urinary Pharmacokinetics:**

The cumulative measured urinary excretion of telavancin, AMI-11352, and AMI-999 is summarized in Table 5. The mean ± SD value for relative telavancin excretion in those without renal impairment was 40.2% ± 6.4 over 48 hours, which was higher than any of the other groups. Combining all the analytes, however, the relative percent recovery was similar (about 50% of the administered dose) for the subjects without renal impairment and those with moderate to severe impairment. The measured renal excretion in the mildly impaired group was only about 31% of the administered dose over 48 hours. No ready explanation for this observation is available except that two subjects (Nos. 008 and 012) had an exceedingly low measured urinary recovery (16–18%) and urine was only collected for 48 hours postdose. In addition, it is noteworthy that the severely impaired subjects excreted a relatively greater proportion of the drug as AMI-11352, compared with the other groups.

**Table 5. Mean ± SD urinary recovery of telavancin, AMI-11352 and AMI-999**

| Parameter | Renal Function | | | |
|---|---|---|---|---|
| | Normal (n=6) | Mild (n=6) | Moderate (n=6) | Severe (n=4) |
| Cumulative total recovery % dose (0-48hr) | 51.8 ± 7.6 | 31.3 ± 12.3 | 44.4 ± 12.6 | 36.4 ± 7.0 |
| % dose as telavancin | 40.2 ± 6.1 | 23.4 ± 10.0 | 31.8 ± 10.8 | 25.4 ± 5.2 |
| % dose as AMI-11352 | 11.1 ± 1.7 | 7.76 ± 3.48 | 12.4 ± 3.1 | 11.0 ± 4.5 |
| % dose as AMI-999 | 0.437 ± 0.103 | 0.145 ± 0.134 | 0.177 ± 0.104 | 0.0629 ± 0.0621 |
| Cumulative total recovery % dose (0-96hr) | - | - | - | 50.5 ± 7.0 |
| % dose as telavancin | - | - | - | 28.0 ± 5.8 |
| % dose as AMI-11352 | - | - | - | 22.3 ± 4.8 |
| % dose as AMI-999 | - | - | - | 0.0629 ± 0.0621 |

**Clearance of Telavancin by Hemodialysis:**

Table 6 shows the amount of telavancin removed by hemodialysis for the individual subjects with ESRD. 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 recovered. The clearance of telavancin based on dilaysi flow rate, dialysate and arterial concentrations of drug entering the dialyzer, indicated that telavancin clearance during dialysis was low, averaging 4.5ml/mi (range 3.7 to 5.6) compared with plasma clearance of 14 ml/hr/kg in normal subjects (16 ml/min for a 70 kg person).

**Table 6. Amount of telavancin removed by hemodialysis**

| Subject ID | Cumulated Amount of Telavancin (mg) Recovered in Dialysate Fluid | % Dose Removed by Hemodialysis | Cl Dialysis (mL/min) |
|---|---|---|---|
| 0025 | | | |
| 0026 | | | |
| 0027 | | | |
| 0028 | | | |
| 0029 | | | |
| 0030 | | | |
| N | 6 | 6 | 6 |
| Mean | 35.9 | 5.92 | 4.50 |
| SD | 16.3 | 1.71 | 0.69 |

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**Dosage Adjustment**

The sponsor's proposed dosage adjustment in patients with normal renal function and renal impairment is shown in Table 7.

**Table 7. Sponsor's proposed dosage regimens of telavancin for patients with normal renal function and renal impairment**

| Creatinine clearance (mL/min) | Dosage Regimen |
|---|---|
| >50 mL/min | 10 mg/kg q24h |
| 30 – 50 mL/min | 7.5 mg/kg q24h |
| <30 mL/min | 10 mg/kg q48h |
| ( | ) |

b(4)

The reviewer evalauated 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 total plasma concentration-time profiles are shown in Figure 3. The mean pharmacokinetic parameters based on simulated plasma concentrations for each regimen are shown in Table 7. Although the mean $C_{max}$ value for subjects with moderate renal impairment was lower than all other groups, the mean $AUC_{0-24}$ was similar to 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. Thus, the results of the PK/PD analysis support the sponsor's proposed dosage adjustment for patients with moderate and severe renal impairment.

The pharmacokinetics of telavancin in subjects with ESRD who received hemodialysis immediately prior to drug administration has not been evaluated. ?

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**Figure 3. Mean simulated plasma concentration-time profiles for subjects with normal renal function and renal impairment**

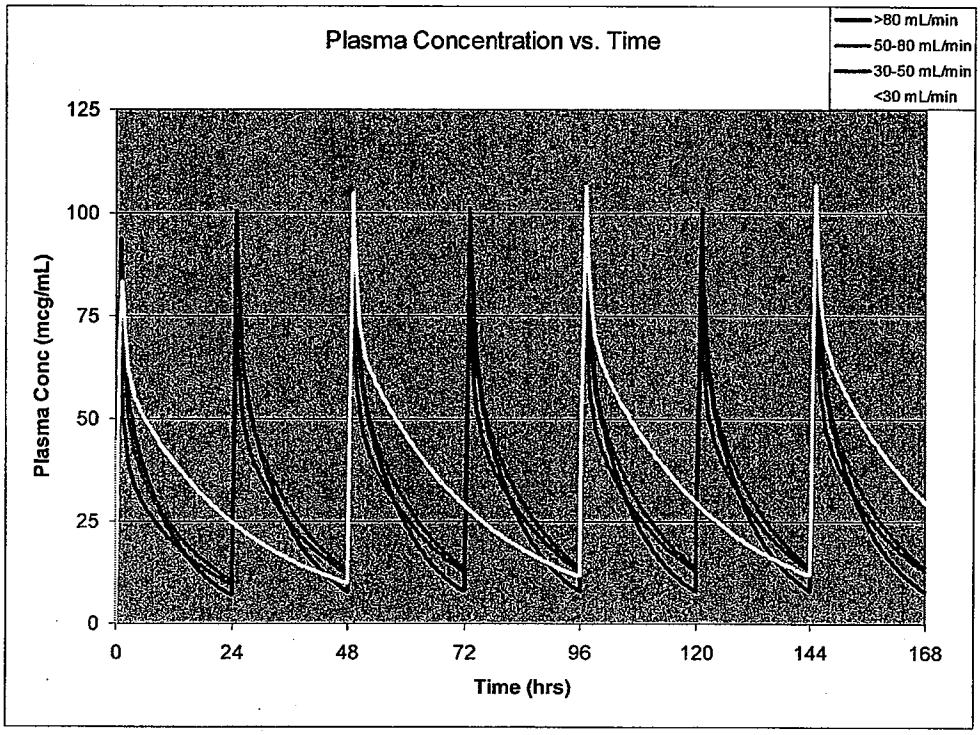


**Table 7. Mean (range) pharmacokinetic parameters on day 7 based on simulated plasma concentrations**

| Dosage Regimen | $AUC_{0-\tau}$ (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 (585 - 925) | 101.3 (80.7 – 126.2) | 7.9 (4.91 – 11.17) | NA |
| **Mild renal impairment ($CL_{CR}$ 50 - <80 mL/min)** | | | | |
| 10 mg/kg q24h | 832 (669 - 1013) | 100.8 (93.0 – 114.0) | 13.8 (8.3 – 21.1) | NA |
| **Moderate renal impairment ($CL_{CR}$ 30 - <50 mL/min)** | | | | |
| 7.5 mg/kg q24h | 712 (430 - 1075) | 78.1 (59.2 – 101.7) | 13.0 (5.6 – 24.6) | NA |
| **Severe renal impairment ($CL_{CR}$ <30 mL/min)** | | | | |
| 10 mg/kg q48h | 1661 (1408 - 1814) | 106.8 (92.8 – 119.3) | 29.6 (24.0 – 32.2) | 11.9 (7.9 – 14.0) |
| 7.5 mg/kg q48h | 1246 (1057 - 1361) | 80.2 (69.7 – 89.5) | 22.2 (18.0 – 24.2) | 8.9 (5.9 – 10.5) |

**CONCLUSIONS:**

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. Plasma clearance was similar in subjects with normal renal function and subjects with mild and moderate renal impairment and approximately 55 and 40% decreased in severely impaired and ESRD groups, respectively, compared to normal subjects. Elimination half-life was approximately 2- to 2.5-fold higher in subjects with severe renal impairment and ESRD compared with subjects with normal renal function. In the mild, moderate, severe, and ESRD groups, there were increases in telavancin exposure (AUC0-$\infty$) of 13%, 29%, 118%, and 79%, respectively, compared with the normal renal function group. Telavancin was not cleared to a significant degree by hemodialysis.

**0016**

**Pharmacokinetics and Safety of Intravenous Telavancin in Subjects With Hepatic Impairment**

Date(s): 22JUL2004 to 24OCT2004

Clinical Sites:

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**OBJECTIVES:**

Primary:

To assess the effect of hepatic impairment on the pharmacokinetics of televancin.

Secondary:

To assess the safety and tolerability of a single intravenous infusion of telavancin in subjects with hepatic impairment.

**FORMULATION:**

Telavancin Batch No. AME009.

**STUDY DESIGN:**

This was a Phase 1, open label, single dose study. Approximately eight adult subjects with moderate hepatic impairment and eight subjects with normal hepatic function were to be enrolled in the study. All subjects were to receive a single 10 mg/kg intravenous infusion of telavancin. The two groups of eight subjects were to be comparable to each other with respect to age, gender and weight.

Group 1: Healthy subjects with no impairment in hepatic function

Group 2: Subjects with moderate hepatic impairment as defined by Childs-Pugh Score B.

**PHARMACOKINETIC ASSESSMENTS:**

Blood (plasma, 5ml) and urine samples were to be obtained for telavancin pharmacokinetic measurements. Concentrations of metabolites, AMI-11352 and AMI-999, were to be measured in plasma and urine. Blood samples were to be taken pre-dose, 1, 2, 4, 6, 8, 12, 24, 36, 48, and 72 hours after administration of study drug. Urine samples were to be collected for 72 hours post-dose. Urine samples were to be collected pre-infusion and cumulative urine collections were to be obtained over the time period 0 – 6, 6 – 12, 12 – 24, 24 – 36, 36 – 48, 48 – 60, and 60 – 72 hours relative to the start of the telavancin infusion.

**BIOANALYTICAL ANALYSIS:**

Concentrations of telavancin, AMI-11352, and AMI-999 in human plasma and urine were determined using HPLC with MS/MS detection.

**Telavancin**

| Criterion | Plasma | Urine | Comments |
|---|---|---|---|
| Concentration range | 0.25 to 100 µg/ml | 0.25 to 100 µg/ml | Satisfactory |
| LLOQ | 0.25 µg/ml | 0.25 µg/ml | Satisfactory |
| Linearity | $R^2 \geq 0.9978$ | $R^2 \geq 0.9981$ | Satisfactory |
| Accuracy | 96.6% to 102.4% | 91% to 98.1% | Satisfactory |
| Precision | 3.7% to 7.2% | 2.7% to 5.2% | Satisfactory |
| Specificity | Acceptable | Acceptable | Satisfactory |
| Stability | Freezer -60° to -80°C | Freezer -60° to -80°C | Satisfactory |
| QC range | 0.75 to 400 µg/ml | 0.75 to 400 µg/ml | Satisfactory |

**AMI-11352**

| Criterion | Plasma | Urine | Comments |
|---|---|---|---|
| Concentration range | 0.25 to 100 µg/ml | 0.25 to 100 µg/ml | Satisfactory |
| LLOQ | 0.25 µg/ml | 0.25 µg/ml | Satisfactory |
| Linearity | $R^2 \geq 0.9960$ | $R^2 \geq 0.9986$ | Satisfactory |
| Accuracy | 94.8% to 103.6% | 95.7% to 100.9% | Satisfactory |
| Precision | 6.2% to 9.0% | 2.6% to 4.9% | Satisfactory |
| Specificity | Acceptable | Acceptable | Satisfactory |
| Stability | Freezer -60° to -80°C | Freezer -60° to -80°C | Satisfactory |
| QC range | 0.75 to 400 µg/ml | 0.75 to 400 µg/ml | Satisfactory |

**AMI-999**

| Criterion | Plasma | Urine | Comments |
|---|---|---|---|
| Concentration range | 0.25 to 100 µg/ml | 0.25 to 100 µg/ml | Satisfactory |
| LLOQ | 0.25 µg/ml | 0.25 µg/ml | Satisfactory |
| Linearity | $R^2 \geq 0.9962$ | $R^2 \geq 0.9976$ | Satisfactory |
| Accuracy | 96.5% to 99.7% | 95.3% to 100.1% | Satisfactory |
| Precision | 4.6% to 5.3% | 2.9% to 4.7% | Satisfactory |
| Specificity | Acceptable | Acceptable | Satisfactory |
| Stability | Freezer -60° to -80°C | Freezer -60° to -80°C | Satisfactory |
| QC range | 0.75 to 400 µg/ml | 0.75 to 400 µg/ml | Satisfactory |

**PHARMACOKINETIC/STATISTICAL ANALYSIS:**

The pharmacokinetic parameters of telavancin, AMI-11352 and AMI-999 were determined by non compartmental analysis.The peak plasma concentration (Cmax) and the time to reach the peak concentration (Tmax) were taken directly from the plasma concentration-time data. Tmax was defined as the time that Cmax was reached. The area under the plasma concentration versus time curve from time zero to 24 hours (AUC0-24) after dosing was calculated using the linear trapezoidal rule. The (AUC0-t) area under the plasma concentration versus time curve from time zero to the last measurable concentration (Clm) was calculated using linear trapezoidal rule. The terminal elimination rate constant (λz) was determined by linear regression of the natural logarithm of plasma concentrations versus time during the terminal phase. The terminal-phase elimination half-life (t1/2) was calculated as ln(2)/λz. The area under the plasma concentration versus time curve from the last measurable concentration (Clm) to infinite time (AUCt-∞) was calculated as Clm/λz. The area under the plasma concentration versus time curve from time 0 hours to infinite time (AUC0-∞) was calculated as AUC0-t + AUCt-∞. The telavancin clearance (CL) was calculated as dose/AUC0-∞. The area under the first moment curve (AUMC) was calculated using the trapezoidal rule. The mean residence time (MRT) of telavancin was calculated as AUMC/AUC. The volume of distribution at steady state was calculated as CL*MRT. The free drug clearance for telavancin was calculated as CL/fu, where fu is the unbound fraction of telavancin in plasma. For AMI-11352 and AMI-999, only Tmax, Cmax, AUC, and $t_{1/2}$ (when obtainable) are reported here. The total amount of telavancin excreted unchanged in urine (Ae) was estimated as:

$$\sum_{0}^{t} U_t * Cu_t$$

where Ut and Cut are the urine volume and telavancin concentration in urine, respectively, for time t (72 hours). The corresponding renal clearance (CLr) was calculated

as Ae/AUC0-72. For the metabolites for which incomplete recovery may have occurred, the corresponding renal clearances (CLr) were estimated as:

$$(\sum_{0}^{72} U_i * Cu_i)/(\int_{0}^{t} C * dt)$$

where t is time of the last measurable concentration.

**RESULTS:**

**Changes in Planned Study:**

Due to a dosing error at the investigational site, five subjects with moderate hepatic impairment received an intravenous dose of telavancin 12.5 mg/kg. They were each re-treated 6 weeks later, at which time the correct dose, telavancin, 10 mg/kg, was administered. For the comparison between healthy subjects and subjects with hepatic impairment, only data from the 10 mg/kg dose were used.

**Study Population:**

A total of 16 subjects were enrolled and received telavancin. Eight subjects were healthy volunteers with normal hepatic function, each of whom received telavancin 10 mg/kg. The other eight subjects had moderately impaired hepatic function as defined by Childs-Pugh Score B. Five of these eight subjects were dosed twice with telavancin, once at 12.5 mg/kg and once 6 weeks later at 10 mg/kg. The groups were well balanced with respect to age, race and sex. The mean age for all subjects enrolled was 56.5 years, the mean weight was 73.4 kg, and the mean height was 165.7cm. All subjects were White. The majority of the subjects (10/16) were male.

**Plasma Pharmacokinetics:**

Mean telavancin plasma concentration-time profiles for normal subjects and subjects with moderate hepatic impairment at the 10 mg/kg dose of telavancin are shown in Figure 1.

Figure 1. Semi-log Plot of Mean ± SD Plasma Concentrations for Telavancin Following Intravenous Administration to Subjects with Normal or Moderately Impaired Hepatic Function at a Dose of 10mg/kg (Study 0016)

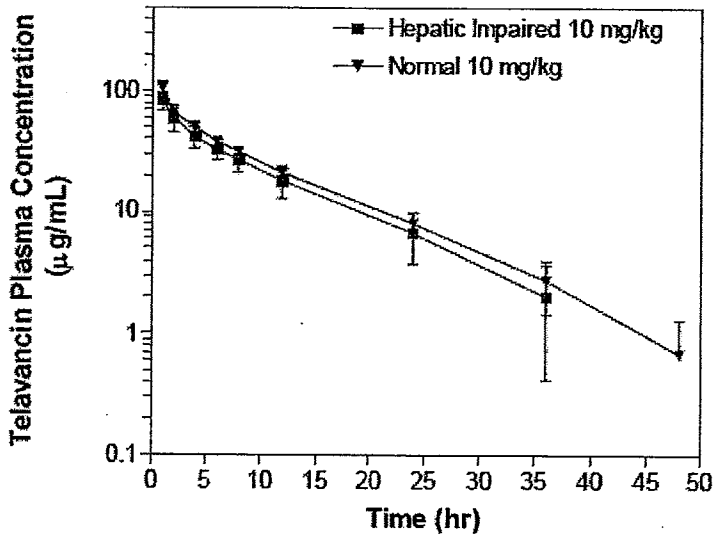


Table 2 shows the mean observed noncompartmental pharmacokinetic parameters of telavancin for both normal subjects and subjects with moderate hepatic impairment.

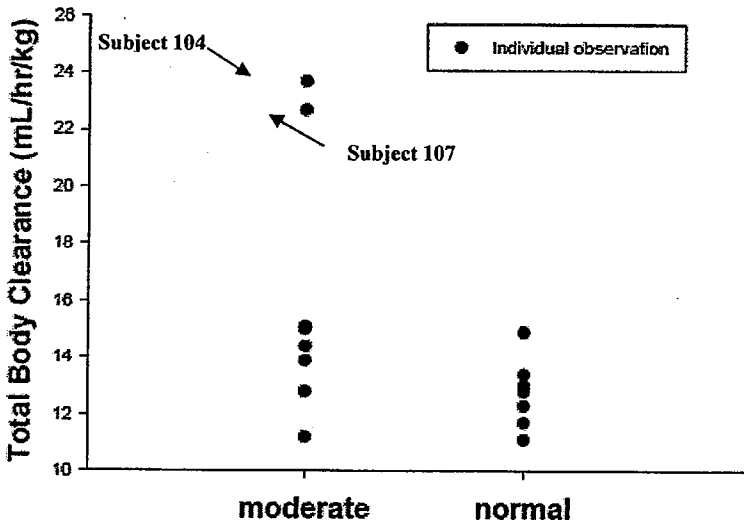
Table 2. Mean (±SD) Telavancin Pharmacokinetic Parameters for Subjects with Normal or Moderately Impaired Hepatic Fuction after Receiving Telavancin 10mg/kg (Study 0016)

| Hepatic Function | Normal (n=8) | Moderately Impaired (n=8) | Moderately Impaired (n=6)* |
|---|---|---|---|
| $C_{max}$ (µg/ml) | 105 ± 12 | 82.8 ± 13.7 | 88.1 ± 11.3 |
| $T_{max}$ (hr) | 1.0 ± 0.0 | 1.0 ± 0.0 | 1.0 ± 0.0 |
| $AUC_{(0-\infty)}$(µg·hr/ml) | 789 ± 69 | 660 ± 159 | 736 ± 86.4 |
| Elimination $T_{½}$ (hr) | 7.3 ± 1.3 | 7.2 ± 2.1 | 7.96 ± 1.89 |
| Cl (ml/hr/kg) | 12.8 ± 1.1 | 16.1 ± 4.6 | 13.7 ± 1.49 |
| $V_{ss}$(ml/kg) | 125 ± 17 | 148 ± 31 | 141.5 ± 32.7 |
| MRT(hr) | 9.9 ± 1.6 | 9.6 ± 2.4 | 10.33 ± 2.19 |
| % Unbound | 11.4 ± 1.0 | 12.6 ± 1.9 | 12.1 ± 1.54 |
| $Cl_{fu}$(ml/hr/kg) | 113 ± 13 | 129 ± 35 | 115.6 ± 23.7 |

*Subjects 104 and 107 were not included in these calculated values

The mean $T_{max}$ values (end of infusion) are the same for both normal subjects and subjects with moderate hepatic impairment. The mean $C_{max}$ value for the subjects with moderate hepatic impairment was 21% less than that observed in normal subjects. The sponsors feel that this is a statistically but not clinically significant difference (ANOVA test, $p < 0.05$). The mean pharmacokinetic parameters such as elimination $t_{½}$, $AUC_{(0-\infty)}$, Cl, $V_{ss}$, MRT, % unbound, and $Cl_{fu}$ obtained from the two groups were similar across the two groups. It should be noted that there is greater variability in the values for total body clearance (and AUC) in the subjects with hepatic impairment compared to normal subjects. This greater variability reflects very high clearance values for two subjects in the hepatic impairment group. The difference in AUC was approximately 16% between the normal and moderately impaired group of subjects. However, when subjects 38103-0104 and 38103-0107 (represent outlier values much higher than the other subjects) were excluded from the calculation the difference in AUC was reduced to approximately 6% between the normal and moderately hepatically impaired group. Thus the 16% difference in AUC values is not due to hepatic impairment, but instead due to subjects that had values that were outliers in the data analysis. Figure 2 shows the mean plasma clearance for the study subjects.

Figure 2. Plot of Mean ± SD Plasma Clearance for Telavancin Following Intravenous Administration to Subjects with Normal or Moderately Impaired Hepatic Function at a Dose of 10 mg/kg (Study 0016)




Subjects 38103-0104 and 38103-0107 from the moderate hepatic impairment group had the highest observed percentage of free telavancin in plasma (Figure 3) and the highest total body CL values observed in the study, 23.7 and 22.7 mL/hr/kg, respectively (Figure 4). The sponsor suggests that because these subjects had relatively low baseline albumin levels (3.7 and 2.8 g/dL), this may have accounted for the higher free telavancin concentrations in these subjects. However, as shown Figure 3 the two subjects that have the highest percent of unbound telavancin are subjects 107 and 105. The greater total body clearance may be related to these observations for subject 107 but not subject 104; however, additional subjects with low albumin values would need to be studied to further evaluate this hypothesis. Subjects 38103-0104 and 38103-0107 influenced the regression line depicted in Figure 4.

Figure 3. Percent Unbound Telavancin in Plasma versus Serum Albumin Levels (Study 0016)

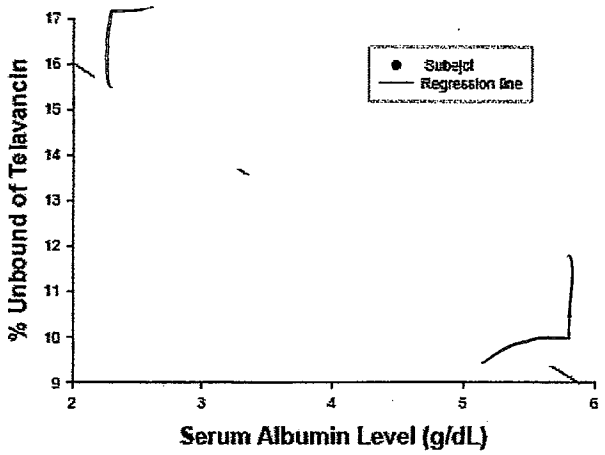
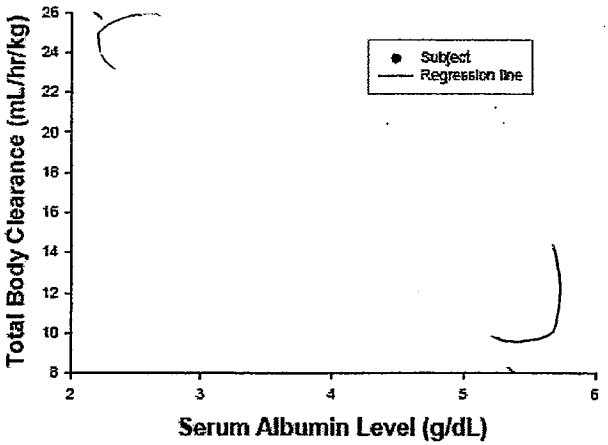



Figure 4. Telavancin Total Body Clearance versus Serum Albumin Levels (Study 0016)




**Pharmacokinetic Disposition of AMI-11352 and AMI-999 from Plasma:**

Figure 5 shows the concentration versus time plot of AMI-11352 levels in plasma. After the administration of telavancin, individual AMI-11352 levels in plasma rose to $T_{max}$ at 4 to 24 hours after dosing and then declined slowly. Similar $T_{max}$ values were observed for normal subjects (13.5 hrs) and subjects with moderate hepatic impairment (15.5 hrs). A meaningful elimination $t_{½}$
For AMI-11352 could not be obtained due to the plateau in concentrations of AMI-11352. AMI-11352 appeared to have slower elimination than telavancin. However, the renal clearance of this metabolite is considerably greater than that of telavancin. One hypothesis for this PK behavior is that due to the presence of a deep compartment for telavancin, there is continued production of AMI-11352 resulting in the appearance of an extended $t_{½}$.

Figure 5. Semi-log Plot of Mean ± SD Plasma Concentrations of AMI-11352 Following Intravenous Administration of Telavancin to Subjects with Normal or Moderately Impaired Hepatic Function at a Dose of 10mg/kg (Study 0016)

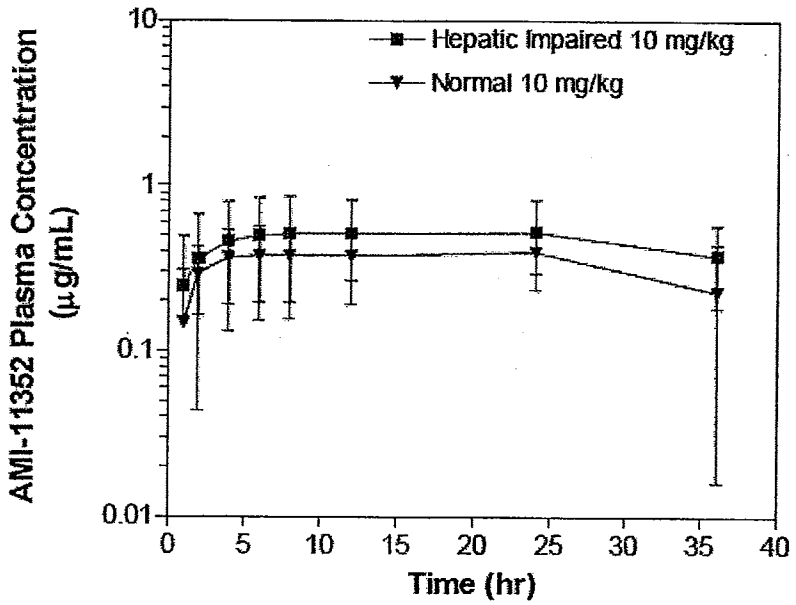



Table 3 shows the mean Pk parameters of AMI-11352 in plasma.

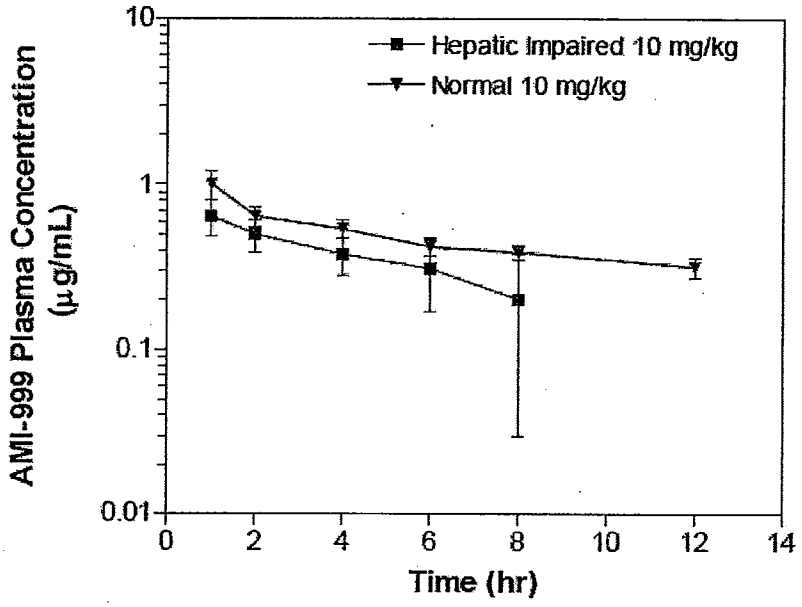
Table 3. Mean (±SD) AMI-11352 Pharmacokinetic Parameters Following Intravenous Administration of Telavancin to Subjects with Normal or Moderately Impaired Hepatic Fuction at a Dose of 10mg/kg (Study 0016)

| Hepatic function | Normal (n=8) | Moderately Impaired (n=8) |
|---|---|---|
| $C_{max}$ (µg/ml) | 0.437 ± 0.104 | 0.566 ± 0.304 |
| $T_{max}$ (hr) | 13.5 ± 9.0 | 15.0 ± 11.5 |
| $AUC_{(0-t)}$(µg·hr/ml) | 13.2 ± 7.9 | 18.0 ± 10.1 |
| Elimination $T_{½}$ (hr) | NC | NC |
| | (AMI-11352/telavancin Ratio) | |
| $C_{max}$ ratio | 0.00419 ± 0.00117 | 0.00688 ± 0.00330 |
| $AUC_{(0-t)}$ratio | 0.0166 ± 0.0086 | 0.0285 ± 0.0140 |

The mean $C_{max}$ and $AUC_{(0-t)}$ values of the metabolite observed from subjects with moderate hepatic impairment were 29.5% and 36.4%, respectively, higher than the corresponding values obtained from the normal subjects. It is possible that the metabolic clearance of AMI-11352 was reduced in subjects with hepatic impairment. Higher mean Cmax and $AUC_{(0-t)}$ ratios of AMI-11352 to telavancin were also observed for the subjects with moderate hepatic impairment compared to normal subjects. However, these ratios were still low suggesting that the higher concentrations of AMI-11352 in subjects with hepatic impairment are of little clinical significance.
After the administration of telavancin, individual subject's AMI-999 levels in plasma were low

and reached $T_{max}$ at the end of infusion (except Subject 38014-0002) and continued to decline to below the limit of quantitation by 12 hours after dosing. Figure 6 shows the concentration versus time profile of AMI-999 in plasma.

Figure 6. Semi-log Plot of Mean ± SD Plasma Concentration of AMI-999 Following Intravenous Administration of Telavancin to Subjects with Normal or Moderately Impaired Hepatic Function at a Dose of 10mg/kg (Study 0016)




Similar mean elimination $t_{1/2}$ values for AMI-999 were obtained from normal subjects and subjects with moderate hepatic impairment (9.8 hours vs. 8.4 hours at 10 mg/kg; 14.1 at 12.5 mg/kg). The mean Cmax and $AUC_{(0-t)}$ values observed for subjects with moderate hepatic impairment were 35.0% and 43.7%, respectively, below the corresponding values obtained from the normal subjects. Marginally lower mean Cmax and $AUC_{(0-t)}$ ratios of AMI-999 to telavancin also observed for the subjects with moderate hepatic impairment compared to normal subjects; however, variability was high and differences between the groups are not considered clinically significant. Table 4 shows the mean PK values of AMI-999 in plasma.

Table 4. Mean (±SD) AMI-999 Pharmacokinetic Parameters Following Intravenous Administration of Telavancin to Subjects with Normal or Moderately Impaired Hepatic Function at a Dose of 10mg/kg (Study 0016)

| Hepatic function | Normal (n=8) | Moderately Impaired (n=8) |
|---|---|---|
| $C_{max}$ (µg/ml) | 0.998 ± 0.199 | 0.649 ± 0.155 |
| $T_{max}$ (hr) | 1.00 ± 0.00 | 1.13 ± 0.35 |
| $AUC_{(0-t)}$(µg·hr/ml) | 5.68 ± 0.63 | 3.20 ± 1.50 |
| Elimination $T_{½}$ (hr) | 9.75 ± 0.87 | 8.42 ± 3.06 |
| | (AMI-999/telavancin Ratio) | |
| $C_{max}$ ratio | 0.00940 ± 0.00118 | 0.00783 ± 0.00131 |
| AUC ratio | 0.00734 ± 0.00089 | 0.00478 ± 0.00141 |

**Urinary Excretion of Telavancin, AMI-11352 and AMI-999:**

There were no apparent differences in urinary recovery of telavancin, AMI-11352, and AMI-999 between normal subjects and subjects with moderate hepatic impairment. Table 5 shows the mean urinary recovery of telavancin, AMI-11352, and AMI-999.

Table 5. Mean (±SD) Urinary Recovery of Telavancin, AMI-11352, and AMI-999 Following Intravenous Administration of Telavancin to Subjects with Normal or Moderately Impaired Hepatic Function at a Dose of 10mg/kg (Study 0016)

| Hepatic function | Normal (n=8) | Moderately Impaired (n=8) |
|---|---|---|
| Cumulative total recovery % dose (0-72 hr) | 50.0 ± 8.9 | 52.1 ± 6.7 |
| % dose as telavancin | 41.8 ± 8.1 | 39.8 ± 5.1 |
| % dose as AMI-11352 | 8.00 ± 2.11 | 12.0 ± 2.6 |
| % dose as AMI-999 | 0.219 ± 0.087 | 0.407 ± 0.178 |
| Renal Clearance (ml/hr/kg) | | |
| Telavancin | 5.3 ± 1.1 | 6.4 ± 2.2 |
| AMI-11352 | 73.0 ± 27.9 | 76.6 ± 26.5 |
| AMI-999 | 3.8 ± 1.3 | 15.5 ± 10.4 |

The mean percentages of the telavancin dose excreted in urine as telavancin, AMI-11352, and AMI-999 within 72 hours were 41.8%, 8.00% and 0.219%, respectively, in normal subjects, while the corresponding values observed in subjects with moderate hepatic impairment were 39.8%, 12.0% and 0.407%, respectively. The mean total percentage of the telavancin dose recovered in urine was 50.0 and 52.1%, respectively, for normal subjects and subjects with moderate hepatic impairment. The mean renal clearances of telavancin, AMI-11352, and AMI-999 were 5.3, 73.0 and 3.8 mL/hr/kg, respectively, in normal subjects, while the corresponding values observed in subjects with moderate hepatic impairment were similar, 6.4, 76.6 and 15.5 mL/hr/kg, respectively.

**CONCLUSIONS:**

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.
Slightly higher mean AMI-11352 Cmax and $AUC_{(0-t)}$ values were observed for subjects with

moderate hepatic impairment compared to normal subjects. However, the mean $AUC_{(0-t)}$ ratios of AMI-11352 to telavancin were only 0.017 and 0.029 for normal subjects and subjects with moderate hepatic impairment, respectively.

Lower mean AMI-999 Cmax and $AUC_{(0-t)}$ values were observed for subjects with moderate hepatic impairment subjects compared to normal subjects. However, the mean $AUC_{(0-t)}$ ratios of AMI-999 to telavancin were only 0.007 and 0.005 for normal subjects and subjects with moderate hepatic impairment, respectively. These differences are not considered clinically significant due to the high variability in these ratios and the low concentrations of AMI-999 which were observed.

There were no apparent differences in urinary recovery of telavancin, and AMI-11352, between normal subjects and subjects with moderate hepatic impairment; recovery of AMI-999 appeared to be greater in subjects with hepatic impairment, with high variability. The total percentage of dose recovered in urine is less than that observed in early clinical studies of telavancin. This apparent discrepancy remains unexplained. The possibility of analytical issues leading to the under-estimation of the analytes (including telavancin, AMI-11352 and AMI-999) excreted has been considered. There were no apparent differences in urinary recovery of telavancin and AMI-11352 between healthy subjects and subjects with hepatic impairment, but the renal clearance of AMI-999 was greater in subjects with hepatic impairment. No explanation is apparent for this observation; however, plasma profiles for this impurity were comparable for both groups of subjects. Five subjects with moderate hepatic impairment received both 10 and 12.5 mg/kg doses.

Evaluation of pharmacokinetic results demonstrated a dose-proportional increase in exposure from 10 mg/kg to 12.5 mg/kg with no difference between doses in clearance or half-life.

*4.1.4. Extrinsic Factors*

0032

**A Phase 1 Study, Double-Blind, Crossover Study to Evaluate the Interaction of Telavancin and Midazolam in Healthy Subjects.**

Date(s): 14SEP2005 to 27OCT2005

Clinical Sites:

C ↄ b(4)

**OBJECTIVES:**

Primary:

The primaryobjective of the study was to assess the effect of telavancin on the pharmacokinetics of midazolam.

Secondary:

A second objective was to determine the pharmacokinetics of telavancin, and safety and tolerability when administered for 7 days.

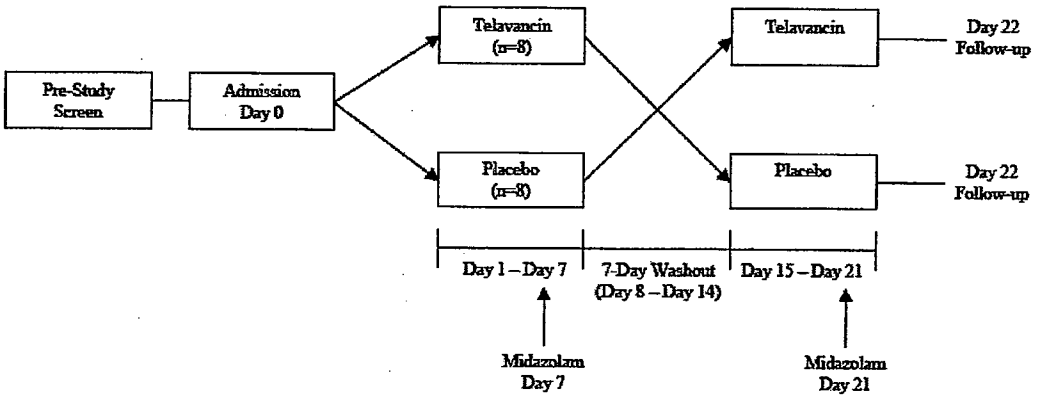
**FORMULATION:**

Each vial of lyophilized telavancin powder was reconstituted with 23 mL of 5% Dextrose Injection USP (D5W). The lot number of the telavancin formulation used in this study was 2213-99-812062. The lot number of midazolam used in this study was 13-165-DK.

**STUDY DESIGN:**

This was a Phase I, randomized, double-blind, placebo-controlled, crossover study. A total of 16 subjects, males and females 18 to 40 years of age, were enrolled in this study. For the first treatment period, subjects were randomized to telavancin 10 mg/kg infused over 60 minutes or placebo for 7 days of once daily treatment. Subjects received the first dose of study medication at the research facility on Study Day 1, and were discharged approximately 1 hour after completion of the first dose of telavancin or placebo, provided the subject was in good health. Subjects returned daily to the research facility for the administration of subsequent doses of telavancin or placebo. On Study Day 7 following the last dose of study medication (end of the telavancin or placebo infusion), each subject received a single dose of 1 mg IV midazolam. Following a washout period of at least 7 days, subjects were crossed over to the alternative treatment for the second treatment period (i.e., telavancin or placebo) for 7 days of once daily treatment before receiving another single, 1 mg IV dose of midazolam following the last dose of study medication on Study Day 21. Subjects returned to the research facility for pharmacokinetic sampling on the evenings of Study Day 6 and Study Day 20. On Study Days 7 and 21, subjects remained in the research facility for a second night to allow for pharmacokinetic sampling. Figure 1 shows the study design.

Figure 1. Study Design Flow Diagram




**PHARMACOKINETIC ASSESSMENTS:**
Blood (6 mL per time point) was collected from a vein in the contralateral arm to that of drug administration at pre-dose (within 30 minutes prior to telavancin/placebo dosing), and at the following time points after administration of midazolam on Study Days 7 and 21: 15 and 30 minutes and 1, 2, 3, 4, 6, 8, 10, 12, and 24 hours. The blood was collected into sodium heparin glass tubes and maintained chilled in an ice bath until plasma was harvested. Samples were centrifuged within 30 minutes of sample collection at 3,000 RPM for 10 minutes at 2 to 8°C, and the collected plasma was divided into two aliquots and transferred to appropriately labeled tubes and kept frozen at approximately -60 to -80°C. One of the two samples was transferred frozen in dry ice to a central laboratory for analysis; the other sample was retained at the site.

**BIOANALYTICAL ANALYSIS:**
Plasma samples were analyzed using a validated bioanalytical method for telavancin, AMI-11352, and AMI-999 using a liquid chromatography (LC) with tandem mass spectrometric detection (MS/MS) system. Midazolam and 1'-hydroxymidazolam and the internal standard (ISTD), ( ) b(4)
were extracted from human plasma using liquid-liquid extraction. After evaporation under nitrogen, the residue was reconstituted and analyzed. These samples were analyzed using a LC/MS/MS system.

**Telavancin**

| Criterion | Plasma | Comments |
|---|---|---|
| Concentration range | 0.25 to 100 µg/ml | Satisfactory |
| LLOQ | 0.25 µg/ml | Satisfactory |
| Linearity | $R^2 \geq 0.9982$ | Satisfactory |
| Accuracy | 96.3% to 103.1% | Satisfactory |
| Precision | 2.6% to 3.9% | Satisfactory |
| Specificity | Acceptable | Satisfactory |
| Stability | Freezer -60° to -80°C | Satisfactory |
| QC range | 0.75 to 400 µg/ml | Satisfactory |

**AMI-11352 (with 1.18 Correction Factor applied)**

| Criterion | Plasma | Comments |
|---|---|---|
| Concentration range | 0.295 to 118 µg/ml | Satisfactory |
| LLOQ | 0.295 µg/ml | Satisfactory |
| Linearity | $R^2 \geq 0.9980$ | Satisfactory |
| Accuracy | 95.6% to 98.7% | Satisfactory |
| Precision | 4.9% to 7.1% | Satisfactory |
| Specificity | Acceptable | Satisfactory |
| Stability | Freezer -60° to -80°C | Satisfactory |
| QC range | 0.885 to 94.4µg/ml | Satisfactory |

**AMI-11352 (without 1.18 Correction Factor applied)**

| Criterion | Plasma | Comments |
|---|---|---|
| Concentration range | 0.25 to 100 µg/ml | Satisfactory |
| LLOQ | 0.25 µg/ml | Satisfactory |
| Linearity | $R^2 \geq 0.9980$ | Satisfactory |
| Accuracy | 96.5% to 102.8% | Satisfactory |
| Precision | 1.4% to 4.5% | Satisfactory |
| Specificity | Acceptable | Satisfactory |
| Stability | Freezer -60° to -80°C | Satisfactory |
| QC range | 0.75 to 80 µg/ml | Satisfactory |

**AMI-999**

| Criterion | Plasma | Comments |
|---|---|---|
| Concentration range | 0.25 to 100 µg/ml | Satisfactory |
| LLOQ | 0.25 µg/ml | Satisfactory |
| Linearity | $R^2 \geq 0.9954$ | Satisfactory |
| Accuracy | 99.6% to 101.7% | Satisfactory |
| Precision | 3.7% to 6.0% | Satisfactory |
| Specificity | Acceptable | Satisfactory |
| Stability | Freezer -60° to -80°C | Satisfactory |
| QC range | 0.75 to 80 µg/ml | Satisfactory |

**Midazolam**

| Criterion | Plasma | Comments |
|---|---|---|
| Concentration range | 0.1 to 100 µg/ml | Satisfactory |
| LLOQ | 0.1 µg/ml | Satisfactory |
| Linearity | $R^2 \geq 0.9965$ | Satisfactory |
| Accuracy | 101% to 103.7% | Satisfactory |
| Precision | 3.3% to 5.9% | Satisfactory |
| Specificity | Acceptable | Satisfactory |
| Stability | Freezer -60° to -80°C | Satisfactory |
| QC range | 0.3 to 70 µg/ml | Satisfactory |

**1'- Hydroxymidazolam**

| Criterion | Plasma | Comments |
|---|---|---|
| Concentration range | 0.1 to 100 µg/ml | Satisfactory |
| LLOQ | 0.1 µg/ml | Satisfactory |
| Linearity | $R^2 \geq 0.9981$ | Satisfactory |
| Accuracy | 93.6% to 96.3% | Satisfactory |
| Precision | 2.4% to 2.7% | Satisfactory |
| Specificity | Acceptable | Satisfactory |
| Stability | Freezer -60° to -80°C | Satisfactory |
| QC range | 0.3 to 70 µg/ml | Satisfactory |

**PHARMACOKINETIC/STATISTICAL ANALYSIS:**

Nominal time was used in pharmacokinetic calculations. The pharmacokinetic parameters of telavancin were determined by non-compartmental analysis. 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 areas under the plasma concentration versus time curve from time zero to 24 ($AUC_{0-24}$) and zero to the last measurable concentration (Clm) ($AUC_{0-t}$) were calculated by the linear trapezoidal rule. The terminal elimination rate constant ($\lambda_z$) 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 area under the plasma concentration versus time curve from the last measurable concentration (Clm) to infinite time ($AUC_{t-\infty}$) was calculated as $Clm/\lambda_z$. The area under the plasma concentration versus time curve from time 0 hours to infinite time ($AUC_{0-\infty}$) was calculated as $AUC_{0-t} + AUC_{t-\infty}$. The midazolam clearance (CL) was calculated as dose/$AUC_{0-\infty}$, and the telavancin clearance (CL) was calculated as dose/$AUC_{0-24}$. The area under the first moment curve (AUMC) was calculated using the trapezoidal rule. The mean residence time (MRT) of telavancin was calculated as AUMC/AUC. The volume of distribution at the steady state ($V_{ss}$) was calculated as CL*MRT. For 1'-hydroxy-midazolam, only $T_{max}$, $C_{max}$, $AUC_{0-t}$, $t_{1/2}$, $AUC_{0-\infty}$, and the corresponding $C_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$ ratios to midazolam ratios are reported. In addition, the $C_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$ ratios for midazolam and 1'-hydroxy-midazolam with and without coadministration of telavancin were also evaluated. For AMI-11352 and AMI-999, only $T_{max}$, $C_{max}$ $AUC_{0-24}$, and the corresponding Cmax, and ($AUC_{0-24}$) to telavancin ratios are reported.

**RESULTS:**

**Study Population**

All 16 subjects (8 per sequence) who received treatment completed the study. The mean age was approximatley 24.8 years, height was approximately 182 cm, and weight was approximately 81kg. No subjects had major protocol deviations.

**Pharmacokinetics**

Figure 2 shows the concentration versus time profile of midazolam, 1'-hydroxy-midazolam and telavancin. Following a single IV dose, plasma levels 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 super-imposable.

Figure 2. Semi-log Plot of Mean + SD Plasma Concentrations of Midazolam and 1'-Hydroxy-Midazolam Following Intravenous Administration of 1mg Midazolam with and without Coadministration of Telavancin at 10 mg/kg via a 60-Minute Intravenous Infusion

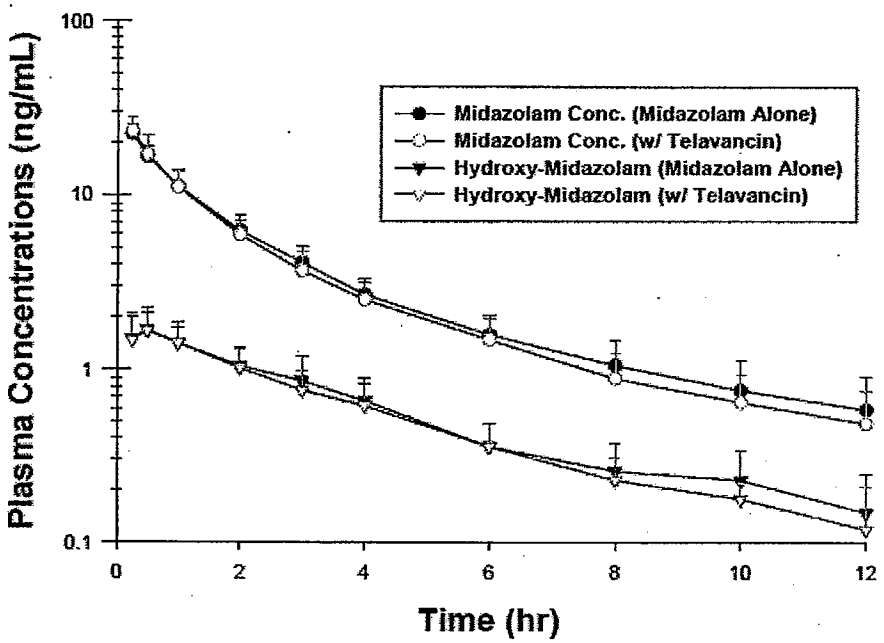



Table 1 summmarizes the mean observed noncompartmental pharmacokinetic parameters for midazolam and 1'-hydroxy-midazolam. The PK parameters for midazolam and 1'-hydroxy-midazolam with and without telavancin were comparable.

Table 1. Mean (±SD) Midazolam and 1'-Hydroxy-Midazolam Pharmacokinetic Parameters for Normal Volunteer Subjects after Receiving 1mg Intravenous Administration of Midazolam with and without Telavancin Intravenous Infusion at 10 mg/kg over 60 minutes

| | Midazolam (N=16) | | 1'-Hydroxy-Midazolam (N=16) | |
|---|---|---|---|---|
| PK Parameters | Alone | w/Telavancin | Alone | w/Telavancin |
| $T_{max}$ (hr) | 0.266 ± 0.063 | 0.266 ± 0.063 | 0.484 ± 0.232 | 0.422 ± 0.120 |
| $C_{max}$ (ng/ml) | 22.6 ± 2.9 | 23.5 ± 4.7 | 1.75 ± 0.44 | 1.77 ± 0.57 |
| $AUC_{0-t}$ (ng·hr/ml) | 45.1 ± 9.6 | 42.7 ± 10.4 | 6.81 ± 1.86 | 6.49 ± 1.85 |
| $AUC_{0-\infty}$ (ng·hr/ml) | 46.8 ± 9.7 | 44.3 ± 10.3 | 8.07 ± 2.3 | 7.46 ± 2.08 |
| $t_{½}$ (hr) | 4.08 ± 1.48 | 3.88 ± 1.46 | 4.36 ± 2.12 | 4.10 ± 1.90 |
| Cl (L/hr) | 22.5 ± 6.2 | 23.8 ± 5.7 | NA | NA |
| $V_{ss}$ (L) | 85.9 ± 23.9 | 84.4 ± 24.3 | NA | NA |
| MRT (hr) | 4.01± 1.42 | 3.67 ± 1.16 | NA | NA |
| | Midazolam with Telavancin/Midazolam Alone | | | |
| $C_{max}$ Ratio* | 1.04 ± 0.18 | | 1.04 ± 0.41 | |
| $AUC_{0-t}$ Ratio* | 0.949 ± 0.084 | | 0.968 ± 0.213 | |
| $AUC_{0-\infty}$ Ratio* | 0.948 ± 0.085 | | 0.944 ± 0.202 | |

*Arithmetic mean of ratios (±SD)

Exploratory analyses were performed using paired t-tests comparing the pharmacokinetic parameters for midazolam when administered alone and when coadministered with telavancin. The mean pharmacokinetic parameters for midazolam including $C_{max}$, elimination $t_{1/2}$, $AUC_{0-t}$, $AUC_{(0-\infty)}$, CL, $V_{ss}$, and MRT obtained with and without coadministration of telavancin were not statistically significantly different from one another ($p>0.05$). The pharmacokinetic parameters for 1'-hydroxy-midazolam with and without telavancin were not statistically significantly different from one another. These observations suggest telavancin did not alter the pharmacokinetic disposition of midazolam and its major metabolite, 1'-hydroxy-midazolam.
The arithmetic mean $C_{max}$, $AUC_{0-t}$, and $AUC_{(0-\infty)}$ ratios (expressed as values for midazolam with telavancin divided by values for midazolam alone) were 1.04, 0.95, and 0.95, respectively, indicating that, based on these ratios, the dispositions of midazolam with telavancin and without telavancin coadministration were not statistically significantly different from one another. The arithmetic mean $C_{max}$, $AUC_{0-t}$, and $AUC_{(0-\infty)}$ ratios for 1'-hydroxy-midazolam were 1.04, 0.97, and 0.94, respectively, indicating that, based on these ratios, the exposures to 1'-hydroxy-midazolam when midazolam was administered with and without telavancin coadministration were not statistically significantly different from one another.

To evaluate the influence of telavancin on the pharmacokinetics of midazolam, an equivalence analysis was performed. The 90% confidence intervals for both the Classical Method and Westlake Method are summarized in Table 2. The associated 90% confidence intervals are contained entirely within (0.8, 1.25) demonstrating that coadministration of midazolam with telavancin does not influence the pharmacokinetics of midazolam to a clinically significant degree.

Table 2. Geometric Mean Ratios and 90% Confidence Intervals (exponentiated) for Midazolam with Telavancin versus Midazolam Alone

| | | 90% Confidence Interval | |
|---|---|---|---|
| Midazolam | Test to Reference Geometric Mean Ratios | Classical Method | Westlake Method |
| $C_{max}$ | 1.03 | 0.956, 1.11 | 0.909, 1.09 |
| $AUC_{0-t}$ | 0.946 | 0.910, 0.984 | 0.918, 1.08 |
| $AUC_{(0-\infty)}$ | 0.944 | 0.908, 0.983 | 0.916, 1.08 |

Semi-log plots (mean + SD) of telavancin, AMI-11352, and AMI-999 plasma concentrations on Day 7 following daily administration of telavancin 10 mg/kg via a 60-minute IV infusion once daily for 7 days are shown in Figure 3. Concentrations of telavancin in plasma declined in an apparent bi-exponential manner. Concentrations of the major metabolite, AMI-11352, increased initially until a $T_{max}$ of 3.0 hours was observed, then decreased over time. Concentrations of the [redacted], AMI-999, decreased in a log-linear manner. b(4)

Figure 3. Semi-log Plot of Mean + SD Plasma Concentrations of Telavancin, AMI-11352 and AMI-999 on Day 7 Following Administration of 10mg/kg Telavancin via a 60-Minute Intravenous Infusion for 7-Days of Daily Dosing

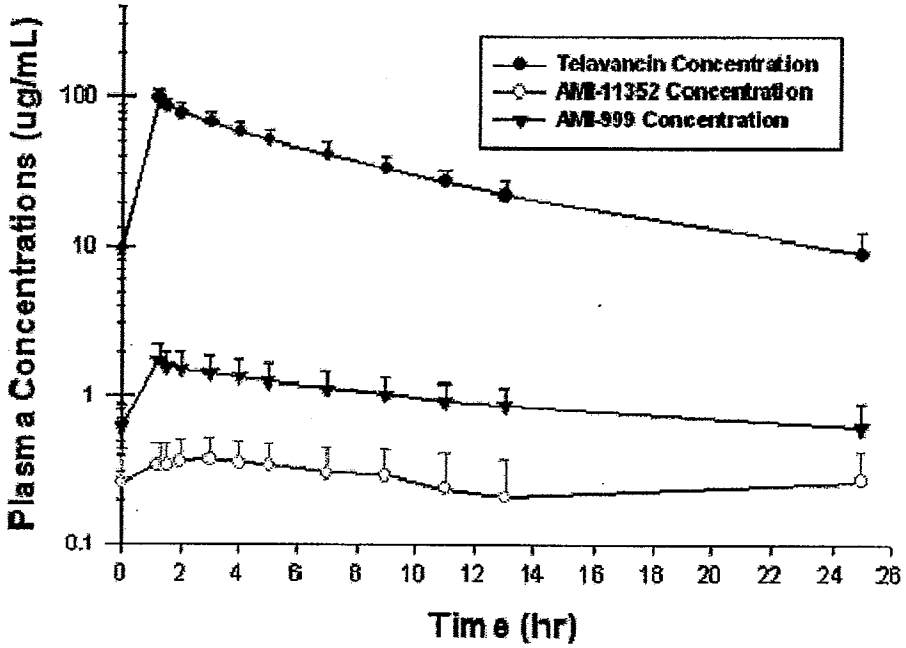



Table 3 summarizes the mean (N=16) observed noncompartmental pharmacokinetic parameters for telavancin and its accompanying analytes. Mean $C_{max}$ and $AUC_{0-24}$ values were much lower for AMI-11352 and AMI-999 than for telavancin. The ratios of AMI-11352 and AMI-999 to telavancin for mean $AUC_{0-24}$ values were approximately 0.008 and 0.029, respectively.

Table 3. Mean (±SD) Telavancin, AMI-11352, and AMI-999 Following Administration of Telavancin at 10mg/kg via a 60-Minute Intravenous Infusion with 1mg Midazolam Intravenous Push

| PK Parameters | Telavancin | AMI-11352 | AMI-999 |
|---|---|---|---|
| $T_{max}$ (hr) | 1.25 ± 0.00 | 3.04 ± 0.69 | 1.27 ± 0.06 |
| $C_{max}$ (µg/ml) | 97.0 ± 13.6 | 0.379 ± 0.161 | 1.73 ± 0.51 |
| $C_{24}$ (µg/ml)[a] | 9.09 ± 3.42 | 0.266 ± 0.163 | 0.618 ± 0.257 |
| $AUC_{0-24}$(µg·hr/ml) | 774 ± 143 | 6.49 ± 3.50 | 23.2 ± 7.5 |
| $t_{½}$ (hr) | 8.86 ± 1.48 | NA | NA |
| Cl (ml/hr/kg) | 13.3 ± 2.1 | NA | NA |
| $C_{max}$ Ratio Analyte/Telavancin | - | 0.00400 ± 0.00175 | 0.0176 ± 0.00333 |
| $AUC_{0-24}$ Ratio Analyte/Telavancin | - | 0.00840 ± 0.00459 | 0.0294 ± 0.0042 |

[a]$C_{24}$ is the concentration 24 hours after completion of the telavancin infusion.
NA=Not applicable

**CONCLUSIONS:**

Following a single IV dose, plasma levels of midazolam and 1'-hydroxy-midazolam with and without coadministration of telavancin declined in a similar bi-exponential manner and the plasma concentration-versus-time curves were almost super-imposable for the two treatments. In addition, the mean pharmacokinetic parameters for midazolam and 1'-hydroxy-midazolam were were not statistically significantly different from one another suggesting that telavancin coadministration did not influence the disposition of midazolam. Results from an equivalence analysis showed that the point estimate of the geometric mean ratios for $C_{max}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ were nearly unity and that the 90% confidence intervals about the geometric mean ratios for $C_{max}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ were within (0.8-1.25), demonstrating that coadministration of midazolam with telavancin does not influence the pharmacokinetics of midazolam to a clinically significant degree. Plasma concentrations of telavancin at 10 mg/kg administered to healthy subjects declined in an apparent bi-exponential manner. Concentrations of ( ) AMI-999, also decreased in a log-linear manner, while that of the major metabolite, AMI-11352, increased initially until a $T_{max}$ of 3.0 hours was observed, then decreased over time. Telavancin 10 mg/kg administered by IV infusion once daily for 7 days had no clinically significant effect on the disposition of midazolam, suggesting that telavancin, at the clinical dose of 10 mg/kg as a 1 hour infusion, will not influence the metabolism of drugs metabolized by CYP3A4 to a clinically significant degree.

b(4)

0035

**An Open, Randomized, Two-Part, 3-Period Crossover Study to Investigate the Potential for Drug Interactions Between Telavancin and Aztreonam and Telavancin and Piperacilin/Tazobactam in Healthy Subjects**

Date(s): 04FEB2006 to 07MAY2006

Clinical Sites: b(4)

**OBJECTIVES:**

To investigate the influence of aztreonam, and the influence of piperacilin/tazobactam on the pharmacokinetics of telavancin in healthy subjects, as well as the reverse, i.e., to investigate the influence of telavancin on the pharmacokinetics of aztreonam and on the pharmacokinetics of piperacillin/tazobactam in healthy subjects.

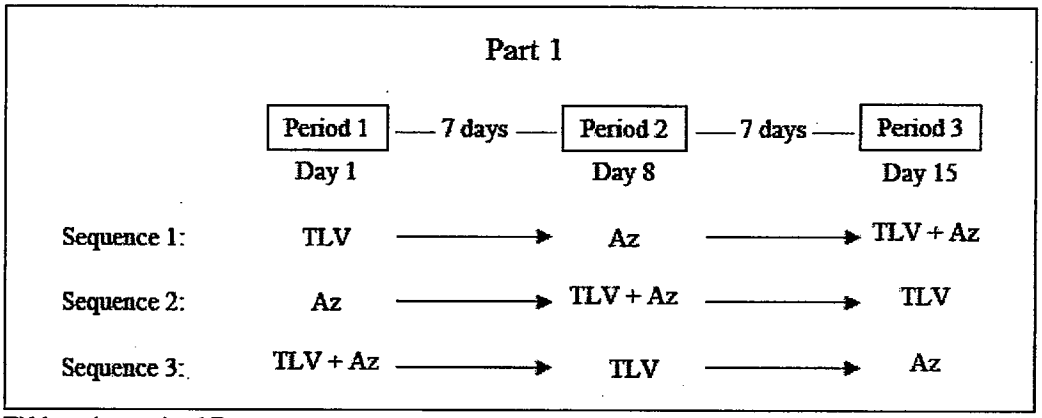
**FORMULATION:**

Telavancin, 10mg/kg body weight. Batch No. 2213-10-829580
Aztreonam 2gm diluted according to package insert. Batch No. LD095943
Piperacillin/Tazobactam 4.5gm diluted according to package insert. Batch No. LN051029

**STUDY DESIGN:**

This was a 2-part study. Each part was to be an open, 3-period, randomized, crossover evaluation in 12 healthy subjects, resulting in a total of 24 planned subjects. Following qualification for entry into the study, subjects were assigned a subject number, and the treatment order was made based on a randomized, balanced allocation schedule that was provided to the investigational site. Subjects were assigned to Part 1 or Part 2 on an alternating basis, as they were qualified.
In Part 1, 14 subjects were enrolled to complete 12 subjects who were to receive, in a randomized fashion, telavancin 10 mg/kg alone infused over 1 hour, aztreonam 2 gm alone infused over 30 minutes, and the combination of telavancin 10 mg/kg and aztreonam 2 gm on 3 separate treatment days (Study Days 1, 8, and 15). See Figure 1. The 14 subjects included 2 who were enrolled, but prematurely discontinued participation in the study and were replaced. One other of these 14 failed to complete all three periods. A washout period of at least 7 days separated each period. The order of treatments in Part 1 was to be assigned according to a randomized 3-sequence allocation schedule as illustrated in Figure 1. Due to procedural and dosing errors, not all subjects in Part 1 received their treatment in the prespecified sequence. Two additional periods were added to Part 1 to allow 12 subjects to complete the study treatments.

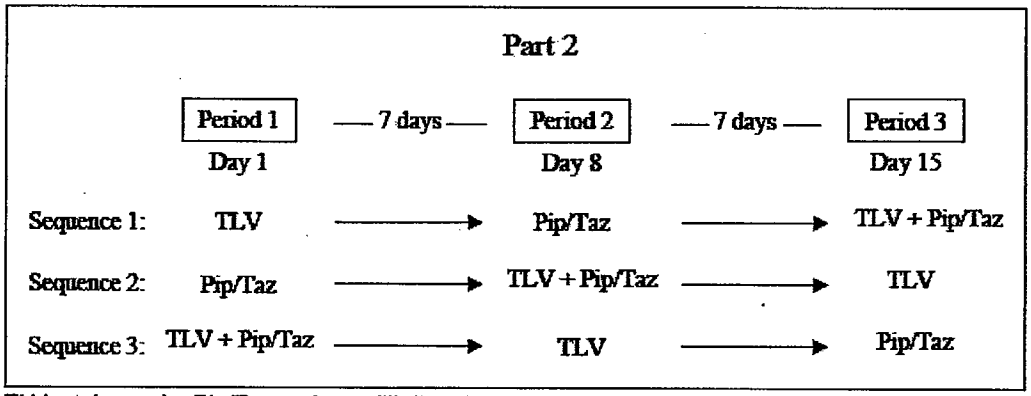
Figure 1. Study Design-Part 1




TLV = telavancin; AZ = aztreonam
N=4 subjects were targeted for each sequence

In Part 2, 12 subjects received, in a randomized fashion, telavancin 10 mg/kg alone, piperacillin/tazobactam 4.5 gm alone, infused over 30 minutes, and the combination of telavancin 10 mg/kg and piperacillin/tazobactam 4.5 gm on 3 treatment days (Study Days 1, 8, and 15). A washout period of at least 7 days separated each period. The order of treatments in Part 2 was assigned according to a randomized 3-sequence allocation schedule as illustrated in Figure 2.

Figure 2. Study Design-Part 2




TLV = telavancin; Pip/Taz = piperacillin/tazobactam
N=4 subjects were targeted for each sequence

Subjects had a 1½-day confinement in each study period. Study medication was to be administered according to randomized sequence on Study Days 1, 8, and 15, with assessments performed pre-dose and post-dose according to the Schedule of Assessments. Subjects were discharged from the Unit following completion of the assessments and were given at least a 7-day washout period before the next treatment period. After the washout period, subjects returned to the Unit in the afternoon on the day prior to receiving treatment in the next study period until all treatments had been administered for that part of the study.

**PHARMACOKINETIC ASSESSMENTS:**
Blood (6 mL per time point) was collected from a vein on the contralateral side to that of study medication administration immediately before the telavancin infusion; within 1 minute of the end of the infusion; 5, 10, 15, 20, 30, 45, 60, and 90 min after the end of infusion; and 2, 3, 4, 6, 8, 12 and 24 hours after to the end of infusion. As appropriate, aztreonam or piperacillin/tazobactam and telavancin plasma concentrations were measured in each sample.
Urine samples were collected into labeled urine collection containers. Urine for measurement of telavancin, aztreonam or piperacillin/tazobactam was collected 30 minutes prior to the administration of the first study medication of the period and at the following times after the start of the infusion: 0-7 hours, 7-12 hours, 12-24 hours, and 24-48 hours.

**BIOANALYTICAL ANALYSIS:**
Plasma and urine samples were analyzed using a validated bioanalytical method for telavancin, AMI-11352 (the major metabolite) and AMI-999 ( ) with LC-MS/MS detection.

b(4)

**Telavancin**

| Criterion | Plasma | Urine | Comments |
|---|---|---|---|
| Concentration range | 0.25 to 100 µg/ml | 0.25 to 100 µg/ml | Satisfactory |
| LLOQ | 0.25 µg/ml | 0.25 µg/ml | Satisfactory |
| Linearity | $R^2 \geq 0.9978$ | $R^2 \geq 0.9978$ | Satisfactory |
| Accuracy | 97.3% to 101.3 % | 93.9% to 97.7% | Satisfactory |
| Precision | 3% to 5% | 2.9% to 5.6% | Satisfactory |
| Specificity | Acceptable | Acceptable | Satisfactory |
| Stability | Freezer -60° to -80°C | Freezer -60° to -80°C | Satisfactory |
| QC range | 0.75 to 80 µg/ml | 0.75 to 80 µg/ml | Satisfactory |

**AMI-11352**

| Criterion | Plasma | Urine | Comments |
|---|---|---|---|
| Concentration range | 0.25 to 100 µg/ml | 0.25 to 100 µg/ml | Satisfactory |
| LLOQ | 0.25 µg/ml | 0.25 µg/ml | Satisfactory |
| Linearity | $R^2 \geq 0.9978$ | $R^2 \geq 0.9965$ | Satisfactory |
| Accuracy | 96.4% to 102.9% | 94.3% to 101.4% | Satisfactory |
| Precision | 3.5% to 5.4% | 3.7% to 7.7% | Satisfactory |
| Specificity | Acceptable | Acceptable | Satisfactory |
| Stability | Freezer -60° to -80°C | Freezer -60° to -80°C | Satisfactory |
| QC range | 0.75 to 80 µg/ml | 0.75 to 80 µg/ml | Satisfactory |

**AMI-999**

| Criterion | Plasma | Urine | Comments |
|---|---|---|---|
| Concentration range | 0.25 to 100 µg/ml | 0.25 to 100 µg/ml | Satisfactory |
| LLOQ | 0.25 µg/ml | 0.25 µg/ml | Satisfactory |
| Linearity | $R^2 \geq 0.9977$ | $R^2 \geq 0.9963$ | Satisfactory |
| Accuracy | 100.5% to 101.5% | 101.9% to 103.6% | Satisfactory |
| Precision | 2.9% to 5.5% | 5.1% to 8.7% | Satisfactory |
| Specificity | Acceptable | Acceptable | Satisfactory |
| Stability | Freezer -60° to -80°C | Freezer -60° to -80°C | Satisfactory |
| QC range | 0.75 to 80 µg/ml | 0.75 to 80 µg/ml | Satisfactory |

Plasma samples were analyzed using a validated bioanalytical method for aztreonam, piperacillin, and tazobactam with LC-MS/MS detection.

**Human Plasma Biological Matrix**

| Criterion | Aztreonam | Piperacillin | Tazobactam | Comments |
|---|---|---|---|---|
| Concentration range | 0.1 to 100µg/ml | 0.05 to 125µg/ml | 0.02 to 49.9µg/ml | Satisfactory |
| LLOQ | 0.1µg/ml | 0.05µg/ml | 0.02µg/ml | Satisfactory |
| Linearity | $R^2 \geq 0.997$ | $R^2 \geq 0.997$ | $R^2 \geq 0.998$ | Satisfactory |
| Accuracy | 95.2% to 104.5% | 93% to 101% | 94.4% to 102% | Satisfactory |
| Precision | 6.1% to 8.6% | 3.7% to 10.7% | 6.3% to 11.7% | Satisfactory |
| Specificity | Acceptable | Acceptable | Acceptable | Satisfactory |
| Stability | Freezer -70°C | Freezer -70°C | Freezer -70°C | Satisfactory |
| QC range | 0.1 to 100µg/ml | 0.05 to 125µg/ml | 0.02 to 49.9µg/ml | Satisfactory |

Testing was required to assess the potential for aztreonam, piperacillin, and tazobactam to interfere with the assays. The potential interfering compounds were spiked into blank matrix at their approximate maximum concentration ($C_{max}$) levels and extracted. There was no significant interference in the chromatographic regions of interest for telavancin, AMI-11352, and AMI-999 (<20.0% of the mean utilized LLOQ) or ISTD (<5.0% of ISTD response in the control zero sample). For the LQC, the mean concentration for each compound showed a RSD of ≤15.0% and mean accuracy within the range of 85.0% to 115.0%. It was therefore concluded that
the methods demonstrated acceptable selectivity for telavancin, AMI-11352, and AMI-999 in the presence of aztreonam, piperacillin, and tazobactam. The methods also demonstrated acceptable selectivity for aztreonam, piperacillin, and tazobactam in the presence of telavancin.

**PHARMACOKINETIC/STATISTICAL ANALYSIS:**

The pharmacokinetic parameters of aztreonam, piperacillin, tazobactam, telavancin, AMI-11352 and AMI-999 were determined by non-compartmental analysis. The following pharmacokinetic parameter estimates were calculated or taken directly from the plasma concentration-time data.
The area under the plasma concentration versus time curve from time zero to 24, $AUC_{(0-24)}$, and the area under the plasma concentration versus time curve from time zero zero to the last measurable concentration, $AUC_{(0-t)}$, respectively, were calculated by the linear trapezoidal rule. The terminal elimination rate constant ($\lambda_z$) was determined by linear regression of the natural logarithm of plasma concentrations versus time during the terminal phase. The terminal elimination half life ($t_{1/2}$) was calculated as $\ln(2)/\lambda_z$. The area under the plasma concentration versus time curve from the last measurable concentration to infinite time $AUC_{(t-\infty)}$, respectively, was calculated as $Clm/\lambda_z$. The areas under the plasma concentration versus time curve from time 0 hours to infinite time $AUC_{(0-\infty)}$, was calculated as $AUC_{(0-t)} + AUC_{(t-\infty)}$. Plasma clearance (CL) for aztreonam, piperacillin, tazobactam and telavancin was calculated using the formula:
$CL = Dose / AUC_{(0-\infty)}$. The area under the first moment curve AUMC was calculated using the trapezoidal rule. Mean residence time (MRT) of telavancin was calculated as AUMC/AUC. The volume of distribution at the steady state (Vss) was calculated as CL*MRT. In addition, the $C_{max}$, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ ratios for aztreonam, piperacillin, tazobactam, and telavancin, with and without study drug coadministration were evaluated. For AMI-11352 and AMI-999, only $T_{max}$, $C_{max}$, $AUC_{(0-24)}$, and $AUC_{(0-t)}$ were reported here. The $C_{max}$, $AUC_{(0-24)}$, $AUC_{(0-\infty)}$ ratios for AMI-11352 and AMI-999, with and without study drug coadministration, were also evaluated. For all analytes including aztreonam, piperacillin, tazobactam, telavancin, AMI-11352, and AMI-999, the total amount excreted in urine was calculated up to 48 hrs post dose and the corresponding percentages (fe) of total administered dose excreted in the urine were estimated. Renal clearances (CLr) were calculated as the ratio of total amount excreted in urine to $AUC_{(0-\infty)}$ for aztreonam, piperacillin, tazobactam and telavancin. For AMI-11352 and AMI-999, $CL_r$ was

calculated as the ratio of amount excreted in urine in 48 hrs to $AUC_{(0-t)}$. to evaluate the influence of telavancin on the PK of aztreonam, piperacillin, and tazobactam an equivalence analysis was performed using the two-one sided statistical test.

**RESULTS:**

**Changes in the Conduct of the Study**

Due to deviations in sampling and/or dosing during Period 1 of Part 1, 7 subjects were to receive their Period 1 treatment out of sequence in a fourth or fifth period. For these subjects, the aztreonam infusion was completed in 25 rather than 30 minutes, and the samples at the end of the infusion and at 5 minutes were not obtained. The 7 subjects who were to receive corrected dosing in Period 4 were Subjects 0101, 0103, 0105, 0106, 0107, 0109, and 0110. A total of 6 subjects were treated in Period 4. Subsequently, it was noted that 3 of the 6 subjects (0105, 0107, and 0110) who were to receive a combination of aztreonam and telavancin in Period 4 did not receive telavancin at that time. These subjects were then to receive their correct treatment in Period 5. Subject 0110, however, did not return to the study site for Period 5 and was discontinued from the study; this subject was not included in the pharmacokinetic analyses. Thus, only 11 subjects completed Part 1 of the study and 5 of these subjects did not receive their treatment in the correct sequence. A summary detailing the actual treatment received by all subjects in Part 1 is provided in Table 1. In Table 1, treatments not given correctly are noted as "deviation", corrections of deviations are noted as "corrected", and the 6 subjects who completed all treatments per protocol are labeled as such in their last period.

Table 1. Actual Doses Received by Subjects in Part 1, Including Subjects with Dosing Deviations

| Subject (Sequence) | Visit | Actual Day | Study medication |
|---|---|---|---|
| 0101 (Az)(TLV+Az)(TLV) | Period 1, Day 1(deviation*) | 1 | Az |
| | Period 2, Day 8 | 8 | TLV+Az |
| | Period 3, Day 15 | 15 | TLV |
| | Period 4, Day 21(corrected) | 27 | Az |
| 0102 (TLV)(Az)(TLV+Az) | Period 1, Day 1 | 1 | TLV |
| | Period 2, Day 8 | 8 | Az |
| | Period 3, Day 15(per protocol) | 15 | TLV+Az |
| 0103 (Az)(TLV+Az)(TLV) | Period 1, Day 1(deviation*) | 1 | Az |
| | Period 2, Day 8 | 8 | TLV+Az |
| | Period 3, Day 15 | 15 | TLV |
| | Period 4, Day 21(corrected) | 27 | Az |
| 0104 (TLV)(Az)(TLV+Az) | Period 1, Day 1 | 1 | TLV |
| | Period 2, Day 8 | 8 | Az |
| | Period 3, Day 15(per protocol) | 15 | TLV+Az |
| 0105 (TLV+Az)(TLV)(Az) | Period 1, Day 1 (deviation*) | 1 | TLV+Az |
| | Period 2, Day 8 | 8 | TLV |
| | Period 3, Day 15 | 15 | Az |
| | Period 4, Day 21(deviation) | 22 | TLV**=Az |
| | Period 5(corrected) | 75 | TLV+Az |
| 0106 (Az) (TLV+Az)(TLV) | Period 1, Day 1(deviation*) | 1 | Az |
| | Period 2, Day 8 | 8 | TLV+Az |
| | Period 3, Day 15 | 15 | TLV |
| | Period 4, Day 21 (corrected) | 22 | Az |
| 0107 (TLV+Az)(TLV)(Az) | Period 1, Day 1 (deviation*) | 1 | TLV+Az |
| | Period 2, Day 8 | 8 | TLV |
| | Period 3, Day 15 | 15 | Az |
| | Period 4, Day 21(deviation) | 22 | TLV**+Az |
| | Period 5(corrected) | 75 | TLV+Az |
| 0108 (TLV)(Az)(TLV+Az) | Period 1, Day 1 | 1 | TLV |
| | Period 2, Day 8 | 8 | Az |
| | Period 3, Day 15(per protocol) | 15 | TLV+Az |
| 0109 (Az)(TLV+Az)(TLV) | Period 1, Day 1(deviation*) | 1 | Az |
| | Period 2, Day 8 | 8 | TLV+Az |
| 0110 (TLV+Az)(TLV)(Az) | Period 1, Day 1(deviation*) | 1 | TLV+Az |
| | Period 2, Day 8 | 8 | Az |
| | Period 3, Day 15 | 15 | Az |
| | Period 4, Day 21(deviation) | 22 | TLV**+Az |
| 0111 (TLV+Az)(TLV)(Az) | Period 1, Day 1(per protocol) | 1 | TLV |
| 0112 (TLV)(Az)(TLV+Az) | Period 1, Day 1 | 1 | TLV |
| | Period 2, Day 8 | 8 | Az |
| | Period 3, Day 15(per protocol) | 15 | TLV+Az |
| 0309 (Az)(TLV+Az)(TLV) | Period 1, Day 1 | 1 | Az |
| | Period 2, Day 8 | 8 | TLV+Az |
| | Period 3, Day 15(per protocol) | 15 | TLV |

Table 1(cont'd). Actual Doses Received by Subjects in Part 1, Including Subjects with Dosing Deviations

| | | | |
|---|---|---|---|
| 0311 (TLV+Az)(TLV)(Az) | Period 1, Day 1 | 1 | TLV+Az |
| | Period 2, Day 8 | 8 | TLV |
| | Period 3, Day 15(per protocol) | 15 | Az |

Deviation*: Shortened aztreonam infusion, missed end infusion and t=5 minute samples
**: Televancin (TLV) was not administered

**Changes in the Planned Analyses**

Seven subjects in Part 1 of the study received dosing out of sequence (see Table 1), and 5 of the 7 completed the protocol having received all 3 treatments correctly, but out of sequence. All data for the periods for which there was a deviation were displayed in separate listings, and all affected tables and listings were footnoted. Only 11 of 14 subjects who participated in Part 1 completed all three treatments. These 11 subjects were considered analyzable for pharmacokinetic characterization and bioequivalence evaluations. Subjects 0109, 0110, and 0111 did not complete the study, therefore they were excluded from descriptive statistics and bioequivalence evaluations. Subject 0109 was replaced by Subject 0309, and Subject 0111 was replaced by Subject 0311; these replacement subjects completed the study without protocol deviations.

In Part 1, because subjects were dosed out of sequence, period/carryover effects could not be accounted for in the statistical analysis. This part of the analysis, therefore, was performed using the option of choosing study design as parallel/other in WinNonLin, as the ANOVA model for a balanced 3-period design was not considered applicable to Part 1 of the study as completed. Subject 0112 had extremely low urine volume reported during the 0-7 hour interval of the aztreonam/telavancin combination period, which appeared to be inconsistent with the other two periods; therefore, he was excluded from the descriptive statistics on percentage urinary recovery and the corresponding renal clearance calculation.

**Disposition of Subjects**

A total of 26 subjects were enrolled, 14 subjects in Part 1 and 12 subjects in Part 2. In Part 1 of the study, 14 subjects (i.e., 12 planned subjects plus 2 replacements) were enrolled, and 11 subjects completed the study. Subjects 0109, 0110, and 0111 discontinued prematurely. Subject 0110 was randomized to the (TLV+Az) (TLV) (Az) sequence but was dosed incorrectly during Period 1 and Period 4. Subject 0110 did not return to the study site for Period 5 and was discontinued from the study; this subject was not replaced. Subject 0109 (sequence [Az] [TLV+Az] [TLV]) who was not dosed per protocol in Period 1 (the aztreonam infusion lasted only 24 minutes) discontinued due to an AE (allergic reaction to telavancin) after completing dosing in Period 2. Subject 0111 (sequence [TLV+Az] [TLV] [Az]) discontinued due to a protocol deviation ("site [i.e., venous access]" occlusion) that occurred after 2 minutes of initiation of the telavancin infusion in Period 1. Subjects 0109 and 0111 were replaced with Subjects 0309 and 0311, respectively. All 12 subjects (4 per sequence) who received treatment in Part 2 completed the study per protocol. Table 2 shows the disposition of study subjects.

Table 2. Disposition of Study Subjects for Part 1

| | Number (%) of Subjects, by Treatment Sequence | | | |
|---|---|---|---|---|
| | (TLV)(AZ)(TLV+AZ) | (AZ)(TLV+Az)(TLV) | (TLV+Az)(TLV)(Az) | All Subjects |
| Subjects Enrolled | 4 | 5 | 5 | 14 |
| Safety Population[a] | 4(100%) | 5(100%) | 5(100%) | 14(100%) |
| Completed Study | | | | |
| Yes | 4(100%) | 4(80%) | 3(60%) | 11(79%) |
| No | 0(0%) | 1(20%) | 2(40%) | 3(21%) |
| If no, primary reason for discontinuation from study | | | | |
| Adverse Event | 0(0%) | 1(20%)[b] | 0(0%) | 1(7%) |
| Subject withdrew consent | 0(0%) | 0(0%) | 0(0%) | 0(0%) |
| Major deviation from the protocol | 0(0%) | 0(0%) | 1(20%)[c] | 1(7%) |
| Termination of the study by the sponsor | 0(0%) | 0(0%) | 0(0%) | 0(0%) |
| Other | 0(0%) | 0(0%) | 1(20%)[d] | 1(7%) |

[a]Received at least one dose of study medication (telavancin or aztreonam)
[b]Subject 0109; replaced by Subject 0309
[c]Subject 0111; replaced by Subject 0311
[d]Subject 0110 was dosed incorrectly during Period 1 and Period 4. This subject did not return to the study site for Period 5 and was discontinued from the study.

**Summary of Protocol Deviations**

The following deviations were reported:

- In Part 1 of the study, Subject 0111 was randomized to the (TLV+Az) (TLV) (Az) sequence. This subject experienced an infusion site occlusion 2 minutes after initiation of the telavancin infusion in Period 1. She was discontinued from the study due to this major protocol deviation.
- In Period 1 of Part 1, 4 subjects (Subjects 0101, 0103, 0106, 0109) who were to receive a 30-minute infusion of aztreonam alone on day 1 received an infusion of aztreonam alone that lasted less than 30 minutes. Additionally, the plasma samples to be collected at end infusion and 5 minutes later were not collected in these subjects. With the exception of Subject 0109, who discontinued due to an AE, these errors were corrected during Period 4 for all subjects.
- In Period 1 of Part 1, 3 subjects (Subjects 0105, 0107, and 0110), who were to receive a

30-minute infusion of aztreonam plus a 60-minute infusion of telavancin on day 1, received aztreonam infusions that lasted less than 30 minutes; 2 of these 3 subjects (Subjects 0107 and 0110) also received telavancin infusions that lasted less than 60 minutes. Additionally, the plasma samples to be collected at end infusion and 5 minutes later were not collected in these subjects. These errors were to have been corrected during Period 4, but all 3 subjects received aztreonam alone during Period 4 instead of telavancin plus aztreonam. The deviations were corrected during Period 5 for 2 of the subjects (Subjects 0105 and 0107); however, Subject 0110 did not return to the site for Period 5 and, therefore, was discontinued from the study.

**Demographics**

Subjects in Part 1 of the study had a mean age of 35.2 years. There were equal numbers of males (7 subjects, 50%) and females (7 subjects, 50%); 86% of subjects were Hispanic or Latino. Demographic characteristics among treatment sequences in Part 1 were comparable. Subjects in Part 2 had a mean age of 40.5 years. There were more males (9 subjects, 75%) than females (3 subjects, 25%); 83% of subjects were Hispanic or Latino. Among treatment sequences, demographic characteristics were generally comparable with the exception of the (TLV+Pip/Taz) (TLV) (Pip/Taz) comprising all male subjects (N=4) compared to the other sequences that included at least one female subject. Subjects had a mean weight of 75.1 kg, mean height of 164.3 cm, and a mean body mass index (BMI) of 27.8 kg/m2, with generally comparable baseline characteristics among the three treatment sequences.
The baseline characteristics of height and weight were not comparable among all 3 treatment sequences in Part 2, reflecting the imbalance in genders between the sequences; subjects in the (TLV+Pip/Taz) (TLV) (Pip/Taz) group were heavier (95 kg vs. 74.1 kg and 77.2 kg) and taller (178.8 cm vs. 165.8 cm and 170.5 cm) than the (TLV) (Pip/Taz) (TLV+Pip/Taz) and (Pip/Taz) (TLV+Pip/Taz) (TLV) groups, respectively. The overall mean BMI was 27.6 kg/m2.

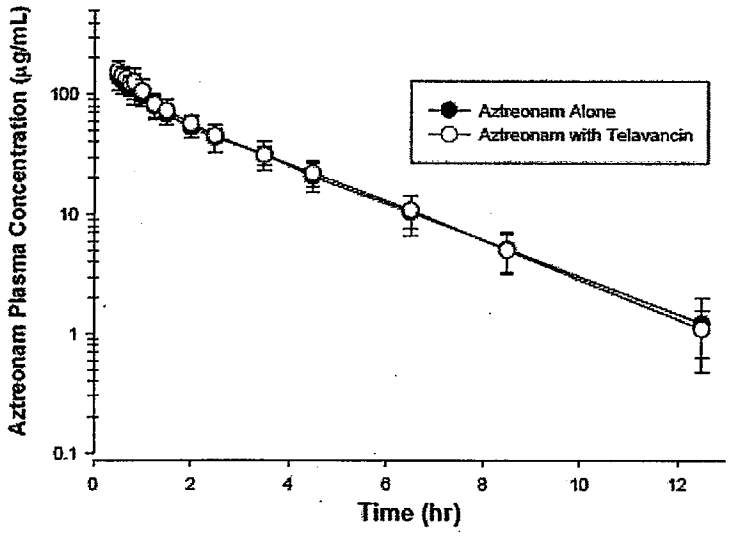
**Pharmacokinetic Data Sets Analyzed**

In Part 1, 11 of 14 subjects were considered analyzable for pharmacokinetic characterization and bioequivalence evaluations. All available data (for intended dosing) were included in the tabulation of non-compartmental parameter estimates. For the equivalence analysis, only subjects who completed both treatments were included (N=11). Subjects 0109, 0110, and 0111 did not complete the study and therefore were excluded from descriptive statistics and bioequivalence evaluations. Subject 0112 had extremely low urine volume reported during 0-7 hours of the aztreonam/telavancin combination period, which appeared to be inconsistent with the other two periods he participated in; therefore, he was excluded from the descriptive statistics on percentage urinary recovery and the corresponding renal clearance calculations for the aztreonam/telavancin combination period. Thus, N=10 for urine parameters for this treatment. In Part 2, all 12 subjects were included in the pharmacokinetic characterization and bioequivalence evaluations. All available data were included in the tabulation of noncompartmental parameter estimates. For the equivalence analysis, only subjects who completed both treatments were included (N=12).

**Aztreonam Pharmacokinetics**

Following a single IV dose, plasma levels of aztreonam with and without coadministration of telavancin declined in a bi-exponential manner with a short distribution phase. The plasma concentration-time curves for aztreonam under each condition were almost superimposable. Mean (±SD) plasma concentration-time profiles of aztreonam after the IV administration of 2 gm of aztreonam with and without coadministration of telavancin at a dose of 10 mg/kg are shown in Figure 2 as a log-linear plot.

Figure 2. Semi-log Plot of Mean ± SD Plasma Concentrations of Aztreonam after the IV Administration of 2 gm of Aztreonam with and without Coadministration of Telavancin (Study 0035)




The mean estimated pharmacokinetic parameters for aztreonam after IV administration of 2 gm of aztreonam with and without coadministration of telavancin at 10mg/kg are shown in Table 3.

Table 3. Mean (±SD) Aztreonam Pharmacokinetic Parameters for Study Subjects after Receiving 2 gm Intravenous Administration of Aztreonam with and without Telavancin Infusion at 10mg/kg (Study 0035)

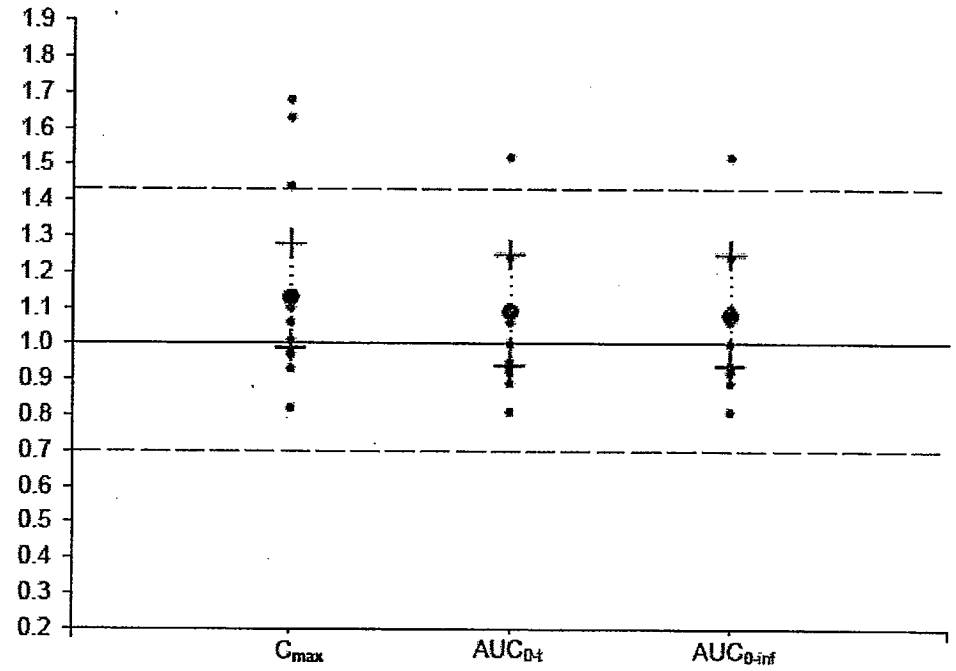
| Plasma PK Parameters | Aztreonam (N=11)[a] | |
|---|---|---|
| | Alone | w/Telavancin |
| $T_{max}$ (hr) | 0.54 ± 0.07 | 0.57 ± 0.11 |
| $C_{max}$ (µg/ml) | 143.9 ± 32.8 | 161.4 ± 35.2 |
| $AUC_{0-t}$ (µg·hr/ml) | 313.9 ± 68.9 | 336.8 ± 62.0 |
| $AUC_{0-\infty}$ (µg·hr/ml) | 317.5 ± 70.8 | 340.0 ± 63.1 |
| $T_{½}$ (hr) | 1.9 ± 0.2 | 1.9 ± 0.2 |
| Cl (ml/min) | 111.3 ± 33.1 | 100.7 ± 16.2 |
| $V_{ss}$ (L) | 16.1 ± 3.4 | 14.4 ± 2.1 |
| MRT (hr) | 2.5 ± 0.3 | 2.4 ± 0.2 |
| | | |
| Urinary Excretion | N = 11 | N = 10[b] |
| $f_e$ (%) | 63.8 ± 15.3 | 72.4 ± 10.0 |
| $Cl_r$ (ml/min) | 67.6 ± 10.8 | 71.7 ± 18.8 |

[a]Three subjects did not complete the study and, therefore, were not included in the analysis.
[b]An additional subject (Subject 112) was excluded due to incomplete urine collection.
$T_{max}$ and $C_{max}$ are sampling time dependent due to IV administration.

The mean pharmacokinetic parameters for aztreonam such as $C_{max}$, elimination $T_{1/2}$, $AUC_{0-t}$, $AUC_{0-\infty}$, Cl, $V_{ss}$, and MRT obtained with and without coadministration of telavancin were not statistically significantly different (ANOVA, $p > 0.05$). Aztreonam was renally excreted, with mean fe and $CL_r$ of 63.8% and 67.6 mL/min, respectively. These two parameters were not statistically significantly different ($p > 0.05$) in the presence of telavancin (72.4% and

71.7 mL/min). These observations suggest that telavancin has no effect on the pharmacokinetic disposition of aztreonam.

Figure 3. Summary of Equivalence Analysis-Aztreonam with Telavancin / Aztreonam Alone




Horizontal line of + represents upper and lower 90% CI limits
• is the geometric mean ratio
• are individual ratios
—— Protocol equivalence interval (0.70, 1.43)

The geometric mean ratios and 90% CIs for aztreonam administered with telavancin versus aztreonam alone are summarized in Table 4. The point estimates of the ratios of geometric means were similar, and the associated 90% CIs met the hypothesis criterion of (0.70, 1.43) specified in the protocol. Although the sponsor used the criterion of 90% C.I. of 0.70 to 1.43 in the protocol, the results of the study show that the all of the 90% C.I.'s are within the 0.80 to 1.25 range that is typically used except for the $C_{max}$ of of aztreonam with telavancin (1.28) which is slightly higher. However the $AUC_{0-t}$ and the $AUC_{0-\infty}$ both fall within the 0.80 to 1.25 range. These results indicate that coadministration of aztreonam with telavancin did not alter the pharmacokinetics of aztreonam to a clinically significant degree.

Table 4. Geometric Mean Ratios and 90% Confidence Intervals for Aztreonam with Telavancin versus Aztreonam Alone

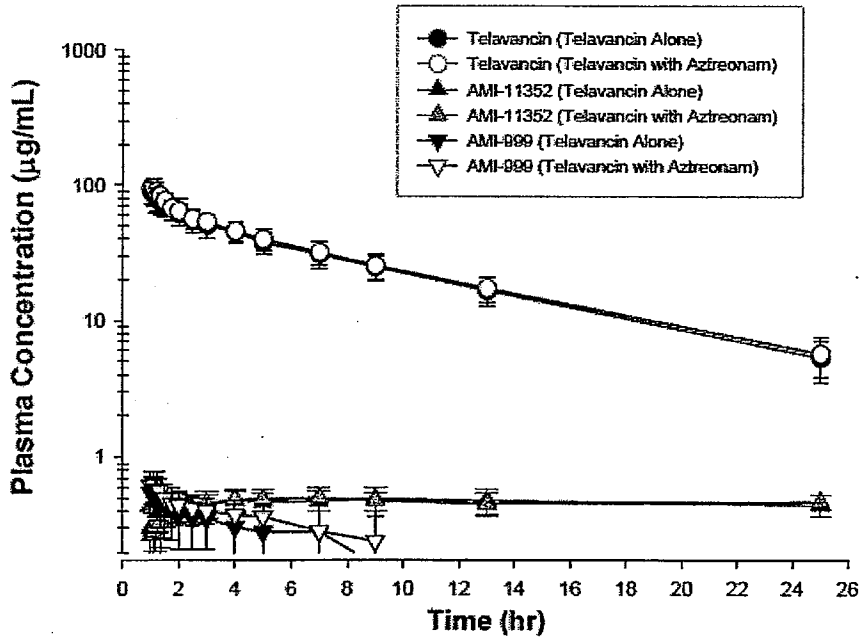
| | Test to Reference Geometric Mean Ratios | 90% Confidence Interval |
|---|---|---|
| $C_{max}$ | 1.13 | 0.989, 1.28 |
| $AUC_{0-t}$ | 1.09 | 0.942, 1.25 |
| $AUC_{0-\infty}$ | 1.08 | 0.941, 1.25 |

**Telavancin, AMI-11352, and AMI-999 Pharmacokinetics**

Concentrations of telavancin in plasma declined in an apparent bi-exponential manner. Concentrations of the major metabolite, AMI-11352, increased slowly and reached $T_{max}$ at variable times. Concentrations of ( ) AMI-999, decreased in a log-linear manner. Mean $C_{max}$ and AUC values were much lower for AMI-11352 and AMI-999 than for telavancin. Plasma concentration-time profiles for telavancin, AMI-11352 and AMI-999, each with and without coadministration of aztreonam, declined in similar manner and the curves for each pair were almost superimposable. Semi-log plots (mean ± SD) of telavancin, AMI-11352 and AMI-999 plasma concentrations after the IV administration of telavancin 10 mg/kg via a 60-minute infusion with and without coadministration of 2 gm of aztreonam are shown in Figure 4.

b(4)

Figure 4. Semi-log Plot of Mean ± SD Plasma Concentrations of Telavancin, AMI-11352 and AMI-999 Following Administration of 10mg/kg Telavancin via a 60-Minute Infusion with and without Coadministration of 2 gm of Aztreonam (Study 0035)




The mean observed noncompartmental pharmacokinetic parameters for telavancin, and for AMI-11352 and AMI-999, with and without coadministration of 2 gm of aztreonam are shown in Table 5 and Table 6, respectively.

Table 5. Mean (±SD) Telavancin Pharmacokinetic Parameters for Study Subjects after Receiving 10mg/kg Telavancin via a 60-Minute Infusion with and without Coadministration of 2 gm Aztreonam (Study 0035)

| PK Parameters | Telavancin (N=11)[a] | |
|---|---|---|
| | Alone | w/Aztreonam |
| $T_{max}$ (hr) | 1.03 ± 0.04 | 1.08 ± 0.12 |
| $C_{max}$ (µg/ml) | 91.9 ± 18.0 | 99.1 ± 17.1 |
| $AUC_{0-t}$ (µg·hr/ml) | 600.8 ± 123.1 | 627.1 ± 109.6 |
| $AUC_{0-\infty}$ (µg·hr/ml) | 656.2 ± 142.3 | 687.5 ± 131.6 |
| $T_{½}$ (hr) | 7.1 ± 0.7 | 7.1 ± 0.9 |
| Cl (ml/hr/kg) | 16.0 ± 3.9 | 15.1 ± 3.0 |
| $V_{ss}$ (ml/kg) | 145.3 ± 32.5 | 136.9 ± 17.3 |
| MRT (hr) | 9.2 ± 0.9 | 9.2 ± 1.1 |
| | | |
| Urinary Excretion | N=11 | N=10[b] |
| $f_e$ (%) | 46.6 ± 10.6 | 59.0 ± 11.5 |
| $Cl_r$ (ml/hr/kg) | 7.4 ± 2.2 | 8.7 ± 1.8 |

[a]Three subjects did not complete the study and, therefore, were not included in the analysis.
[b]An additional subject (Subject 112) was excluded due to incomplete urine collection.
$T_{max}$ and $C_{max}$ are sampling time dependent due to IV administration

Table 6. Mean (±SD) AMI-11352 and AMI-999 Pharmacokinetic Parameters for Study Subjects after Receiving 10mg/kg Telavancin via a 60-Minute Infusion with and without Coadministration of 2 gm Aztreonam (Study 0035)

| PK Parameters | AMI-11352 (N=11) | | AMI-999 (N=11) | |
|---|---|---|---|---|
| | Alone | w/Aztreonam | Alone | w/Aztreonam |
| $T_{max}$ (hr) | 9.6 ± 6.1 | 5.5 ± 2.2 | 1.1± 0.2 | 1.1 ± 0.1 |
| $C_{max}$ (µg/ml) | 0.52 ± 0.10 | 0.53 ± 0.08 | 0.58 ± 0.16 | 0.67 ± 0.18 |
| $AUC_{0-24}$(µg·hr/ml) | 10.8 ± 1.8 | 10.8 ± 1.7 | 4.14 ± 3.10 | 4.57 ± 2.40 |
| $AUC_{0-t}$ (µg·hr/ml) | 11.2 ± 1.9 | 11.2 ± 1.8 | 3.64 ± 3.13 | 3.98 ± 2.43 |
| $f_e$(%) | 5.6 ± 1.9 | 6.7 ± 2.2 | 0.32 ± 0.09 | 0.40 ± 0.08 |
| $Cl_r$ (ml/hr/kg) | 50.0 ± 15.6 | 60.6 ± 19.7 | 25.8 ± 47.0 | 15.5 ± 6.8 |

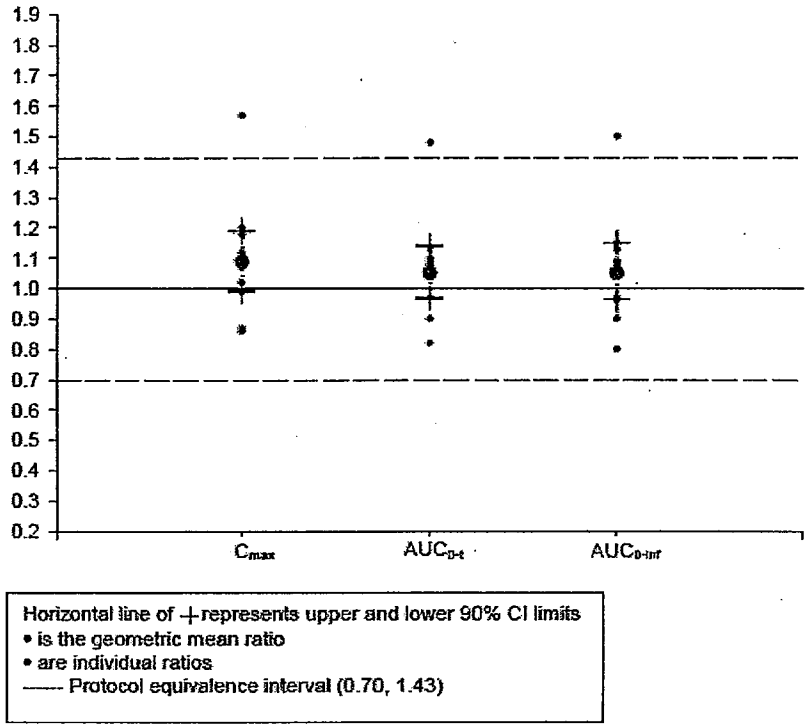
The mean pharmacokinetic parameters for telavancin obtained with and without coadministration of aztreonam were not statistically significantly different (ANOVA, $p > 0.05$). Similar to aztreonam, telavancin was also renally excreted, with mean $f_e$ and $Cl_r$ of 46.6% and 7.4 mL/hr/kg, respectively. These two parameters were statistically significantly higher in the presence of aztreonam (59.0% and 8.7 mL/hr/kg; ANOVA, $p < 0.05$). However, since all other pharmacokinetic parameters for telavancin remained unchanged, the differences observed in $f_e$ and $Cl_r$ are considered to be of limited clinical significance. These observations suggest aztreonam has no effect on the pharmacokinetic disposition of telavancin, AMI-11352, and AMI-999. (Note that plasma concentrations of AMI-11352 and AMI-999 were of secondary interest and only represent a small fraction of the AUC of telavancin. A statistical analysis of the pharmacokinetics of AMI-11352 and AMI-999 was not done.)

**Effect of Aztreonam on Telavancin Pharmacokinetics: Equivalence Analysis**

Figure 5 depicts the geometric mean ratio (large filled circles) and bounds of the 90% confidence limits (horizontal lines of crosses) for the equivalence analysis of telavancin with aztreonam versus telavancin alone. The results indicate the spread of the individual equivalence results for the subjects in Part 1 of the

study and show that there is no clustering of extreme ratios at either end of the confidence limits. These results indicate that coadministration of telavancin with aztreonam did not alter the pharmacokinetics of telavancin to a clinically significant degree.

Figure 5. Summary of Equivalence Analysis-Telavancin with Aztreonam ÷ Telavancin Alone




The geometric mean ratios and 90% CIs for telavancin with aztreonam versus telavancin alone are summarized in Table 7. The point estimates of the ratios of geometric means were similar, and the associated 90% CIs met the hypothesis criterion of (0.70, 1.43) specified in the protocol.

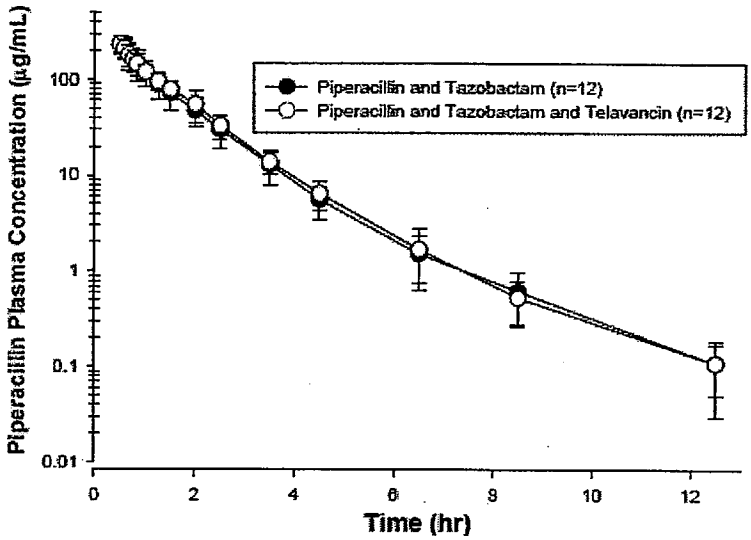
Table 7. Geometric Mean Ratios and 90% Confidence Intervals for Telavancin with Aztreonam/ Telavancin Alone

| Telavancin | Test to Reference Geometric Mean Ratios | 90% Confidence Interval |
|---|---|---|
| $C_{max}$ | 1.09 | 0.991, 1.19 |
| $AUC_{0-t}$ | 1.05 | 0.968, 1.14 |
| $AUC_{0-\infty}$ | 1.05 | 0.965, 1.15 |

**Piperacillin Pharmacokinetics**

Following a single IV dose of tazobactam/piperacillin with and without coadministration of telavancin, plasma levels of piperacillin declined in similar bi-exponential manner with a short distribution phase. The plasma concentration-time curves for the two treatments were almost superimposable. Mean (±SD) plasma concentration-time profiles of piperacillin after the IV administration of 4.5 gm of piperacillin/tazobactam with and without coadministration of telavancin 10 mg/kg are shown in Figure 6 as a log-linear plot.

Figure 6. Semi-log Plot of Mean ± SD Plasma Concentrations of Piperacillin after the IV Administration of 4.5 gm of Piperacillin/Tazobactam with and without Coadministration of Telavancin (Study 0035)




The mean observed noncompartmental pharmacokinetic parameters for piperacillin after the IV administration of 4.5 gm of piperacillin/tazobactam with and without coadministration of telavancin at 10 mg/kg dose are presented in Table 8. The pharmacokinetic parameters for piperacillin with and without telavancin were not statistically significantly different
(ANOVA, $p > 0.05$). Piperacillin was renally excreted, with mean $f_e$ and $Cl_r$ of 60.4% and 153.0 mL/min, respectively. These two parameters were not significantly different in the presence of telavancin (71.1% and 167.8 mL/min). These observations suggest that telavancin has no effect on the pharmacokinetic disposition of piperacillin.

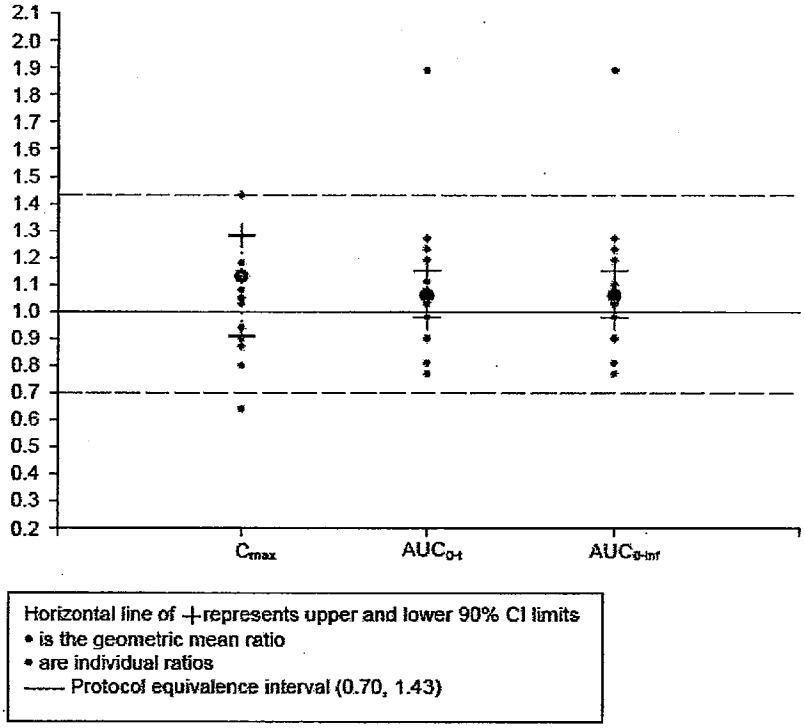
Table 8. Mean (±SD) Piperacilllin Pharmacokinetic Parameters for Study Subjects after Receiving 4.5 gm Intravenous Administration of Piperacillin/Tazobactam with and without Telavancin Infusion at 10mg/kg (Study 0035)

| PK Parameters | Piperacillin (N=12) | |
|---|---|---|
| | Alone | w/Telavancin |
| $T_{max}$ (hr) | 0.51 ± 0.03 | 0.51 ± 0.03 |
| $C_{max}$ (µg/ml) | 236.9 ± 46.8 | 235.3 ± 49.7 |
| $AUC_{0-t}$ (µg·hr/ml) | 278.0 ± 74.4 | 289.0 ± 51.9 |
| $AUC_{0-\infty}$ (µg·hr/ml) | 278.2 ± 74.4 | 289.3 ±51.9 |
| $T_{½}$ (hr) | 1.2 ± 0.2 | 1.1 ± 0.2 |
| Cl (ml/min) | 291.2 ± 92.1 | 237.8 ± 45.5 |
| $V_{ss}$ (L) | 17.9 ± 4.6 | 17.4 ± 3.6 |
| MRT (hr) | 1.2 ± 0.1 | 1.2 ± 0.1 |
| $f_e$ (%) | 60.4 ± 24.3 | 71.1 ± 23.3 |
| $Cl_r$ (ml/min) | 153.0 ± 69.8 | 167.8 ± 58.6 |

**Effect of Telavancin on Piperacillin Pharmacokinetics: Equivalence Analysis**

To evaluate the influence of telavancin on the pharmacokinetics of piperacillin, an equivalence analysis was performed. From the TOST procedure based on analyses of piperacillin $\ln(C_{max})$, $\ln(AUC_{0-t})$, and $\ln(AUC_{0-\infty})$, the 90% CIs were generated for the Classical TOST method. Figure 7 depicts the geometric mean ratio (large filled circles) and bounds of the 90% confidence limits (horizontal lines of crosses) for the Classical equivalence analysis of piperacillin with telavancin versus piperacillin/tazobactam alone. The results indicate the spread of the individual equivalence results for the subjects in Part 2 of the study and show that there is no clustering of extreme ratios at either end of the confidence limits. These results indicate that coadministration of piperacillin with telavancin did not alter the pharmacokinetics of piperacillin to a clinically significant degree. This figure mistakenly has the horizontal line representing the upper 90% C.I. limit of $C_{max}$ appearing at approximately 1.3 when it is actually 0.99 ( most likely human error). The remainder of this figure is accurate.

Figure 7. Summary of Equivalence Analysis-Piperacillin with Telavancin ÷ Piperacillin/Tazobactam Alone




The geometric mean ratios and 90% CIs for piperacillin administered with telavancin versus piperacillin/tazobactam alone are summarized in Table 9. The point estimates of the ratios of geometric means were similar, and the associated 90% CIs met the hypothesis criterion of (0.70, 1.43) specified in the protocol.

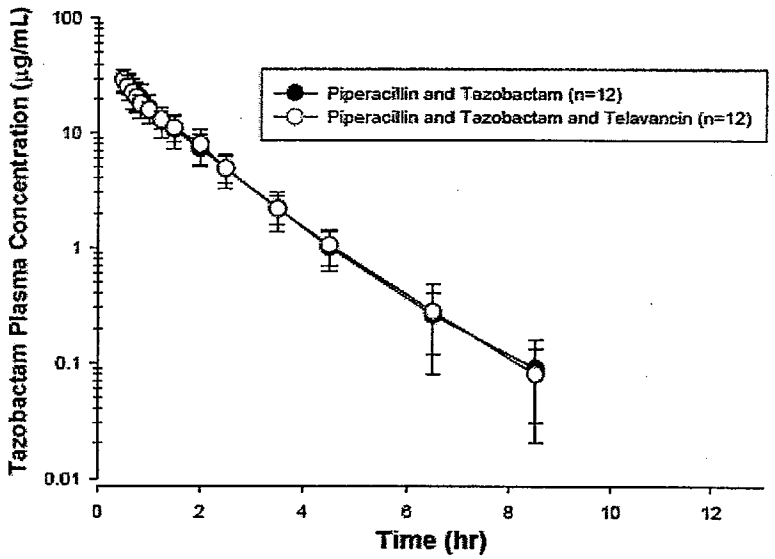
Table 9. Geometric Mean Ratios and 90% Confidence Intervals for Piperacillin with Telavancin versus Piperacillin/Tazobactam Alone

| Parameter | Test to Reference Geometric Mean Ratios | 90% Confidence Interval |
|---|---|---|
| $C_{max}$ | 0.99 | 0.910, 1.08 |
| $AUC_{0-t}$ | 1.06 | 0.979, 1.15 |
| $AUC_{0-\infty}$ | 1.06 | 0.979, 1.15 |

**Tazobactam Pharmacokinetics**

Following a single IV dose of tazobactam/piperacillin, with and without coadministration of telavancin, plasma levels of tazobactam declined in similar mono-exponential manner and the plasma concentration-time curves were almost superimposable. Mean (±SD) plasma concentration-time profiles of tazobactam after the IV administration of 4.5 gm of piperacillin/tazobactam with and without coadministration of telavancin 10 mg/kg are shown in Figure 8 as a log-linear plot.

Figure 8. Semi-log Plot of Mean ± SD Plasma Concentrations of tazobactam after the IV Administration of 4.5 gm of Piperacillin/Tazobactam with and without Coadministration of Telavancin (Study 0035)




The mean pharmacokinetic parameter estimates for tazobactam after the IV administration of 4.5 gm of piperacillin/tazobactam with and without coadministration of telavancin 10 mg/kg are presented in Table 10. The mean pharmacokinetic parameters for tazobactam with and without telavancin were not statistically significantly different (ANOVA, $p > 0.05$). Tazobactam was renally excreted, with mean $f_e$ and $Cl_r$ of 65.3% and 141.6 mL/min, respectively. These two parameters were not statistically significantly different ($p > 0.05$) in the presence of telavancin (67.6% and 148.0 mL/min). These observations suggest telavancin has no effect on the pharmacokinetic disposition of tazobactam.

Table 10. Mean (±SD) Tazobactam Pharmacokinetic Parameters for Study Subjects after Receiving 4.5 gm Intravenous Administration of Piperacillin/Tazobactam with and without Telavancin Infusion at 10 mg/kg (Study 0035)

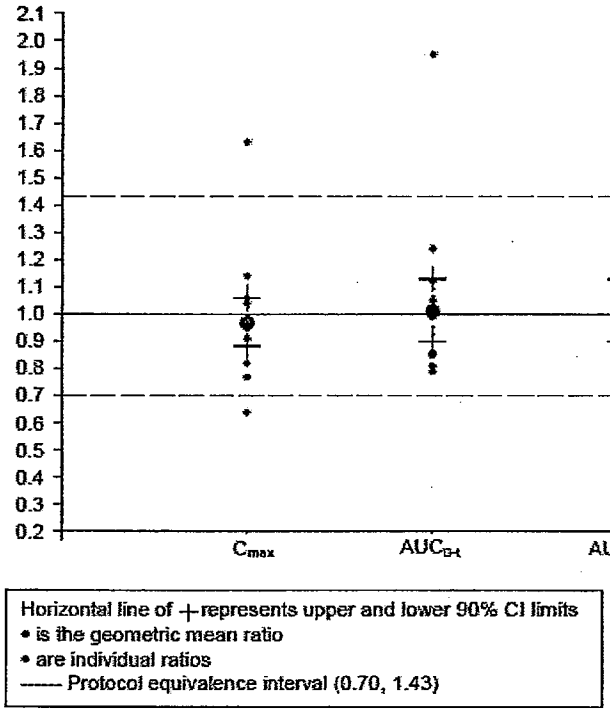
| PK Parameters | Tazobactam (N=12) | |
|---|---|---|
| | Alone | w/Telavancin |
| $T_{max}$ (hr) | 0.51 ± 0.03 | 0.52 ± 0.04 |
| $C_{max}$ (µg/ml) | 30.1 ± 6.8 | 29.2 ± 6.4 |
| $AUC_{0-t}$ (µg·hr/ml) | 39.45 ± 10.58 | 39.25 ± 7.54 |
| $AUC_{0-\infty}$ (µg·hr/ml) | 39.57 ± 10.59 | 39.34 ± 7.54 |
| $T_{½}$ (hr) | 1.0 ± 0.2 | 1.0 ± 0.2 |
| Cl (ml/hr) | 226.4 ± 68.3 | 220.0 ± 47.9 |
| $f_e$ (%) | 65.3 ± 15.5 | 67.6 ± 17.1 |
| $Cl_r$ (ml/min) | 141.6 ± 29.8 | 148.0 ± 48.4 |
| $V_{ss}$ (L) | 17.0 ± 4.2 | 17.0 ± 3.3 |
| MRT (hr) | 1.3 ± 0.1 | 1.3 ± 0.1 |

$T_{max}$ and $C_{max}$ are sampling time dependent due to IV administration

**Effect of Telavancin on Tazobactam Pharmacokinetics: Equivalence Analysis**

To evaluate the influence of telavancin on the pharmacokinetics of tazobactam, an equivalence analysis was performed. Figure 9 depicts the geometric mean ratio (large filled circles) and bounds of the 90% confidence limits (horizontal lines of crosses) for the equivalence analysis of tazobactam with telavancin versus piperacillin/tazobactam alone. The results indicate the spread of the individual equivalence results for the subjects in Part 2 of the study and show that there is no clustering of extreme ratios at either end of the confidence limits. These results indicate that coadministration of tazobactam with telavancin did not alter the pharmacokinetics of tazobactam to a clinically significant degree.

Figure 9. Summary of Equivalence Analysis- Tazobactam with Telavancin ÷ Piperacillin/Tazobactam Alone




The geometric mean ratios and 90% CIs for tazobactam administered with telavancin versus piperacillin/tazobactam alone are summarized in Table 8-9. The point estimates of the ratios of geometric means were similar, and the associated 90% confidence intervals met the hypothesis criterion of (0.70, 1.43) specified in Study Protocol 0035.

Table 10. Geometric Mean Ratios and 90% Confidence Intervals for Tazobactam with Telavancin versus Piperacillin/Tazobactam Alone

| Parameter | Test to Reference Geometric Mean Ratios | 90% Confidence Intervals |
|---|---|---|
| $C_{max}$ | 0.97 | 0.885, 1.06 |
| $AUC_{0-t}$ | 1.01 | 0.903, 1.13 |
| $AUC_{0-\infty}$ | 1.01 | 0.902, 1.13 |

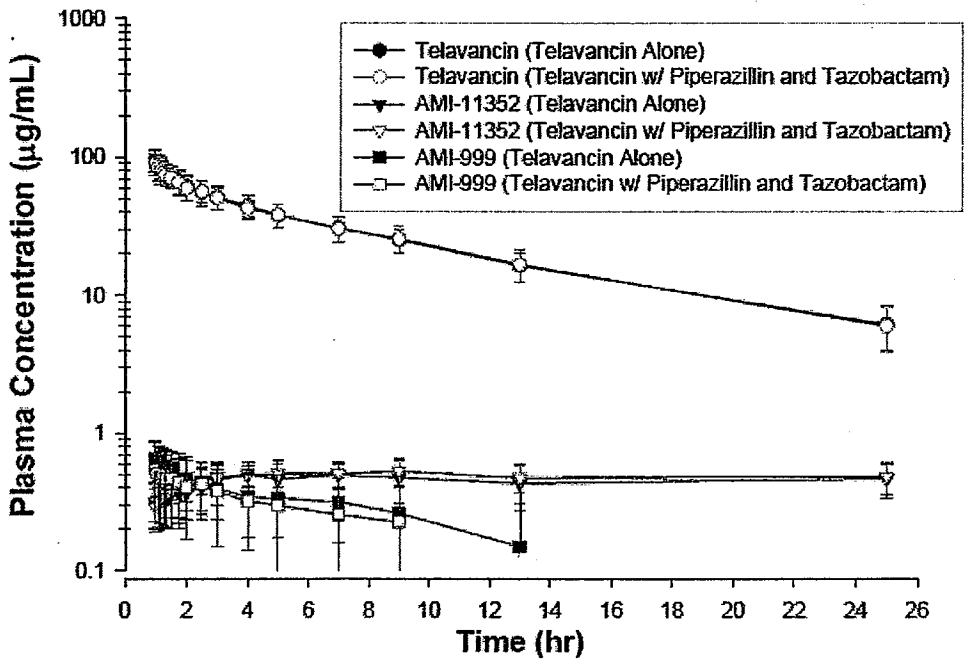
**Telavancin, AMI-11352, and AMI-999 Pharmacokinetics**

In general, concentrations of telavancin in plasma declined in an apparent bi-exponential manner. Concentrations of the major metabolite, AMI-11352, increased slowly and reached $T_{max}$ at variable times. Concentrations of ( ) AMI-999, also decreased in a log-linear manner. Plasma concentration-time profiles for telavancin, AMI-11352, and AMI-999 with and without coadministration of piperacillin/tazobactam declined in similar manner, and the curves for telavancin and AMI-11352 for each of the two treatments were almost superimposable, while the curves for AMI-999 were quite similar. Semi-log plots (mean ± SD) of telavancin,

b(4)

AMI-11352, and AMI-999 plasma concentrations after the IV administration of telavancin 10 mg/kg via a 60-minute infusion with and without coadministration of 4.5 gm of piperacillin/tazobactam are shown are shown in Figure 10.

Figure 10. Semi-log Plot of Mean ± SD Plasma Concentrations of Telavancin, AMI-11352, and AMI-999 Following Administration of 10mg/kg Telavancin via a 60-Minute Infusion with and without Coadministration of 4.5 gm of Piperacillin/Tazobactam (Study 0035)




The mean observed noncompartmental pharmacokinetic parameters of telavancin with and without coadministration of 4.5 gm of piperacillin/tazobactam are presented in Table 11, and mean observed noncompartmental pharmacokinetic parameters of AMI-11352 and AMI-999 with and without coadministration of 4.5 gm of piperacillin/tazobactam are presented in Table 12. The mean pharmacokinetic parameters for telavancin (such as $C_{max}$, elimination $t_{1/2}$, $AUC_{0-t}$, $AUC_{0-\infty}$, Cl, $V_{ss}$, and MRT) obtained with and without coadministration of piperacillin/tazobactam were not statistically significantly different (ANOVA, $p > 0.05$). Similar to piperacillin and tazobactam, telavancin was also renally excreted, with mean fe and CLr of 49.0% and 7.1 mL/hr/kg, respectively. These two parameters were not statistically significantly different in the presence of piperacillin and tazobactam (49.7% and 7.8 mL/hr/kg). The mean pharmacokinetic parameters for AMI-11352 and AMI-999 with and without piperacillin/tazobactam were not different. Mean Cmax and AUC values were much lower for AMI-11352 and AMI-999 than for telavancin. These observations suggest piperacillin/tazobactam has no effect on the pharmacokinetic disposition of telavancin, AMI-11352, and AMI-999. A statistical analysis of the pharmacokinetics of AMI-11352 and AMI-999 was not done.

Table 11. Mean (±SD) Telavancin Pharmacokinetic Parameters for Study Subjects after Receiving 10mg/kg Telavancin via a 60-Minute Infusion with and without Coadministration of 4.5 gm of Piperacillin/Tazobactam (Study 0035)

| PK Parameters | Telavancin (N=12) | |
|---|---|---|
| | Alone | With Piperacillin/Tazobactam |
| $T_{max}$ (hr) | 1.0 ± 0.1 | 1.0 ± 0.1 |
| $C_{max}$ (µg/ml) | 95.7 ± 15.8 | 89.9 ± 15.4 |
| $AUC_{0-t}$ (µg·hr/ml) | 611.0 ± 122.3 | 605.2 ± 120.3 |
| $AUC_{0-\infty}$ (µg·hr/ml) | 679.4 ± 147.6 | 671.5 ± 147.9 |
| $T_{½}$ (hr) | 7.3 ± 1.2 | 7.3 ± 1.1 |
| Cl (ml/hr/kg) | 15.9 ± 6.4 | 15.7 ± 4.3 |
| $V_{ss}$ (ml/kg) | 146.5 ± 26.0 | 147.0 ± 19.7 |
| MRT (hr) | 9.6 ± 1.5 | 9.7 ± 1.5 |
| $f_e$ (%) | 49.0 ± 19.4 | 49.7 ± 10.5 |
| $Cl_r$ (ml/hr/kg) | 7.1 ± 2.1 | 7.8 ± 2.5 |

$T_{max}$ and $C_{max}$ are sampling time dependent due tto IV administration

Table 12. Mean (±SD) AMI-11352 and AMI-999 Pharmacokinetic Parameters for Study Subjects after Receiving 10mg/kg Telavancin via a 60-Minute Infusion with and without Coadministration of 4.5 gm of Piperacillin/Tazobactam (Study 0035)

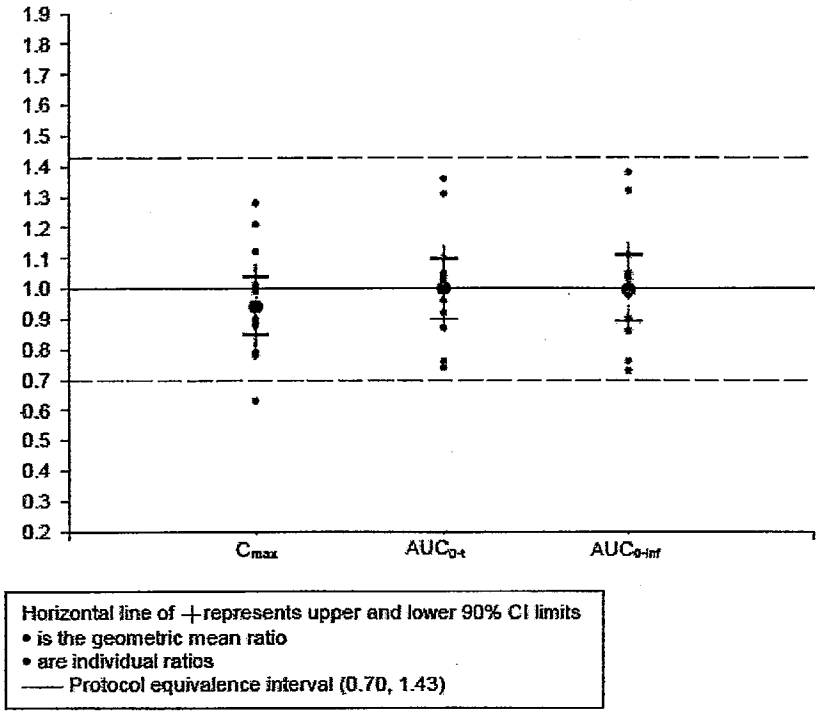
| PK Parameters | AMI-11352 (N=12) | | AMI-999 (N=12) | |
|---|---|---|---|---|
| | Alone | with Piperacillin/Tazobactam | Alone | With Piperacillin/Tazobactam[a] |
| $T_{max}$ (hr) | 9.8 ± 9.2 | 7.5± 5.9 | 1.1 ± 0.1 | 1.2 ± 0.5 |
| $C_{max}$ (µg/ml) | 0.55 ± 0.10 | 0.56 ± 0.11 | 0.67 ± 0.21 | 0.65 ± 0.24 |
| $AUC_{0-24}$ (µg·hr/ml) | 10.5 ± 3.1 | 11.2 ± 2.4 | 4.66 ± 2.25 | 4.32 ± 2.80 |
| $AUC_{0-t}$ (µg·hr/ml) | 11.0 ± 3.2 | 11.7 ± 2.5 | 3.85 ± 1.80 | 3.58 ± 2.24 |
| $f_e$ (%) | 4.4 ± 1.9 | 4.6 ± 1.7 | 0.3 ± 0.2 | 0.3 ± 0.1 |
| $Cl_r$ (ml/hr/kg) | 44.3 ± 23.3 | 40.3 ± 13.3 | 9.7 ± 7.1 | 22.3 ± 41.2 |

[a]Subject 0211 had no detectable AMI-999 concentration, therefore, no pharmacokinetic parameters could be obtained

**Effect of Piperacillin/Tazobactam on Telavancin Pharmacokinetics: Equivalence Analysis**

To evaluate the influence of piperacillin/tazobactam on the pharmacokinetics of telavancin, an equivalence analysis was performed. Figure 11 depicts the geometric mean ratio (large filled circles) and bounds of the 90% confidence limits (horizontal lines of crosses) for the equivalence analysis of telavancin with piperacillin/tazobactam versus telavancin alone. The results indicate the spread of the individual equivalence results for the subjects in Part 2 of the study and show that there is no clustering of extreme ratios at either end of the confidence limits. These results indicate that coadministration of telavancin with piperacillin/tazobactam did not alter the pharmacokinetics of telavancin to a clinically significant degree.

Figure 11. Summary of Equivalence Analysis-Telavancin with Piperacillin/Tazobactam ÷ Telavancin Alones




The geometric mean ratios and 90% CIs for telavancin administered with piperacillin/tazobactam versus telavancin alone are summarized in Table 13. The point estimates of the ratios of geometric means were similar, and the associated 90% CIs met the hypothesis criterion of (0.70, 1.43) in Study Protocol 0035.

Table 13. Geometric Mean Ratios and 90% Confidence Intervals for Telavancin with Piperacillin/Tazobactam versus Telavancin Alone

| Parameter | Test to Reference Geometric Mean Ratios | 90% Confidence Interval |
|---|---|---|
| $C_{max}$ | 0.94 | 0.847, 1.04 |
| $AUC_{0-t}$ | 1.00 | 0.900. 1.10 |
| $AUC_{0-24}$ | 1.00 | 0.892, 1.11 |

**CONCLUSIONS**

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.

*4.1.5. General Biopharmaceutics*

*4.1.6. Patient Studies/Exploratory PK/PD Analyses*

*4.1.7. In vitro Studies*

**01-6424-PH-08**

**TITLE: Effect of Dose-Fractionation on the Efficacy of AMI-6424 against Methicillin-Resistant *Staphylococcus Aureus* (MRSA 33591) Infection in the Mouse Neutropenic Thigh Model**

Study Location: ( )

Study Initiation Date(s): 11/8/00

Study Completion Date(s): 6/19/01

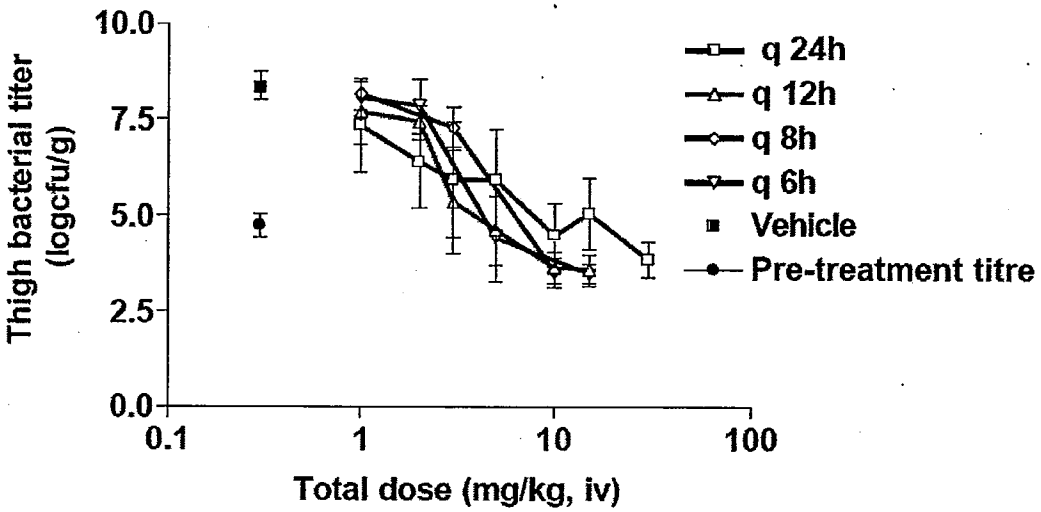
**MATERIALS AND METHODS:**
AMI-6424 (Lot No. 17 and 25) was synthesized at ( ). Isoflurane anesthetic was obtained from ( ). Organisms were cultivated in brain-heart infusion (BHI) broth obtained from ( ). Triptic soy (TS) agar plates were purchased from ( ). AMI-6424 was dissolved in 2 to 10% hydroxypropyl-b-cyclodextrin (HP-b-CD). Dosing volumes were approximately 100 mL. Animals (female NSA mice, 15 to 30 g) were acquired from ( / ) and allowed access to food and water *ad libitum*. MRSA strain No. 33591 was obtained from the ( ) Colonies were swabbed off an initial plate and grown overnight in BHI broth. The following morning, a subculture was grown and the inoculum was diluted from this source. The final i noculum was in BHI broth. b(4) b(4)
Neutropenia was induced via 200 mg/kg intraperitoneal (IP) injection of cyclophosphamide given four and two days prior to the inoculation of bacteria. This treatment regimen induced severe leucopenia and generally decreased the neutrophil count to approximately 100 cells/mm3. The bacterial inoculum concentration was ~106 CFU/mL. Animals were lightly anesthetized with isoflurane (2.5% for induction followed by 1% for maintenance) and 50 mL of the bacterial inoculum was injected into the anterior thigh. One hour after the inoculation, animals were dosed intravenously (IV) with vehicle or various regimens of the drug. At 0 h and 24 h post-treatment, the animals were euthanized (CO2 asphyxiation) and the anterior and posterior thigh collected aseptically. The thigh was placed into 10 mL sterile saline and homogenized. Dilutions of the homogenate were plated onto TS agar plates which were incubated overnight. The number of bacterial colonies on a given plate was multiplied by the dilution factor, divided by the thigh weight (in grams) and expressed as log CFU/g. The dose-fractionation studies were performed in female NSA mice for q 12 h and q 6 h dosing at 1, 2, 5, and 15 mg/kg. Trough levels were measured following two, three or four doses to determine the degree of accumulation.

**PHARMACOKINETIC/STATISTICAL ANALYSIS:**
The pharmacokinetic parameters of AMI-6424 were determined by non-compartmental analysis (Model 201) using WinNonlin, Version 3.2 (Pharsight, Mountain View, California). The area under the curve (AUC) from the time of dosing to the last measurable concentration (AUC(0-t)) was calculated by the linear trapezoidal rule. Effective Dose of 50% (ED50) estimates are expressed as mean with 95% confidence intervals (CI). A two-tailed Students t-test was used to compare ED50 estimates between treatments. $P < 0.05$ was considered to be statistically significant.

**RESULTS:**

The pre-treatment thigh bacterial titer was 4.7 ± 0.3 log CFU/g. In vehicle treated controls, the titer after 24 h was 8.4 ± 0.3 log CFU/g. AMI-6424 (1, 2, 3, 5, 10, and 15 mg/kg, IV), dosed either as a single dose (q 24 h), two divided doses (q 12 h), three divided doses (q 8 h) or four divided doses (q 6 h), produced dose-dependent reduction in thigh bacterial titre. Figure 1 displays the effect of dose fractionation.

Figure 1. Effect of Dose-Fractionation on the Efficacy of AMI-6424 against MRSA 33591 in the Murine Neutropenic Thigh Model (Study 01-6424-PH-08)




There appears to be a good relationship between log CFU/g and dose with a $R^2$ of 0.97. This is shown in Figure 2.

Figure 2. Plot of the Dose-Dependent Pharmacodynamics of AMI-6424 Dosed q24h (Study 01-6424-PH-08)

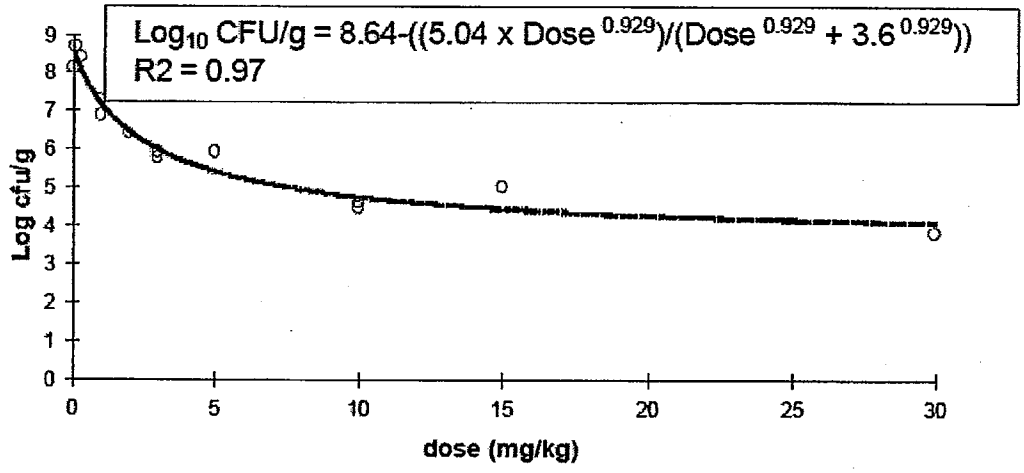
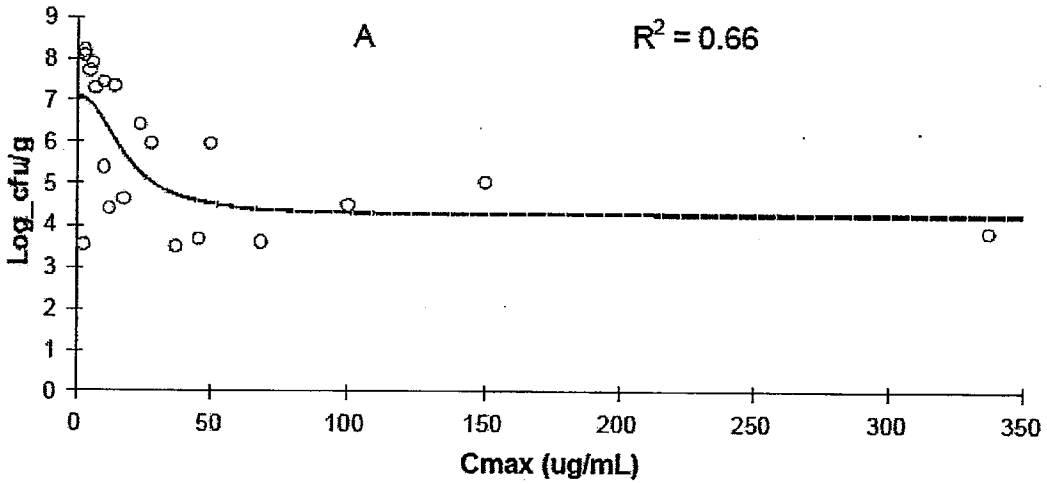
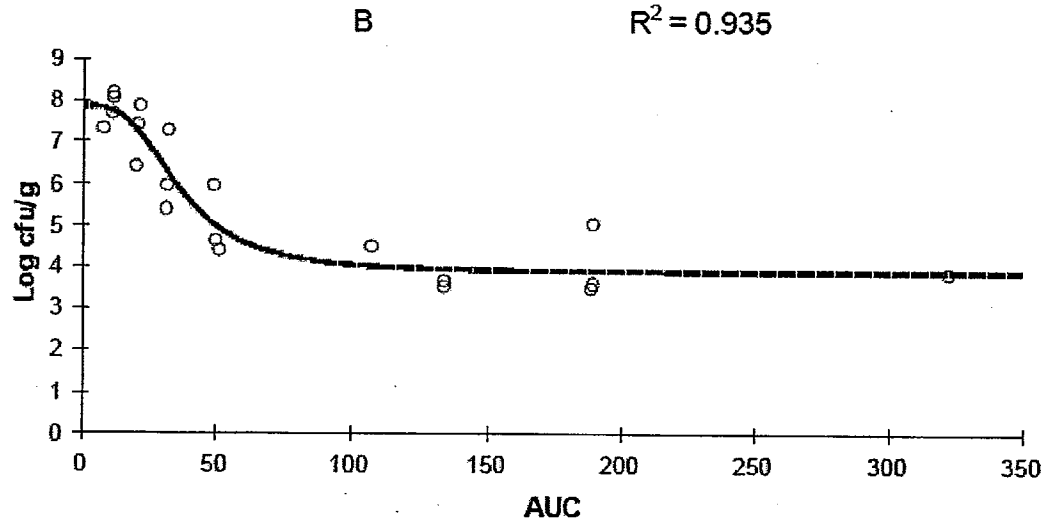
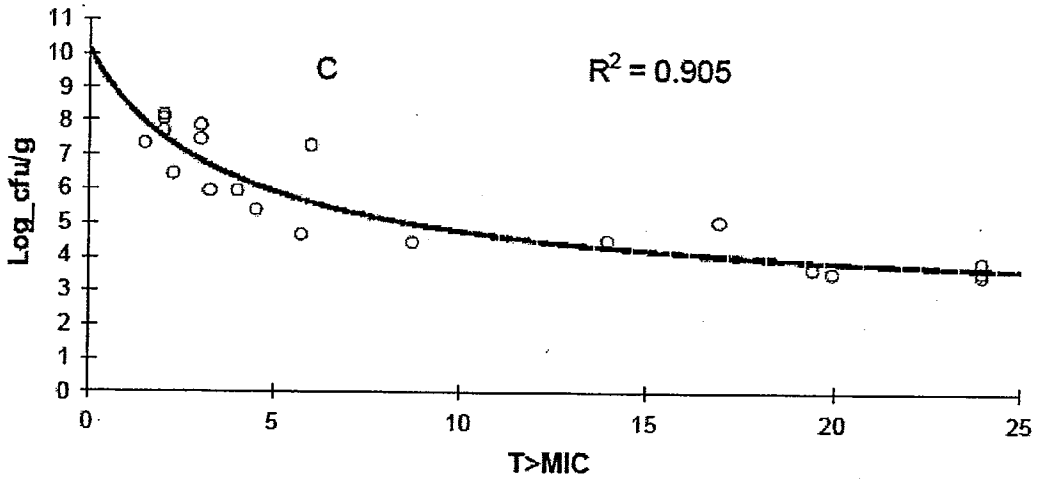


Figure 3 A, B, and C shows the relationship between the three PK parameters ($C_{max}$, AUC and T>MIC) and log CFU/g. There was a poor correlation between $C_{max}$ and log CFU/g ($R^2$ =0.66). In contrast, a good correlation was noted between AUC and T>MIC vs. log CFU/g ($R^2$ =0.94 and 0.91, respectively) which was described by a sigmoidal curve.

Figure 3. Relationship Between log CFU/g and $C_{max}$ (A), AUC (B), and T>MIC (C); (Study 01-6424-PH-08)






**CONCLUSIONS:**

The results from this study show that the efficacy of AMI-6424 against MRSA in the neutropenic thigh model is not affected by the dosing interval. The correlation between AUC vs. logCFU/g suggest that the AUC is the primary pharmacodynamically-linked variable.

**01-6424-PH-09**

**TITLE: Pharmacodynamic Analysis of the Efficacy of AMI-6424 Against Multiple Strains of Clinically Relevant Gram Positive Organisms in the Mouse Neutropenic Thigh Model**

Study Location:

Study Initiation Date(s): 6/8/00 b(4)

Study Completion Date(s): 12/10/01

**MATERIALS AND METHODS:**

AMI-6424 (Lot No. 7, 10, 32, 23) was synthesized at . Isoflurane anesthetic was obtained from . Organisms were cultivated in brain heart infusion (BHI) broth obtained from . Triptic soy (TS) agar plates were purchased from . Blood agar plates were obtained from b(4)
AMI-6424 was dissolved in hydroxypropyl-β-cyclodextrin [(HP-β-CD) 1:10 ratio]. Dosing volumes were approximately 100 µL. MRSA strain No. 33591 and MSSA strain No 13709 were obtained from the . Vancomycin-resistant *Enterococcus faecalis* (VRE), strain No. A256 was obtained from . All other clinical isolates (MRSA MCJ25, MRSA SFVA06, MRSA MGH10, MSSA KPB01, MSSA KPB04, MSSA MED415, MRSE SFVA01, MSSE SU03, PRSP SU2, PRSP CHM11, PSSP SU10, PSSP SU07) were obtained from clinical hospitals or academic institutions. For the majority of the strains, colonies were swabbed off an initialplate and grown overnight in BHI broth. The following morning, a subculture was grown and the inoculum was diluted from this source. The final inoculum was in BHI broth. In the case of PSSP and PRSP strains, colonies were swabbed off an initial plate and grown overnight in BHI broth in a C02 incubator. Animals (male CD-1 mice, 15 to 30 g) were acquired from , and allowed access to food and water *ad libitum*. Neutropenia was induced via 200 mg/kg intraperitoneal (IP) injection of cyclophosphamide given four and two days prior to the inoculation of bacteria. This treatment regimen induced severe leucopenia and generally decreased the neutrophil count to approximately 100 cells/mm3. The bacterial inoculum concentration was ~106 CFU/mL. Animals were lightly anesthetized with isoflurane (2.5% for induction followed by 1% for maintenance) and 50 µL of the bacterial inoculum was injected into the anterior thigh. One hour after the inoculation, animals were dosed intravenously (IV) with vehicle or various regimens of the drug. At 0 h and 24 h post-treatment, the animals were euthanized (CO2 asphyxiation) and the anterior and posterior thigh collected aseptically. The thigh was placed into 10 mL sterile saline and homogenized. For the majority of strains, dilutions of the homogenate were plated onto TS agar plates which were incubated overnight. In case of PSSP/PRSP strains, dilutions of the homogenate were plated onto blood agar plates which were incubated overnight in a C02 incubator. The number of bacterial colonies on a given plate was multiplied by the dilution factor, divided by the thigh weight (in grams) and expressed as log CFU/g. Vehicle (HP-β-CD, q 24 h), AMI-6424 (0.1, 0.3, 1, 3, 10, and 50 mg/kg, IV., q 24 h), vancomycin (15 mg/kg, IV., q 12 h).

**PHARMACOKINETIC/STATISTICAL ANALYSIS:**

Data are expressed as Mean 7 Standard deviation (SD). Dose-response curves are fitted with a four parameter logistic equation using GraphPad Prism, Version 3.00 for Microsoft Windows® (GraphPad Software, San Diego, California). The equation used is as follows: Y = Min + (Max–Min)/(1 + 10 □((log

ED50 –X)* Hillslope)), where X is the logarithm of dose, Y is the response (log CFU/g). Y starts at Min. (fixed to the 24 h. vehicle control response) and approaches asymptotically to Max. with a sigmoidal shape. The pharmacodynamic endpoints which were calculated are: ED50: Dose required to produce 50% of the maximum response. ED50 estimates are expressed as mean with 95% confidence intervals (CI). A two-tailed Students t-test was used to compare ED50 estimates between treatments. $P < 0.05$ was considered to be statistically significant.

**RESULTS:**

AMI-6424 produced dose-dependent reduction in thigh titre against all the tested gram positive strains. Vancomycin (15 mg/kg, IV., q 12 h) was also efficacious against all the strains except VRE A256 (data not shown). Table 1 summarizes the dose estimates required to attain different pharmacodynamic endpoints and Figures 1-2 shows the corresponding dose-response curves. T The stasis dose estimate was 6.3mg/kg, IV for MRSA and 2.5 mg/kg, IV for MSSA. The maximal killing (defined as reduction in thigh titre from pre-treatment values) was 2 log CFU/g for MSSA and 1 log CFU/g for MRSA.

Table 1. Doses of AMI-6424 Required to Attain Different Pharmacodynamic Endpoints Against Multiple Gram Positive Organisms in the Mouse Neutropenic Thigh Model

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

Figures 1 and 2 show the efficacy of telavancin against MRSA 33591 and MSSA 13709

Figure 1. Efficacy of Telavancin against MRSA 33591in the Murine Neutropenic Thigh Model

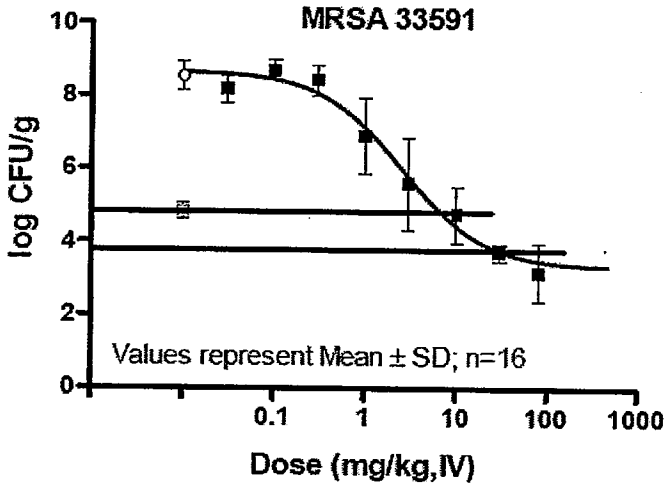
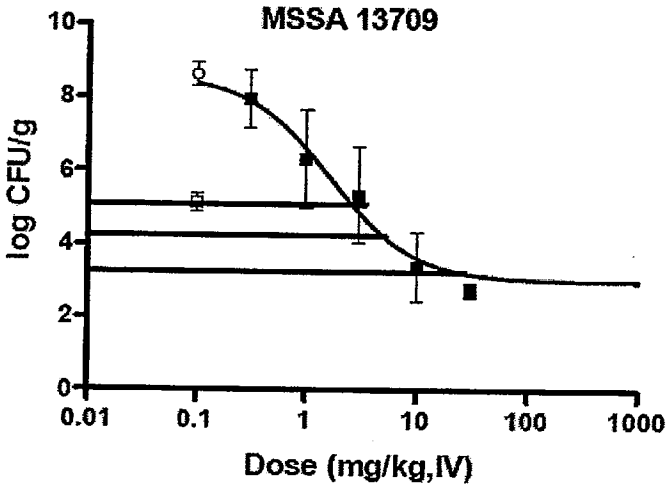


Figure 5. Efficacy of Telavancin against MSSA 13709 in the Murine Neutropenic Thigh Model




**CONCLUSIONS:**

The results from this study have shown that AMI-6424, dosed once in 24 hours, is potent and efficacious against a range of clinically relevant gram positive organisms.

01-6424-PK-13

**TITLE: In Vitro Metabolism of AMI-6424**

Report Date: 10/11/01

**MATERIALS AND METHODS:**

Male rat, dog, and human liver microsomes were obtained from [redacted]. Microsomes from transfected human B-lymphoblastoid cells expressing human CYPs 2D6, 3A4 or 4A11, as well as control microsomes from B-lymphoblastoid cells transfected with the expression vector alone (without N CYP cDNA) were obtained from [redacted] b(4)

Microsomal protein concentrations as provided by the manufacturers were 20 mg/mL for the liver microsomal stocks, and 10 mg/mL for the heterologously expressed CYP preparations. Incubations (500 µL volume) contained AMI-6424 (20 µg/mL) and microsomal proteins (1 mg/mL) in 100 mM KH2PO4 (pH 7.4), and reactions were initiated by the addition of an NADPH-regenerating system after a three-minute preincubation at 37oC. Control incubation was preformed without NADPH-regenerating system to assess non-oxidative metabolism for AMI-6424.

Aliquots of 100 µL were withdrawn at 0, 30, and 60 minutes after initiation of the reaction, and added to tubes containing 50 µL of acetonitrile. The precipitated microsomal protein was pelleted by centrifugation and the supernatants were analyzed by reverse phase HPLC with UV detection. For liver microsomal incubations, positive control incubations were performed in parallel with testosterone (100 µM) as the substrate. For incubations with CYPs 2D6 and 3A4, dextromethorphan (25 µM) and testosterone (100 µM) were used as positive control substrates, respectively. The formation of dextrorphan and 6-ß-hydroxytestosterone were monitored, respectively.

AMI-6424 was incubated with rat, dog, and human plasma at 37°C, at a concentration of 20 µg/mL in a total volume of 500 µL. Aliquots of 100 µL were withdrawn at 0, 30, and 60 minutes, and the plasma proteins were precipitated using twice the volume of ice-cold ethanol. Precipitated protein was pelleted by centrifugation and AMI-6424 in the supernatant was analyzed by HPLC with UV detection. Results were presented as percent of the initial value. Positive control incubations were run in parallel with tetracaine, a plasma esterase substrate.

Metabolic incubations of index substrates with human liver microsomes were performed as described for assessment of metabolic stability in previous section. The index reactions used were dextromethorphan O-demethylation (a CYP2D6 marker) and testosterone 6-ß-hydroxylation (a CYP3A marker). The concentration of dextromethorphan and testosterone used was 25 µM and 200 µM, respectively, and reactions were performed for 20 minutes at microsomal protein concentrations of 0.5 mg/mL and 1 mg/mL, respectively. The effects of co-incubation with AMI-6424 at concentrations of 10 µg/mL and 100 µg/mL were investigated. The effects of 100 µg/mL vancomycin were also investigated in parallel, and appropriate positive control inhibitors (1 µM quinidine for CYP2D6, and 1 µM ketoconazole for CYP3A4) were included in the assays.

Dextrorphan and 6-ß-hydroxytestosterone formations were measured by reverse phase HPLC with UV detection and results were expressed as percent inhibition of metabolite formation.

For kinetic analysis and IC50 determination, a range of concentration for AMI-6424, Vancomycin, quinidine and ketoconazole were used. Drug concentrations of 10 µg/mL to 250 µg/mL of AMI-6424 and Vancomycin were used and 0.008–0.8 µg/mL and 0.005–0.5 µg/mL were used for quinidine and ketoconazole, respectively.

**RESULTS:**

**Stability in Liver Microsomes:**

The stability data of AMI-6424 is shown in Table 1. Table 1 summarized the half-lives and percent AMI-6424 remianing following 60 minutes incubation in liver microsomes from rat, dog, and human. AMI-6424 was stable in rat, dog and human liver microsomes with or without NADPH. The metabolic activity

of the microsomal preparations was confirmed in positive control incubations with testosterone that demonstrate NADPH-dependent metabolism from all three species studied.

Table 1. *In Vitro* Stability of AMI-6424 and Testosterone (a Positive Control) in Liver Microsomes from Rat (RLM), Dog (DLM) and Human (HLM); (Study 01-6424-PK-13)

| Biological Matrices | With NADPH-regenerating System | | | | Without NADPH-regenerating System | | | |
|---|---|---|---|---|---|---|---|---|
| | % Remaining Following Incubation Time (min) | | | $T_{1/2}$ (min) | % Remaining Following Incubation Time (min) | | | $T_{1/2}$ (min) |
| | 0 | 30 | 60 | | 0 | 30 | 60 | |
| AMI-6424 | | | | | | | | |
| RLM | 100 | 99.8 | 99.0 | >60 | 100 | 99.5 | 99.4 | >60 |
| DLM | 100 | 94.4 | 100.7 | >60 | 100 | 120.1 | 117.4 | >60 |
| HLM | 100 | 102.0 | 111.1 | >60 | 100 | 99.7 | 103.1 | >60 |
| Testosterone | | | | | | | | |
| RLM | 100 | 3.8 | 0 | 6.3 | 100 | 114.4 | 128.7 | >60 |
| DLM | 100 | 74.2 | 37.7 | 42.6 | 100 | 89.3 | 94.6 | >60 |
| HLM | 100 | 14.6 | 3.9 | 12.8 | 100 | 102.1 | 111.9 | >60 |

**Stability in Heterologously Expressed Human CYP Isoforms:**
The *in vitro* metabolism of AMI-6424 was determined with cDNA-expressed human CYP2D6, 3A4 and 4A11. The results are summarized in Table 2. Little or no metabolism of AMI-6424 was detected *in vitro* following 60 min incubation with selected cDNA-expressed CYP enzymes. The metabolic activity of the microsomal preparations was confirmed in positive control incubations.
Dextromethorphan was metabolized by cDNA-expressed CYP2D6 to dextrorphan and cDNA-expressed CYP3A4 demonstrated testosterone 6-ß-hydroxylase activity, confirming the metabolic competence of these recombinant CYP preparation. Data are shown in Table 2. Control microsomes from vector-transfected cells did not metabolize either index substrates.
Rviewer Note: The percent remaining for the 3A4 substrate in testosterone is 85.4%. We expect to see a more rapid turnover for the control substrate. It is unknown if the integrity of the enzyme is adequate based upon this number. After this study was conducted, the sponsor conducted a human drug interaction study with midazolam (Study 0032). The results showed that telavancin had no significant effect on the disposition of midazolam and will not influence the metabolism of drugs metabolized by CYP3A4 to a clinically significant degree.

Table 2. *In Vitro* Stability of AMI-6424, testosterone (a Positive Control) and Dextromethorphan in cDNA-expressed Human CYP2D6, 3A4 and 4A11;(Study 01-6424-PK-13)

| Compound | % Remaining After Incubation Time (min) | | | |
|---|---|---|---|---|
| | 0 | 30 | 60 | |
| AMI-6424 | | | | $T_{1/2}$ (min) |
| Vector | 100 | 99.1 | 99.0 | >60 |
| 2D6 | 100 | 98.4 | 97.7 | >60 |
| 3A4 | 100 | 96.5 | 97.0 | >60 |
| 4A11 | 100 | 95.2 | 93.7 | >60 |
| Testosterone | | | | |
| Vector | 100 | 114.6 | 113.1 | >60 |
| 3A4 | 100 | 116.5 | 85.4 | >60 |
| Dextromethorphan | | | | |
| Vector | 100 | 104.6 | 105.9 | >60 |
| 2D6 | 100 | 65.8 | 43 | 49.3 |

**Stability in Plasma:**
Table 3 summarized the half-lives and % AMI-6424 remaining following 60 minutes incubation in plasma from rat, dog, and human. AMI-6424 was stable in rat, dog, and human plasma and no degradation of AMI-6424 was detected in vitro following 60 min incubation at 37°C. The apparent increase in AMI-6424 concentration with incubation time that is observed in some cases is an artifact, and is related to loss due to evaporation of plasma water. Time-dependent degradation of tetracaine (a positive control for esterase activity) was shown in rat and human plasma and data are shown in Table 3. However, no degradation was observed in dog plasma.

Table 3. *In Vitro* Stability of AMI-6424 and Tetracaine (a Positive Control) in Plasma from Rat, Dog, and Human; (Study 01-6424-PK-13)

| Biological Matrices | % Remaining Following Incubation Time (min) | | | $T_{1/2}$ (min) |
|---|---|---|---|---|
| | 0 | 30 | 60 | |
| AMI-6424 | | | | |
| Rat plasma | 100 | 112.6 | 137.6 | >60 |
| Dog plasma | 100 | 114 | 131.3 | >60 |
| Human plasma | 100 | 135.4 | 177.5 | >60 |
| Tetracaine | | | | |
| Rat plasma | 100 | 76.2 | 26.5 | 31.3 |
| Dog plasma | 100 | 124.2 | 110.3 | >60 |
| Human plasma | 100 | 56.8 | 0 | 36.8 |

**In Vitro Assessment of Metabolic Inhibitory Drug Interaction Potential:**
The results of the inhibition studies are provided in Table 4. The activities of CYPs 2D6 and 3A in human liver microsomes were unaltered by co-incubation with AMI-6424 at a concentration of 10 µg/mL. However, at the higher concentration studied (100 µg/mL), a weak inhibitory effect was noted towards both cytochromes (21% inhibition of CYP2D6 activity and 31% inhibition of CYP3A activity). The inhibitory effect of 100 µg/mL of AMI-6424 on CYP3A activity in human microsomes was slightly greater than vancomycin (31% vs. 17% inhibition). As expected, the positive control inhibitors yielded almost complete inhibition of the target cytochromes.

Table 4. The Effect of AMI-6424, Vancomycin and Known Inhibitors on the Metabolic Activities of CYP 3A4 and 2D6 in Human Liver Microsomes; (Study 01-6424-PK-13)

| Inhibitor | % Inhibition of CYP2D6 Activity | % Inhibition of CYP3A Activity |
|---|---|---|
| 10 µg/mL AMI-6424 | -1.3 | 1.1 |
| 100 µg/mL AMI-6424 | 21.1 | 31.4 |
| 100 µg/mL Vancomycin | -1.3 | 17.4 |
| 1 µM Quinidine | 78.0 | Not determined |
| 1 µM Ketoconazole | Not determined | 97.3 |

Further kinetic studies of the inhibition process using multiple inhibitor concentrations to estimate the 50% inhibition concentration (IC 50) and compare it with the plasma concentrations of AMI-6424 attained in humans. Results are shown in Figure 1and Figure 2. Based on the data presented in Table 4 and previously published Km values of the index reactions used in the study, an initial estimate of the IC50 values for inhibition of CYPs 2D6 and 3A4 by AMI-6424 is approximately 187 and 103 µg/mL, respectively. Similar IC 50 values estimated for these two CYP isoforms with distinct substrate specificity are consistent with the possibility of nonspecific inhibition of microsomal CYP activity by high concentrations of AMI-6424. The *in vivo* consequences of such nonspecific effects resulting from membrane perturbation that are observed *in vitro*, are currently unknown. These preliminary results presented in Table 4 suggest that AMI-6424 is at best, only a moderate inhibitor of the activity of CYPs 3A and 2D6.

Figure 1. The Effect of AMI-6424, Vancomycin, or Ketoconazole on Testosterone 6-β-hydroxylase Activity in Human Liver Microsomes

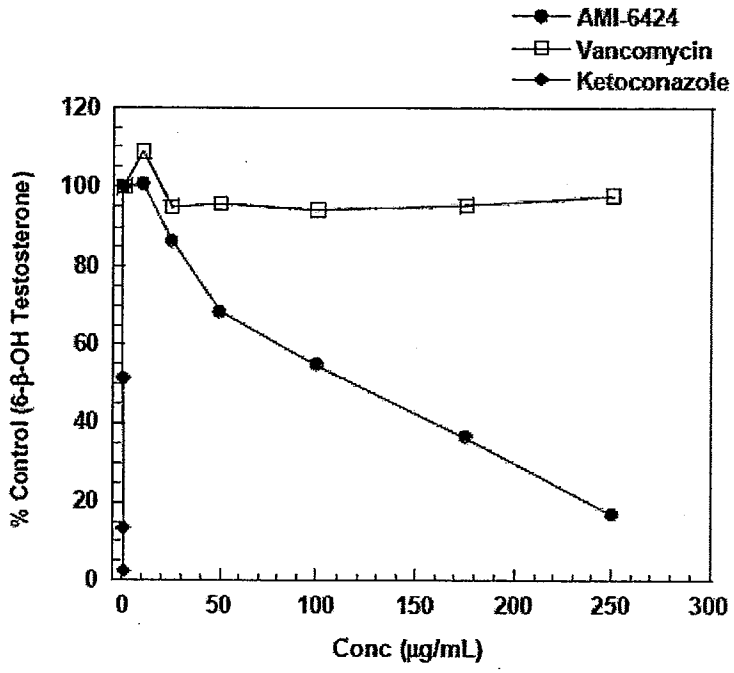
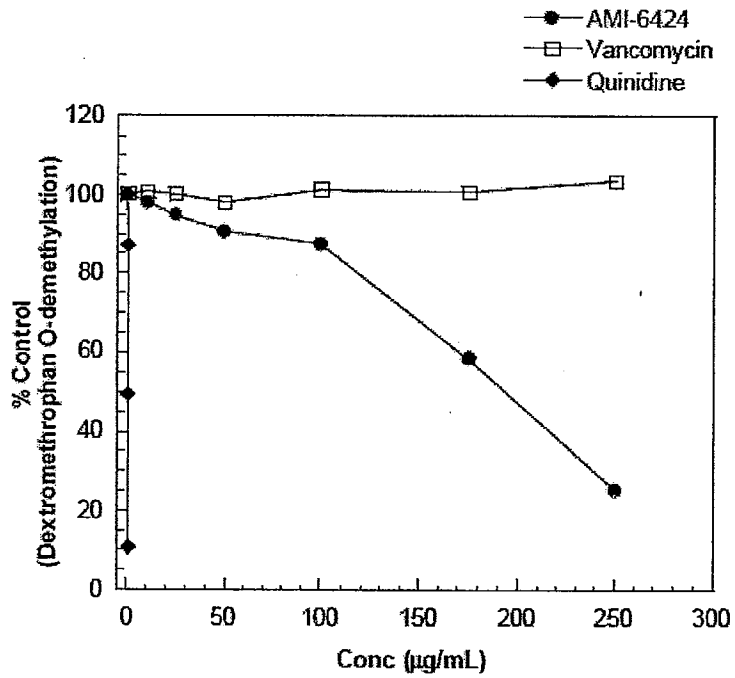



Figure 2. The Effect of AMI-6424, Vancomycin or Quinidine on Dextromethorphan O-demethylase Activity in Human Liver Microsomes



**CONCLUSIONS:**

The *in vitro* stability of AMI-6424 has been evaluated in liver microsomes, plasma or with selected cDNA-expressed CYP enzymes. Little or no metabolism of AMI-6424 was detected *in vitro* following 60 minute incubation in the liver microsomes and plasma from rat, dog, and human. Similar results were observed for AMI-6424 with cDNA-expressed human CYP 3A4, 2D6, and 4A11. The potential of AMI-6424 to cause pharmacokinetic drug interactions in humans was evaluated via inhibition of the major drug-metabolizing CYPs 2D6 and 3A4, using *in vitro* studies of representative index reactions catalyzed by human liver microsomes. The results showed that AMI-6424 exhibits weak inhibitory effects on the activity of CYP3A and 2D6 at a concentration of 100 µg/mL. This study appeared to be well conducted and I concur with the results. For the inhibition part of the study, the sponsor decided to conduct another study because this study was conducted a long time ago and a new study was needed to meet the current recommendations of studying approximately five isoenzymes.

**05-6424-PK-31**

**Title: The inhibitory potential of TD-6424 on the metabolic activity of five major CYP450 enzymes**

Report Date: 03MAR2006

**MATERIALS AND METHODS:**

Acetaminophen, α-naphthoflavone, dextromethorphan, diclofenac, dimethyl sulfoxide (DMSO), glucose-6-phosphate, glucose-6-phosphate dehydrogenase, 4′-hydroxydiclofenac, furafylline, 6β-hydroxytestosterone, ketoconazole, magnesium chloride, metoclopramide, midazolam, NADP, phenacetin, quinidine, sucrose, sulfaphenazole, testosterone, ticlopidine, Trizama base and troleandomycin were purchased from ( ) Dipotassium hydrogen phosphate and potassium dihydrogen phosphate were purchased from ( ) b(4)
Acetonitrile, methanol, and perchloric acid were purchased from ( )
Dextrorphan, (±)-4′-hydroxymephenytoin, and *S*-mephenytoin were purchased from ( )
( ) Formic acid was purchased from ( ) EDTA was purchased from ( ) 1′-Hydroxymidazolam was purchased from ( ) High purity water was prepared at ( )
(Modafinil was donated by ( ) 17β-*N,N*-Diethylcarbamoyl-4-methyl-4-aza-5α -androstan-3-one (4-MA) donated from ( ) Tienilic acid was donated from ( ) The internal b(4)
standards used were ( )
( ) The sources of these standards are not provided due to the proprietary nature of this information. The purity of chemicals received as complementary samples is not available. The purity, lot numbers and expiration dates of all other chemicals listed above is maintained in the Testing Facility files. Human liver microsomes from donated livers were prepared and characterized by ( ) A pool of nine individual human liver microsomal samples was used for this study ( ) sample code numbers 71, 72, 76, 79, 99, 101, 105, 140 and 142). TD-6424 (Lot no. 70493AA006) was manufactured by ScinoPharm Taiwan, Ltd. A 0.7 mM TD-6424 stock solution was prepared in 5% dextrose for injection (Notebook reference: 1408-1 and 1408-4) and was stored at ( ) in a secure location at -15 to -25°C. A sub-stock solution of TD-6424 (target concentration of 0.5 mM) in a 5% dextrose solution was prepared from the 0.7 mM stock solution and solubility testing was conducted to qualitatively assess TD-6424 solubility in the test system. An aliquot (200 µL) of the sub-stock solution (0.5 mM TD-6424 in a 5% dextrose solution) was added to an 800 µL mixture (target pH 7.4) containing high purity water, potassium phosphate buffer (50 mM), MgCl2 (3 mM), EDTA (1 mM), and human liver microsomes (0.1 mg/mL and 0.05 mg/mL) at the final concentrations listed. A qualitative visual comparison of the tube to which TD-6424 was added with a control tube containing the same components without TD-6424 indicated that TD-6424 was soluble in the testing system. The sub-stock solution (0.5 mM TD-6424), along with dilutions to working solutions (0.5, 1.5, 5, 15, 50, and 150 µM TD-6424) were prepared fresh daily, as needed. The study was conducted at ( ) with ( ) protocol no. XT045013 as part of the study titled "*In Vitro* Evaluation of Telavancin, TD-2749 and TD-6301 as Inhibitors of Human Cytochrome P450 Enzymes". The basis for many of the following incubation conditions is described in the following references: Madan, *et al.* (2002) and Pearce, *et al.* (1996). All incubations were conducted in duplicate at approximately 37°C in 400 µL incubation mixtures (target pH 7.4) containing high purity water, potassium phosphate buffer (50 mM), MgCl2 (3 mM), EDTA (1 mM), an NADPH-generating system (always the mixture of the following: 1 mM NADP, 5 mM glucose-6-phosphate, glucose-6-phosphate dehydrogenase (1 unit/mL), and marker substrate (approximately equal to Km), at the final concentrations indicated, unless otherwise noted. Incubations were conducted in accordance with ( ) SOP L3250. b(4)
Pooled human liver microsomes (from nine individuals) were used as the source of enzymes. Due to the possibility that TD-6424 may bind to microsomal protein or lipids, an attempt was made to design these

experiments such that, in as many cases as possible, the microsomal protein, incubation time, and phosphate buffer concentration were 0.1 mg/mL, 5 minutes and 50 mM, respectively, for assays performed with human liver microsomes. Exceptions were made for the midazolam 1′-hydroxylation assays, in which a slightly different protein concentration was used to allow the rate of reaction to be measured under initial rate conditions; that is, the product formation increased with increased protein concentration and incubation time, such that the percent metabolism of the marker substrate did not exceed 20%. Since it is not imperative that the concentration of marker substrate be exactly equal to Km, the marker substrate concentrations was rounded up or down, as applicable, to simplify the experimental design. For example, the Km for diclofenac 4′-hydroxylation activity was determined to be 3.7 μM, which was adjusted up to 4 μM. Thus, the final incubation concentration of diclofenac was 4 μM. The Tecan liquid handling system was used to conduct all remaining incubation steps, with the exception of the centrifugation. Aliquots of the buffer mixtures were automatically added to 96-well plates at the appropriate locations in duplicate. Aliquots of a substrate working solution were added to the 96-well plates, prior to initiating reactions, to give the final concentrations. Reactions were initiated with the addition of an aliquot of an NADPH-generating system and were carried out in duplicate. Reactions were automatically terminated at approximately 5 minutes, by the addition of the appropriate internal standard and stop reagent; ( ) b(4)

) Precipitated protein was removed by centrifugation (920 x g for 10 minutes at 10°C). Standards and QC samples were similarly prepared with the addition of authentic metabolite standards. To examine its ability to act as a metabolism-dependent inhibitor, TD-6424 (at the same concentrations used to evaluate direct inhibition) was pre-incubated at 37 ± 1°C, in duplicate, with human liver microsomes and an NADPH-generating system for approximately 30 minutes. This pre-incubation allowed for the generation of intermediates that could inhibit human CYP enzymes. The pre-incubations were initiated with the addition of an aliquot of an NADPH-generating system. After the pre-incubation period, the marker substrate (at a concentration approximately equal to its Km) was automatically added and the incubation continued for 5 minutes to measure the residual marker CYP activity. Reactions were automatically terminated, at approximately 5 minutes, by the addition of the appropriate internal standard and stop reagent; ( ) b(4)

). Precipitated protein was removed by centrifugation (920 x g for 10 minutes at 10°C). Incubations containing no TD-6424 (vehicle only) and incubations that contained TD-6424 but were not pre-incubated, served as negative controls.

**RESULTS:**

The inhibitory effect of TD-6424 on the metabolic activity of five major CYP450s with zero and 30 minutes preincubation is shown in Table 1 and Table 2, respectively. The corresponding graphic presentation of the inhibition and percent of control for the five major CYP450 enzymes with TD-6424 concentration ranged from 0.1-100 μM is presented in Figures 1-6. The calculated IC50 values are summarized in Table 3. TD-6424 caused direct inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 (as measured by testosterone 6β-hydroxylation and midazolam 1′-hydroxyaltion) with IC50 values of 40 μM, 89 μM, 54 μM, 35 μM, 25 μM, and 14 μM, respectively. However, the inhibition assay was conducted in the absence of serum albumin, the concentrations of TD-6424 tested (0.1-100 μM) and thereofore represent free drug. The highest concentration of TD-6424 (100 μM; 176 μg/mL) examined in this study is approximately fifteen-fold higher than the unbound peak plasma concentration (Cmax) in human at a dose of 10 mg/kg (11.4 μg/mL, 6.5 μM). At a concentration of 10 μM, little or no inhibition was observed for TD-6424 on the activity of CYP1A2, CYP2C9, CYP2C19 and CYP2D6. Under the experimental conditions examined, 10 μM TD-6424 had an effect on the activity of CYP3A4/5 (as measured by both testosterone 6β-hydroxylation and midazolam 1′-hydroxylation) with approximately 20-40% decrease in enzyme activity. This study appears to be well conducted and I concur with the results. These results support the study design of an on-going drug-drug interaction study with TD-6424 and midazolam in healthy volunteers. Under the experimental conditions examined, there was little or no evidence that TD-6424 caused metabolism-dependent inhibition of CYP1A2, CYP2C9,

CYP2C19, CYP2D6, or CYP3A4/5 (as measured by testosterone 6β-hydroxylation and midazolam 1′-hydroxyaltion), as little or no increase in inhibition was observed upon pre-incubation (Tables 2-3, Figures 1-6). It should be noted that the potential for TD-6424 to cause metabolism-dependent inhibition was determined by comparison of IC50 values (with and without pre-incubation) and by visual inspection of the data and IC50 plot. In those cases when the slope factor for the IC50 value is significantly greater than 1, potential for metabolism-dependent inhibition was determined by visual inspection of the data alone.

Table 1. The Effect of TD-6424 on the Activity of CYP1A2, 2C9, 2C19, 2D6, and 3A4 in Human Liver Microsomes (with zero-minute pre-incubation)

| | CYP1A2 | | CYP2C9 | | CYP2C19 | | CYP2D6 | | CYP3A4/5 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Testosterone 6β-hydroxylation | | Midazolam 1′-hydroxylation | |
| [TD-6424, μM][a] | Activity[b] | %SC[c] | Activity[b] | %SC[c] | Activity[b] | %SC[c] | Activity[b] | %SC[c] | Activity[b] | %SC[c] | Activity[b] | %SC[c] |
| NSC | 497 | NA | 1020 | NA | 99.4 | NA | 131 | NA | 4570 | NA | 1020 | NA |
| 0 | 501 | 100 | 1050 | 100 | 113 | 100 | 121 | 100 | 4750 | 100 | 1060 | 100 |
| 0.1 | 537 | 107 | 1080 | 103 | 134 | 118 | 123 | 101 | 5220 | 110 | 1070 | 101 |
| 0.3 | 549 | 110 | 1220 | 116 | 135 | 119 | 126 | 104 | 5230 | 110 | 1050 | 99.3 |
| 1 | 545 | 109 | 1170 | 112 | 123 | 108 | 130 | 107 | 5000 | 105 | 1020 | 96.4 |
| 3 | 535 | 107 | 1200 | 114 | 112 | 98.6 | 126 | 104 | 4950 | 104 | 1010 | 95.7 |
| 10 | 465 | 92.8 | 1240 | 118 | 103 | 91.3 | 106 | 87.1 | 3720 | 78.2 | 620 | 58.6 |
| 30 | 352 | 70.2 | 1050 | 99.9 | 88.6 | 78.2 | 72.5 | 59.7 | 2100 | 44.1 | 260 | 24.6 |
| 100 | 22.9 | 4.56 | 315 | 30.0 | 24.9 | 22.0 | 9.06 | 7.46 | 485 | 10.2 | 39.9 | 3.77 |

a: Test article (TD-6424) concentration (units, μM). TD-6424 was dissolved in 5% dextrose solution.

b: Measured enzyme activity (units, pmol/mg protein/min). Values are the average of duplicate determinations, unless otherwise noted.

c: Enzyme activity expressed as a percentage of the solvent control.

NSC: No solvent control

NA: Not applicable

Table 2. The Effect of TD-6424 on the Activity of CYP1A2, 2C9, 2C19, 2D6, and 3A4 in Human Liver Microsomes (with 30 minutes pre-incubation)

| | CYP1A2 | | CYP2C9 | | CYP2C19 | | CYP2D6 | | CYP3A4/5 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Testosterone 6β-hydroxylation | | Midazolam 1'-hydroxylation | |
| [TD-6424, μM][a] | Activity[b] | %SC[c] | Activity[b] | %SC[c] | Activity[b] | %SC[c] | Activity[b] | %SC[c] | Activity[b] | %SC[c] | Activity[b] | %SC[c] |
| NSC | 432 | NA | 1210 | NA | 161 | NA | 85.5 | NA | 5070 | NA | 1030 | NA |
| 0 | 361 | 100 | 1020 | 100 | 124 | 100 | 62.7 | 100 | 4230 | 100 | 923 | 100 |
| 0.1 | 354 | 98 | 975 | 95.9 | 119 | 95.3 | 60.6 | 96.8 | 4400 | 104 | 872 | 94.4 |
| 0.3 | 380 | 105 | 1100 | 108 | 130 | 104 | 65.9 | 105 | 4700 | 111 | 961 | 104 |
| 1 | 371 | 103 | 1060 | 104 | 121 | 97 | 63.5 | 101 | 4650 | 110 | 902 | 97.8 |
| 3 | 371 | 103 | 1090 | 107 | 121 | 96.9 | 62.5 | 99.8 | 4390 | 104 | 850 | 92.1 |
| 10 | 310 | 85.9 | 1080 | 106 | 101 | 81.1 | 49.7 | 79.3 | 3480 | 82.4 | 559 | 60.6 |
| 30 | 213 | 59.1 | 939 | 92.3 | 88.7 | 71.3 | 29 | 46.4 | 1980 | 46.8 | 189 | 20.4 |
| 100 | NA | NA | 169 | 16.7 | 18.1 | 14.6 | 4.69 | 7.49 | 69.5 | 1.64 | NA | NA |

a: Test article (TD-6424) concentration (units, μM). TD-6424 was dissolved in 5% dextrose solution.

b: Measured enzyme activity (units, pmol/mg protein/min). Values are the average of duplicate determinations, unless otherwise noted.

c: Enzyme activity expressed as a percentage of the solvent control.

NSC: No solvent control

NA: Not applicable

Table 3. Summary of Results: In Vitro Evaluation of TD-6424 as an Inhibitor of Human CYP Enzymes

| Enzyme | | Direct inhibition | | Metabolism-dependent inhibition (MDI) | | |
|---|---|---|---|---|---|---|
| | | Zero-minute pre-incubation | | 30-minute pre-incubation | | |
| | CYP reaction | IC50 (μM) | Maximum inhibition at 100 μM (%)[a] | IC50 (μM) | Maximum inhibition at 100 μM (%)[a] | MDI Potential[b] |
| CYP1A2 | Phenacetin *O*-deethylation | 40 | 95 | 33 | 100 | little or no |
| CYP2C9 | Diclofenac 4'-hydroxylation | 69 | 70 | 63 | 83 | little or no |
| CYP2C19 | *S*-Mephenytoin 4'-hydroxylation | 54 | 78 | 43 | 85 | little or no |
| CYP2D6 | Dextromethorphan *O*-demethylation | 35 | 93 | 26 | 93 | little or no |
| CYP3A4/5 | Testosterone 6β-hydroxylation | 25 | 90 | 26 | 98 | little or no |
| CYP3A4/5 | Midazolam 1'-hydroxylation | 14 | 96 | 13 | 100 | little or no |

Notes: Values were calculated using the average data obtained from duplicates for each incubation condition. The IC50 values were calculated using XLFit.

[a] Maximum inhibition (%) is calculated using the following formula and data for the highest concentration of test article for which usable data were collected from the IC50 determinations (results are rounded to two significant figures): Maximum inhibition (%) = 100% – Percent solvent control.

[b] Metabolism-dependent inhibition was determined by comparison of IC50 values with and without pre-incubation and by visual inspection of the IC50 plot.

Figure 1. Inhibition of CYP1A2 (phenacetin O-deethylation) by TD-6424: IC50 Determination

(N=2; mean values are presented)

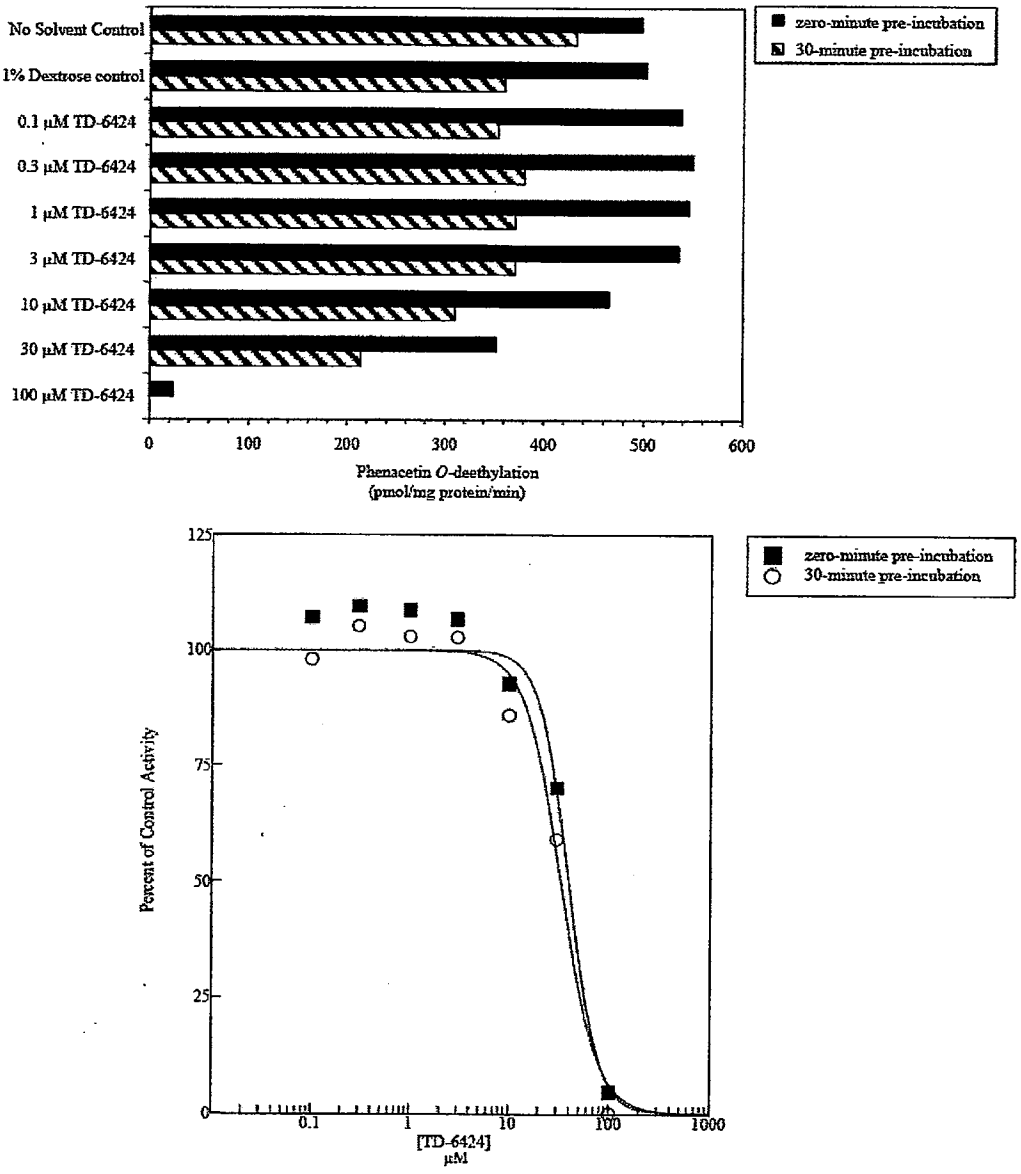


Figure 2. Inhibition of CYP2C9 (dicloenac 4'-hydroxylation) by TD-6424: IC50 Determination

(N=2; mean values are presented)

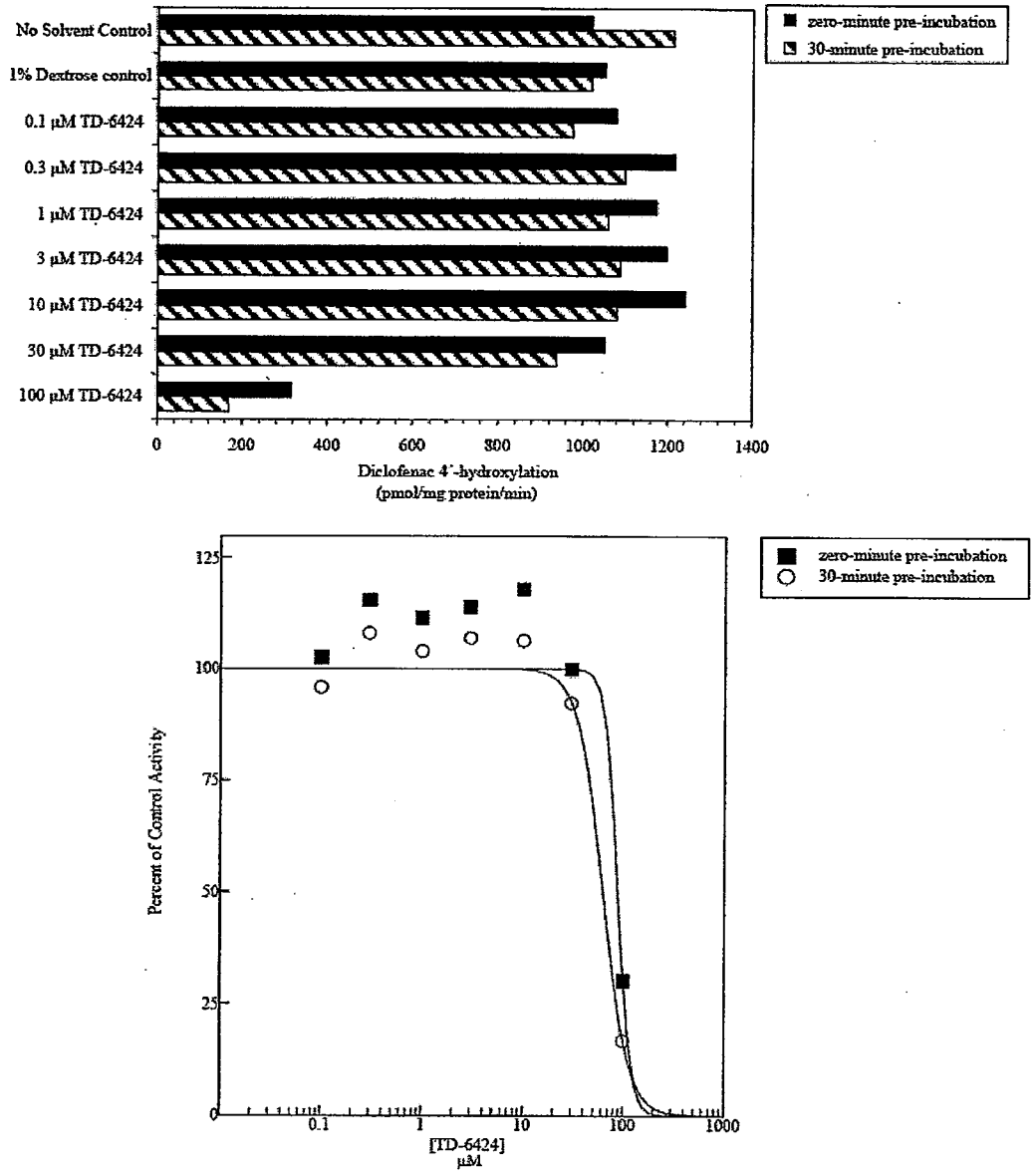


Figure 3. Inhibition of CYP2C19 (S-mephenytoin 4′-hydroxylation) by TD-6424: IC50 Determination

(N=2; mean values are presented)

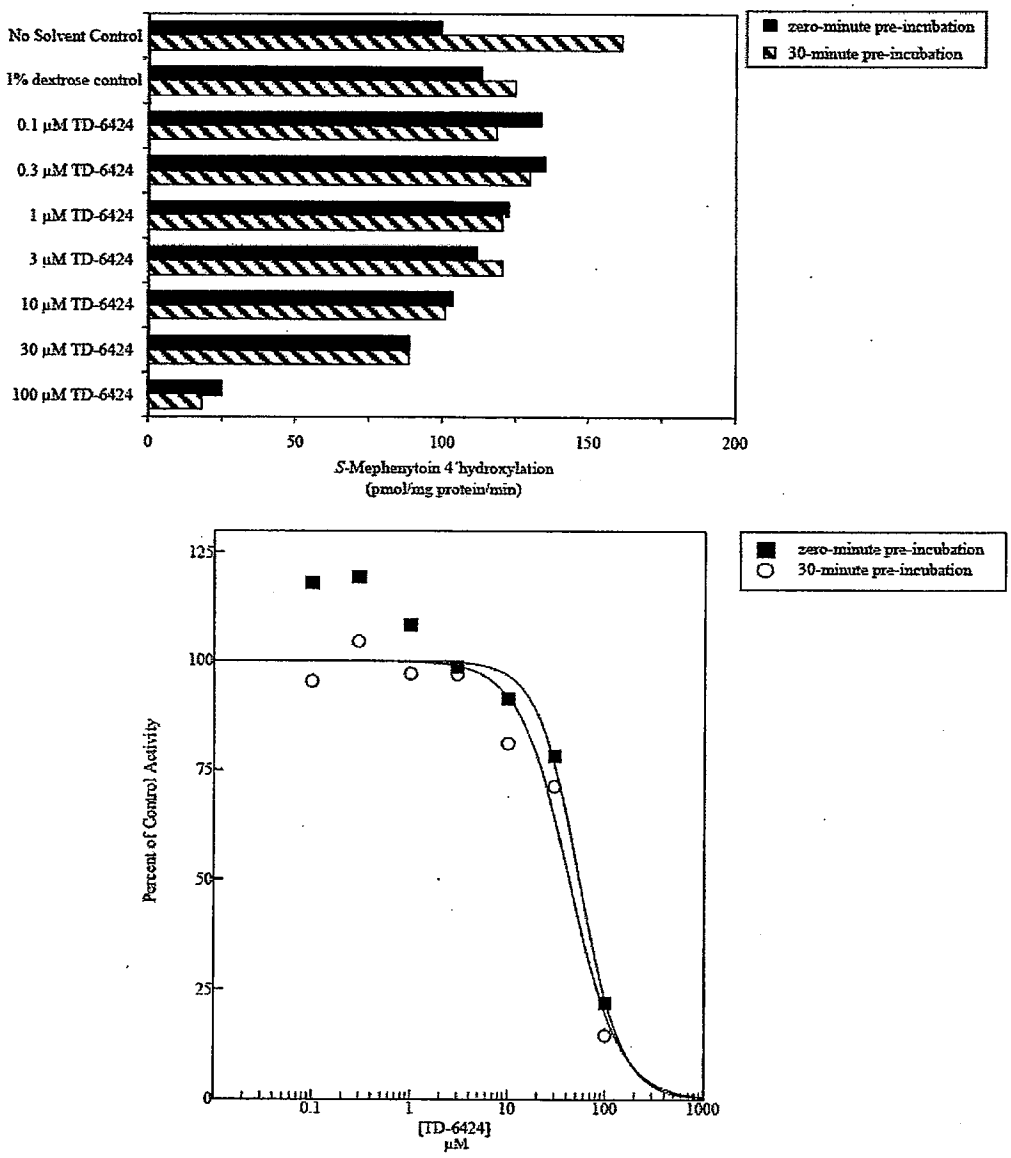


Figure 4. Inhibition of CYP2D6 (dextromethorphan O-demethylation) by TD-6424: IC50 Determination

(N=2; mean values are presented)

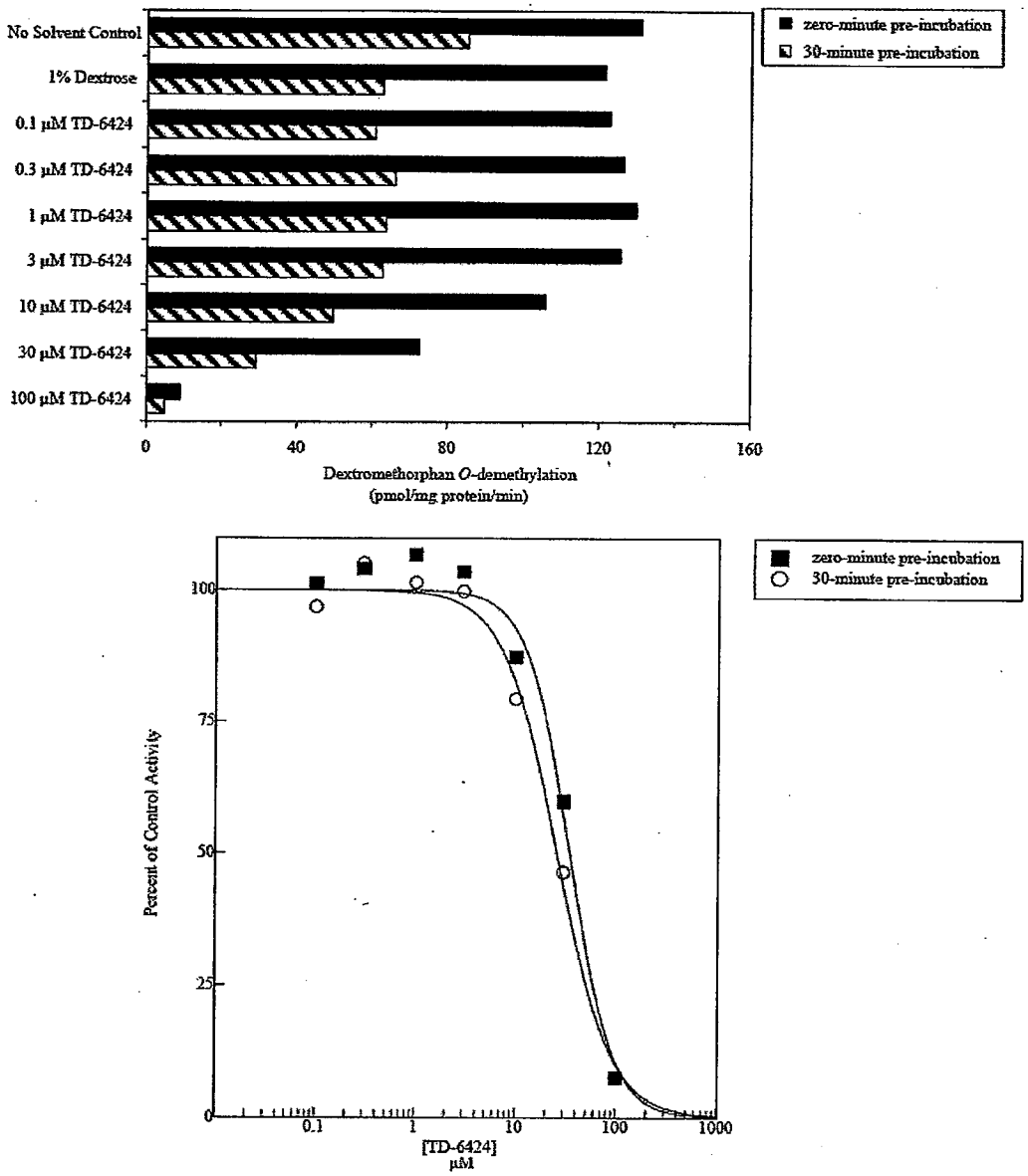


Figure 5. Inhibition of CYP3A4/5 (testosterone 6β-hydroxylation) by TD-6424: IC50 Determination

(N=2; mean values are presented)

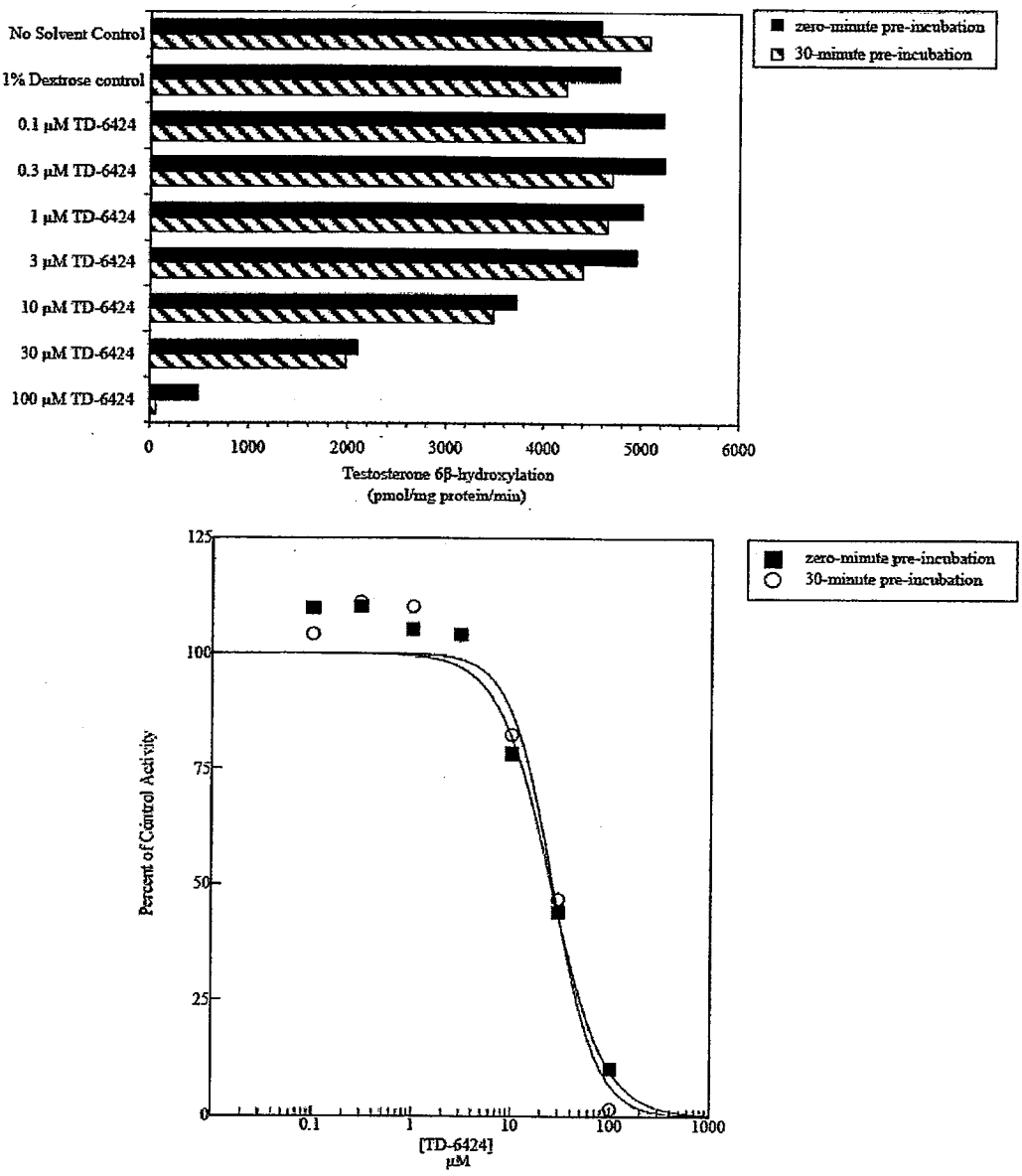
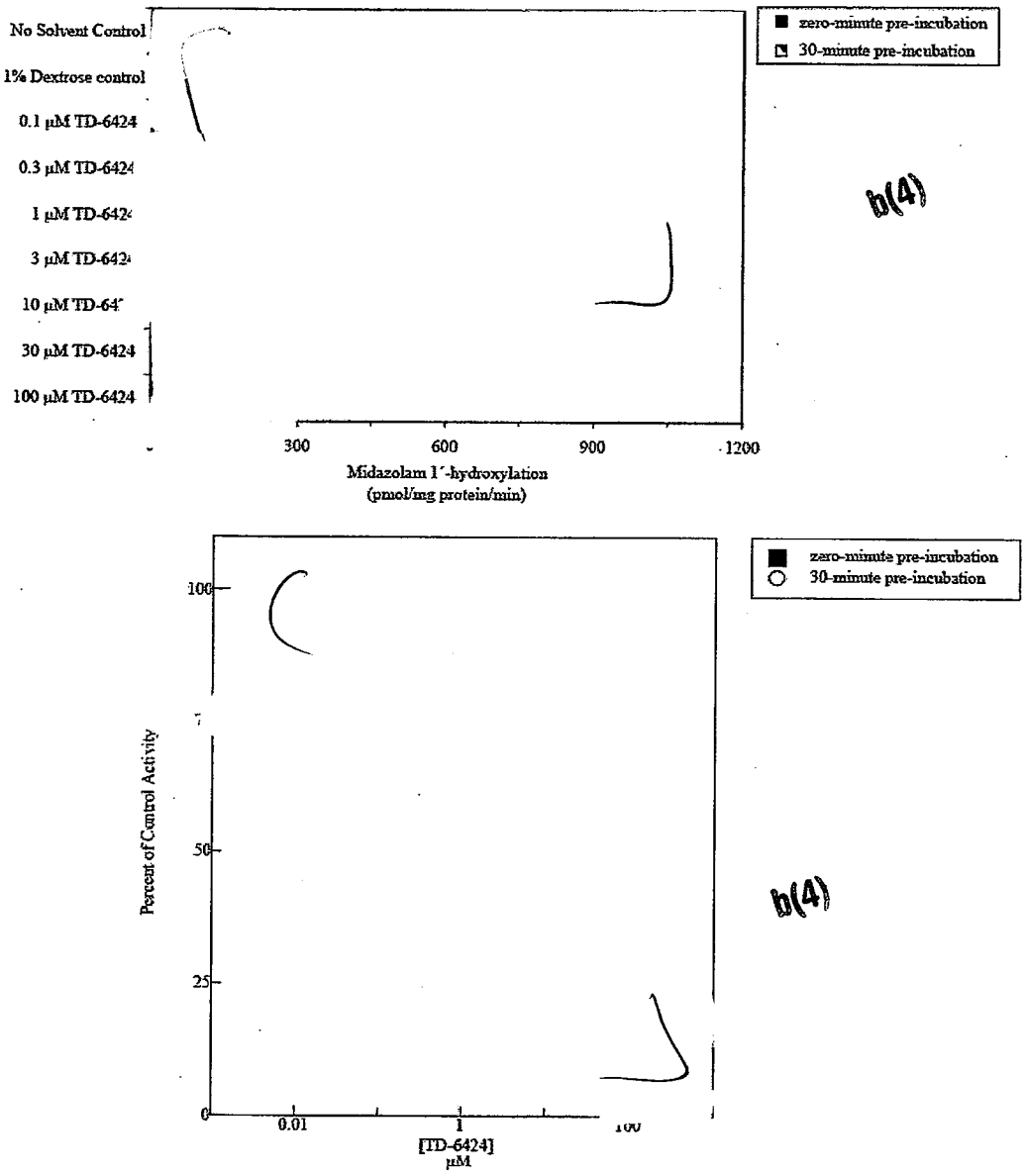


Figure 6. Inhibition of CYP3A4/5 (midazolam 1′-hydroxylation) by TD-6424: IC50 Determination



01-6424-PK-14

**TITLE: Plasma Protein Binding of AMI-6424 in Rat, Mouse, Dog, and Human**

Report Date: 12/14/01

b(4)

**MATERIALS AND METHODS:**

AMI-6424 hydrochloride salt (lot No. AB03016) was synthesized by ( ), ( ) with the potency of 80.6%. 3H-AMI-6424 trifluroacetate salt (lot No. 104-081-000) was synthesized by ( ) at 1 mCi/mL and the specific activity of 8.9 Ci/mmol. Three lots of human plasma were collected at the( ) and pooled. The pool was aliquoted and stored at approximately –20–C and was used only once after thawing, avoiding additional freeze/thaw cycles. Pooled lots of sodium heparinized rat, dog, and mouse plasma were obtained from commercial suppliers and pooled again by species to provide uniform test matrices. The dog plasma was bled from a mix of mongrels, and the mouse plasma was bled primarily from CD-1 mice, but could contain plasma from other strains. The strain of rat plasma used could not be identified. Each pool was stored in 10 mL aliquots at –20°C. Each aliquot was used only once after thawing, thus avoiding additional freeze/thaw cycles. Plasma pH was checked daily prior to use and adjusted to approximately pH 7.4 (± 0.1) by bubbling with CO2 if necessary. A Krebs Physiological Buffer, pH 7.4, was used. In addition, to minimize water shift (Donnan Effect) in the case of long equilibration time, Dextran, a high molecular weight compound, was added to the buffer at a concentration of 5% (w:v).

A Krebs Physiological Buffer, pH 7.4, was used. In addition, to minimize water shift (Donnan Effect) in the case of long equilibration time, Dextran, a high molecular weight compound, was added to the buffer at a concentration of 5% (w:v).

A Spectrum Multi-Equilibrium Dialyzer was used for dialysis. Teflon semi-microcells, having an approximately 1-mL capacity per side, were used for dialysis. Re-generated cellulose membranes with a molecular weight cutoff of 12,000-14,000 were used for dialysis. Membranes were treated before use by soaking them for ~20 minutes in Krebs Physiological Buffer.

Samples (1 mL) of fortified plasma, pre-warmed to 37°C, were added to the donor side of the dialysis cells. The buffer (1 mL), pre-warmed to 37°C, was added to the receptor side. The dialysis cells were placed in a water bath set at 37°C and rotated at approximately 30 rpm. At the designated time, the cells were removed from the water bath and the plasma and buffer from each cell was removed using plastic labware. An aliquot from each side of the cell was transferred into scintillation cocktail and counted on a beta counter.

Initially, dialysis was conducted from human plasma to buffer for 4, 6, 16, and 24 hours to determine the minimum time required reaching equilibrium. This experiment was conducted in triplicate at one concentration (10 µg/mL) of the radiolabeled test article. Equilibrium was obtained when the percent of unbound test material remained constant (< 10% change) between time points. It was anticipated that for small molecules equilibrium would be attained within 2 to 6 hours, however larger molecules may take longer. Time-points 6, 16, and 24 hour were evaluated with and without 5% Dextran added to the buffer to evaluate water shift (Donnan Effect). Blank plasma was used to confirm water shift had occurred at the longer timepoints. Protein concentration of the undialyzed (control) and dialyzed blank plasma at each time point was determined by a modified Lowry experiment and results were compared. Non-specific binding (NSB) was also evaluated as part of the time to equilibration experiment.

**RESULTS:**

The results of *in vitro* binding of AMI-6424 to human plasma proteins are presented in Table 1. Overall, AMI-6424 is highly protein-bound and exhibited a species-independent protein binding in human, rat, dog, and mouse plasma. Over the concentration range studied (0.1 to 100 µg/mL), AMI-6424 was slightly more protein bound at 100 µg/mL and this was observed consistently in all species examined. In

summary, AMI-6424 was 93.1–94.3%, 93.4–95.6%, 91.5–94.3%, and 93.8-96.2% bound in human, rat, dog, and mouse plasma, respectively.

Table 1. *In Vitro* Human Plasma Protein Binding

| | Plasma | Plasma ED | Buffer ED | % NSB | % Bound | % Free |
|---|---|---|---|---|---|---|
| 0.1 µg/mL AMI-6424 | | | | | | |
| Mean | 93758 | 85808 | 5711 | 2.4 | 93.3 | 6.7 |
| C.V.% | 0.9 | 1.9 | 3.2 | 44.4 | 0.2 | 2.1 |
| 1.0 µg/mL AMI-6424 | | | | | | |
| Mean | 94739 | 86569 | 5951 | 2.3 | 93.1 | 6.9 |
| C.V.% | 0.6 | 0.7 | 3.2 | 16.8 | 0.2 | 2.7 |
| 10 µg/mL AMI-6424 | | | | | | |
| Mean | 96267 | 88084 | 6046 | 2.2 | 93.1 | 6.9 |
| C.V.% | 0.2 | 1.7 | 4.7 | 92.4 | 0.2 | 3.1 |
| 100 µg/mL AMI-6424 | | | | | | |
| Mean | 95410 | 87907 | 4968 | 2.6 | 94.3 | 5.7 |
| C.V.% | 0.9 | 0.7 | 5.0 | 63.4 | 0.3 | 4.8 |

b(4)

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**CONCLUSIONS:**

The results indicated that AMI-6424 was highly protein-bound and exhibited a species-independent protein binding in human, rat, dog, and mouse plasma. Over the concentration range studied (0.1 to 100 µg/mL), AMI-6424 was slightly more protein bound at 100 µg/mL and this was observed consistently in all species examined. In summary, AMI-6424 was 93.1–94.3%, 93.4–95.6%, 91.5–94.3%, and 93.8–96.2% bound in human, rat, dog, and mouse plasma, respectively.

*4.1.8. Thorough QT Study*

# Interdisciplinary Review Team for QT Studies
# Response to a Request for Consultation: QT Study Review

| | |
|---|---|
| **IND or NDA** | 22110 |
| **Generic Name** | Telavancin for Injection |
| **Sponsor** | Theravance |
| **Indication** | Complicated skin and skin structure infections |
| **Dosage Form** | Solution for injection |
| **Therapeutic Dose** | 10mg/kg infused over 60 minutes every 24 hours |
| **Duration of Therapeutic Use** | 7 to 14 days |
| **Maximum Tolerated Dose** | Maximum tested dose 15 mg/kg |
| **Application Submission Date** | 19 December 2006 |
| **Review Classification** | TQT study report in standard NDA |
| **Date Consult Received** | 12 February 2007 |
| **Date Consult Due** | 26 May 2007 |
| **Clinical Division** | DAIOP / HFD 520 |
| **PDUFA Date** | 19 October 2007 |

## Summary

### Overall Summary of Findings

In this 'thorough QT/QTc study' the effects of administering two doses (7.5 mg/kg and 15 mg/kg infused intravenously over 60 minutes) of telavancin were assessed at steady state after three days of once daily dosing. At both doses, the baseline- and placebo-corrected QTcF interval was lengthened greater than 10 msec, the threshold of regulatory concern (Table 3). The mean Cmax of the supratherapeutic dose (15 mg/kg) represents a 50% increase in exposure over the highest clinical dose of 10 mg/kg (expected mean Cmax of 122 μg/ml based on linear pharmacokinetics).

**Table 3: Maximum Mean Effect by Dose Group (E14 Primary Analysis)**

| Dosing Regimen | Mean Cmax, 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 very little metabolism and is predominantly excreted unchanged in the urine (Table 4). 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 Cmax and 118% increase in AUC. Based on the mean elimination half-life for these subjects, it is expected that at steady state mean Cmax is approximately 190 μg/ml. Hence, the observed exposures after administration of repeated doses of 15 mg/kg of telavancin are acceptable.

A step-wise linear mixed-effects model described the relationship between telavancin concentrations and ΔΔQTcF (Figure 7, Table 11). This model was used because the observed median values (and inter-quartile range) for the

change from baseline QTcF immediately after infusion at Tmax was similar for both dose groups (Figure 6) 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 12).

## Responses to Questions posed by review division

None.

## Reviewer's Comments

- In this study moxifloxacin 400 mg by IV infusion was administered daily for three days. Moxifloxacin should be administered as a single dose for assay sensitivity. Repeat dosing of moxifloxacin is not optimal because plasma concentrations accumulate resulting in larger effects on the QTc than desired for assay sensitivity.
- The sponsor used the predose value as the baseline. We recommend a time-matched baseline adjustment for a parallel studies to account for within-subject diurnal variation.
- As detailed below, several adverse events due to ventricular arrhythmias and/ or cardiac events have occurred during clinical studies of telavancin. We recommend the DAIOP clinical reviewer of the NDA review all adverse events, particularly those the sponsor identifies as due to a ventricular arrhythmia or cardiac arrest, to explore whether they were associated with QT prolongation or torsade de pointes.

# Proposed label

The sponsor proposed labeling under WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY sections of the label (original labeling is presented in Appendix 0), and we have edited the label to reflect our concerns regarding telavancin and QT prolongation. These recommendations are only our suggestions for labeling. We defer all final labeling decisions to the review division.

**5. WARNINGS AND PRECAUTIONS**

**5.4 QTc Prolongation**

b(4)

**12 CLINICAL PHARMACOLOGY**

**12.2 Pharmacodynamics**

b(4)

The sponsor has also proposed including the following in the label:


b(4)

We suggest the following may be acceptable, if it accurately reflects the results of the phase 3 trials:


b(4)

*Reviewers' comment: As detailed below, several adverse events due to ventricular arrhythmias and/ or cardiac event have occurred during clinical studies of telavancin. If any of these events were due to torsade de pointes or associated with QT prolongation, the label should advise practitioners of its occurrence.*

## BACKGROUND

### Indication

The proposed indication for intravenous telavancin is the treatment of complicated skin and skin structure infections (cSSSI) caused by *Staphylococcus aureus* (including methicillin-resistant strains, ), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus anginosus grp.* (including *S.anginosus, S.intermidius* and *S.constellatus*) and *Enterococcus faecalis* (vancomycin-susceptible isolate only)

b(4)

### Drug Class

Telavancin (AMI-6424, TD-6424) is derived from a synthetic modification of vancomycin and is a purified lipoglycopeptide

### Market approval status

The sponsor has submitted an NDA seeking approval to market telavancin

### Preclinical Information

According to the sponsor, preclinical studies suggested that prolongation of QTc interval in human was possible.

"Although no notable receptor/ion channel binding or inhibition of enzyme activity was observed in receptor binding studies, telavancin did cause a decrease in hERG potassium ion channel currents in an exploratory (non-GLP) assay. In the GLP assay, 50% inhibition could not be obtained even at 600 µg/mL, a concentration approximately 40-fold higher than the highest expected free plasma concentration in humans (Cmax ≈ 200 µg/mL, approximately 90-92% protein binding).

The effects of telavancin on action potential duration (APD) were also evaluated in canine and ovine Purkinje fibers. In canine Purkinje fibers, modest (<11%) increases in duration required to reach 60% and 90% repolarization (APD60, APD90) were observed at concentrations of 50 and 150 µg/mL and a stimulation frequency of 1 Hz. These increases were not dose dependent and were not observed at other stimulation frequencies (e.g., 0.5 Hz). At clinically relevant concentrations of 5, 50 and 150 µg/mL, telavancin had no effect on any of the cardiac action potential parameters measured in ovine Purkinje fibers.

Of note is that studies in anesthetized and conscious dogs failed to demonstrate an effect on QTc intervals even after repeated dosing at 100 mg/kg/day. Using the average plasma concentration of 389 µg/mL (approximately 90-92% protein binding) at 100 mg/kg in the conscious dog study, exposure to the free fraction at this dose is estimated to be approximately 2-fold higher than the highest observed free plasma concentration in humans. Based on separate toxicokinetic data in dogs, exposure of the free fraction at this dose (Cmax ≈ 477 µg/mL, approximately 90-92% protein bound) is estimated to be about 2.4-fold higher than the highest observed free plasma concentration in humans. Although the in vivo assays failed to detect an effect on cardiac repolarization, the observation of effects in two of the in vitro assays (hERG, canine Purkinje fiber), even at high concentrations, suggested that a prolongation of the QTc interval in man was possible."

## Clinical Experience

In the initial phase 2 study (I6424-202a) of patients with cSSSI randomized to IV telavancin (7.5 mg/kg q 24 hours) or IV standard therapy, the sponsor reports in the IB that the mean change from baseline in QTcF for the telavancin group was approximately 6 msec longer than for standard therapy.

In the second phase 2 study (I6424-202b) of patients with cSSSI randomized to IV telavancin (7.5 mg/kg qd initially but amended to 10 mg/kg qd) or IV standard therapy, the sponsor reports in the IB that the mean change from baseline in QTcF for the telavancin group was approximately 12 msec longer than for standard therapy.

In the phase 3 studies, two deaths possibly due to ventricular arrhythmias in subjects treated with telavancin were assessed by the investigator as possibly/probably drug related. Subject 0017-02010-0546 was a 65 year old male who died of 'ventricular arrhythmia' after two days of treatment with Telavancin. Subject 0018-01002-2474 was a 75 year old female who died of 'cardiac arrest' after six days of treatment with Telavancin.

Additionally, in one ongoing blinded phase 3 study comparing telavancin to Vancomycin in the treatment of Hospital Acquired Pneumonia, subject 0015-38102-4060, a 62 year old male, had 'ventricular tachycardia' assessed by the investigator as possibly/probably drug related.

## Clinical Pharmacology

Table 4 summarizes the key features of telavancin clinical pharmacology.

**Table 4: Highlights of Clinical Pharmacology**

| | | |
|---|---|---|
| Therapeutic dose | 10 mg/kg intravenously q 24hr | |
| Maximum tolerated dose | 15 mg/kg intravenously q 24hr | |
| Principal adverse events | Most common adverse events: dysgeusia, nausea, vomiting, headache and foamy urine. Dose limiting adverse events are nausea and vomiting | |
| Maximum dose tested | Single Dose | 15 mg/kg |
| | Multiple Dose | 15 mg/kg q 24 hr for 7 days |
| Exposures Achieved at Maximum Tested Dose | Single Dose | Mean (± SD) Cmax: 179±10 mg/L and AUC $_{0-\infty}$: 1430 ± 202 mg.hr/L |
| | Multiple Dose | Mean (± SD) Cmax: 186±27 mg/L and AUC $_{0-24}$: 1282 ± 201 mg.hr/L |
| Range of linear PK | 1 mg/kg to 15 mg/kg | |

| | | |
|---|---|---|
| Accumulation at steady state | ≤ 5% at does up to 15 mg/kg for 7 days | |
| Metabolites | AMI-11352, which has ~10% antibiotic activity of telavancin, is only detectable metabolite in "meaningful" quantity | |
| Absorption | Absolute/Relative Bioavailability | Not absorbed |
| | Tmax | NA |
| Distribution | Vd/F or Vd | 119 ± 14 mL/kg (%CV) |
| | % bound | 90% |
| Elimination | Route | Renal, 80%<br>Feces <1% |
| | Terminal t½ | 8.0 (SD 1.5) hours for parent<br>Terminal t½ not calculated for metabolite due to slow appearance rate in plasma and limits of assay sensitivity |
| | CL/F or CL | 12.0 ± 1.9 mL/hr per kg |
| Intrinsic Factors | Age | Population pharmacokinetics indicated no effect of age on pharmacokinetics of telavancin<br>Cmax young=93.6 (SD=14.2) mg/L,<br>Cmax elderly= 87.7 (9.7) mg/L<br>AUC $_{0-\infty}$ young= 747 (129) mg.hr/L,<br>AUC $_{0-\infty}$ elderly = 829 (92) mg.hr/L |
| | Sex | Population pharmacokinetics indicated 10% reduction of clearance of telavancin in females (difference not apparent in PK studies)<br>At 7.5 mg/kg for 3 days:<br>Cmax male= 87.0 (14.5) mg/L, Cmax female= 88.2 (10.0) mg/L<br>AUC $_{0-24}$ male= 608 (104) mg.hr/L,<br>AUC $_{0-24}$ female= 585 (86) mg.hr/L |
| | Race | Population pharmacokinetics indicated no effect of race on pharmacokinetics of telavancin |
| | Hepatic & Renal Impairment | <u>Hepatic impairment</u>:<br>Cmax normal= 105 (12) mg/L, Cmax moderate impairment= 82.8 (13.7) mg/L<br>AUC $_{0-\infty}$ normal= 789 (69) mg.hr/L,<br>AUC $_{0-\infty}$ moderate impairment= 660 (159) mg.hr/L<br><br><u>Renal impairment</u>:<br>See **Table 5** |
| Extrinsic Factors | Drug interactions | Telavancin as a direct inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5, with IC50 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. Under the experimental conditions examined, 10 μM (~18 μg/mL, ~20% of peak total drug concentrations) telavancin had an effect on the activity of CYP3A4/5.<br>Telavancin was metabolically stable in liver S9 fractions and liver slices from human samples, and with seven human recombinant CYP450 enzymes (1A2, 2C9, 2C19, 2D6, 3A4, 3A5, and 4A11).<br>With respect to Cmax and AUC, no effects of telavancin on:<br>Midazolam (and 1"-hydroxy-midazolam)<br>Aztreonam<br>Piperacillin<br>Tazobactam<br>With respect to Cmax and AUC, no effects of aztreonam, piperacillin, tazobactam on telavancin.<br>All conclusions based on two-one-sided test (classical approach) looking at geometric mean ratios |
| | Food Effects | NA |
| Expected High Clinical Exposure Scenario | A predictable worst case scenario might be failure to dose adjust in patients with severe renal dysfunction or patients receiving hemodialysis, i.e., dosing to steady state at 10 mg/kg/day rather than every other day. Cmax and AUC under these conditions would be approximately 135 mg/L and 1638 mg.hr/L, respectively, and about 50% greater than expected concentrations at the 10 mg/kg/day dose in patients with normal renal function. These concentrations are within the range of those achieved at 15 mg/kg in healthy subjects in the thorough ECG study. | |

**Table 5: Noncompartmental Mean (±SD) Pharmacokinetic Parameters of Telavancin in Subjects with and without Renal Dysfunction (Study I6424-103a, dose = 7.5 mg/kg)**

| Parameter | Degree of Renal Impairment | | | | |
|---|---|---|---|---|---|
| | Normal | Mild | Moderate | Severe | ESRD |
| No. of subjects | 6 | 6[a] | 6 | 4 | 6 |
| CrCL (mL/min)[b] | 93.8 ± 10.8 | 64.1 ± 9.7 | 40.3 ± 7.0 | 21.0 ± 6.3 | NA |
| $C_{max}$ (µg/mL) | 70.6 ± 11.2 | 65.9 ± 2.7 | 65.8 ± 12.1 | 71.8 ± 7.1 | 52.1 ± 10.1 |
| $T_{max}$ (hr) | 1.0 ± 0.0 | 1.0 ± 0.0 | 1.0 ± 0.0 | 1.0 ± 0.0 | 1.0 ± 0.0 |
| $AUC_{0\text{-}48t}$ (µg•hr/mL) | 554 ± 92 | 608 ± 81 | 683 ± 169 | 1060 ± 70 | 898 ± 264 |
| $AUC_{0\text{-}\infty}$ (µg•hr/mL) | 560 ± 93 | 633 ± 101 | 721 ± 200 | 1220 ± 120 | 1010 ± 341 |
| % increase in $AUC_{0\text{-}\infty}$ compared to normal | NA | 13 ± 18 | 29 ± 36 | 118 ± 21 | 79 ± 61 |
| Elimination $T_{1/2}$ (hr) | 6.90 ± 0.60 | 9.61 ± 2.93 | 10.6 ± 2.4 | 14.5 ± 1.3 | 11.8 ± 2.8 |
| CL(mL/hr/kg) | 14 ± 2 | 12 ± 2 | 11 ± 3 | 6 ± 1 | 8 ± 3 |
| $V_{ss}$ (mL/kg) | 131 ± 16 | 157 ± 19 | 156 ± 24 | 136 ± 9 | 157 ± 27 |

[a] Pharmacokinetic data were evaluated for 6 of the 7 patients in the mild renal impairment group due to the development of "red man syndrome" in one subject in this group.
[b] Baseline mean creatinine clearance
NA = Not applicable

# SPONSOR'S SUBMISSION

## Overview (Submitted Materials)

Study I6424-10a was a QT study designed in response to the 2002 FDA and Health Canada Concept paper. The sponsor noted that the protocol for the study did not include two elements currently recommended in the ICH E14 guideline:

- Multiple ECGs –typically triplicate –at each assessment time point, which are then averaged. Instead a single ECG requirement was acquired at each time point.
- Enrollment of more than 60 subjects per arm in parallel studies in order to achieve adequate power. Study I6424-104a was designed to enroll 40 subjects per treatment arm. The sponsor stated that if the study had enrolled 60 subjects per arm study, the confidence intervals would have been reduced by ~ 82% shortening the lengths of the confidence intervals of 10 msec ( the approximate length of several intervals in the study) to about 8 msec. Thus had study I6424-104a enrolled 60 subjects per arm, it might have ruled out a 10 msec increase at a few additional time points.

*Reviewer's comment: The sponsor's assertion is speculative because it assumes that the point estimate for the true mean would have been the same. Increasing the sample size would have decreased the confidence interval but also would have increased the precision of the point estimate for the mean; whether the point estimate would have increased or decreased is unknown.*

## QT Study

*Title*

Safety and Pharmacokinetics of Intravenous Telavancin in Healthy Subjects

*Protocol Number*

Clinical Study Report: I6424-104a

*Objectives*

Primary

Assess the safety (including the effect of telavancin on ECG intervals and morphology, focusing on the QTc) and tolerability of intravenous administration telavancin.

Secondary

- Assess the pharmacokinetic disposition of telavancin in healthy subjects
- Assess the effects of telavancin on coagulation tests

*Design*

**Description**

Randomized, double-blind, placebo-group, gender-stratified, multi-dose Phase 1 study with negative and positive control arms in healthy volunteers. 40 subjects /group were randomly assigned to receive IV placebo for telavancin (negative control), moxifloxacin 400 mg IV (positive control), telavancin 7.5 mg/kg IV, or telavancin 15 mg/kg IV. On Day 0, all subjects received an infusion of 250 mL D5W to account for any potential effects of an infusion on ECG intervals. On days 1, 2, and 3, subjects received their assigned study medication infusion.

**Sponsor's Justification for Design**

Moxifloxacin was used as the positive control in this study since it has been shown to prolong the QT interval and could provide confirmation of assay sensitivity. Furthermore, moxifloxacin at a daily dose of 400 mg is approved for the treatment of both uncomplicated (7- day course) and complicated (7- to 21-day course) skin and skin structure infections, the latter being the target indication for telavancin. It has been reported that following a course of daily IV dosing with moxifloxacin, (400 mg; 1 hour infusion each day) the mean (± SD) change in QTc from the Day 1 pre-dose value is 9 msec (± 24) on Day 1 and 3 msec (± 29) on Day 3.

The negative control was a placebo version of telavancin that contained all excipients.

**Controls**

The Sponsor used both placebo and positive (moxifloxacin) controls.

**Blinding**

A commercially available formulation of moxifloxacin was used but all study treatments were supplied in an opaque sleeve.

*Study Subjects*

160 subjects entered study and 149 male and female subjects (age 18 to 40) completed treatment.

*Dosing Regimens*

**Treatment Arms**

- Test product: telavancin, 7.5 or 15 mg/kg administered IV in 250 ml D5W over 60 minutes
- Negative control: Telavancin vehicle (placebo), 1.5 ml/kg of reconstituted solution in 250 ml D5W over 60 minutes
- Positive control: Moxifloxacin 400 mg in 250 ml in 0.8% saline (Avelox® IV premix bag) over 60 minutes.

The first infusion day was designated Day 0 and the subsequent dosing days were Days 1, 2, and 3. On Day 0, each subject was to be administered a 60-minute IV infusion of 250 mL D5W. On Days 1, 2, and 3, subjects were to be administered a 60-minute IV infusion of the study medication based on their randomization assignment.

### Sponsor's Justification for Doses

Two dose levels of telavancin (7.5 and 15 mg/kg) were investigated in this study. At the time of initiation of the current study, available non-clinical and clinical data suggested that telavancin at 7.5 mg/kg administered once daily would be clinically efficacious. In Study I6424-101a, serum samples obtained 24 hours post start-of-infusion of this dose (representative of a trough concentration) were found to be bactericidal against strains of methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae* in an ex vivo functional assay. The anticipated clinical efficacy of the 7.5-mg/kg dose administered once daily was further supported by data from experimental animal models of infection, coupled with estimates of population pharmacokinetics, and assessed in a pharmacodynamic model. As the primary objective of this study was to assess the effect of telavancin on the QTc interval, a 2-fold higher dose level (15 mg/kg) was also investigated.

After the current study was completed, Phase 2 and Phase 3 studies have evaluated telavancin at a dose of 10 mg/kg. The 15 mg/kg dose of telavancin used in the current study provided concentrations of telavancin higher than those achieved at a 10 mg/kg dose of the drug because of a suggestion of QTc prolongation in the initial Phase 1 study of telavancin, the potential for untoward reactions including renal toxicity and "Red-man syndrome", and the limited number of subjects previously treated with the 15 mg/kg dose, the sponsor did not consider it advisable to investigate a higher dose in this study.

### Instructions with regard to meals

Not applicable (intravenous administration)

### Study Assessments

**Table 6: Highlights of Schedule of Interventions**

| Study Day | 0 | 1, 2 | 3 |
|---|---|---|---|
| **Intervention** | No treatment | Single dose / day | Single dose |
| **12-Lead ECGs** | Record ECGs[#1] (Baseline) | Record ECGs[#2] | Record ECGs[#1] |
| **PK Samples for drug** | None collected | Not collected | Collected [#3] |

[#1] Pre-infusion, immediately post infusion and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 15, 17, and 23 hours after the end of the infusion
[#2] Day 1 (immediately post infusion), and Day 2 (pre-infusion and immediately post infusion) for safety
[#3] pre-infusion, 0.5, 1, 2, 4, 6, 8, 12, 24, 36, and 48hr after the end of the infusion

### Sponsor's justification for sampling schedule

The sponsor did not provide the justification for sampling schedule.

### Baseline

Time-matched baseline was used. At each time point of measurement, for each subject, the baseline ECG intervals were the ECG values obtained at the corresponding time point on Day -1 of that period.

*ECG Collection*

ECG machines were supplied for the Sponsor by ( ) ECGs were digitally acquired and the tracings were transmitted electronically from the investigative site to the core reading laboratory ( ) where the ECGs were to be processed, including manual determination of interval durations (RR, PR, QRS, and QT/QTc) and morphological assessments. b(4)

*Sponsor's Results*

### Study Subjects

160 subjects entered the study and 149 completed with approximately 40 subjects per treatment group. The demographic and baseline characteristics are presented in Table 7.

## Table 7: Demographic and Baseline characteristics

| | Placebo | Moxifloxacin 400 mg | Telavancin 7.5 mg/kg | Telavancin 15 mg/kg |
|---|---|---|---|---|
| | N=40 | N=40 | N=40 | N=39 |
| Age, yrs | | | | |
| Mean (SD) | 28.8 (5.87) | 27.9 (5.92) | 27.7 (4.47) | 26.9 (5.86) |
| Median | 28.0 | 26.5 | 27.0 | 25.0 |
| Min, Max | 18, 40 | 18, 40 | 20, 37 | 18, 40 |
| Sex, N (%) | | | | |
| Male | 23 (57.5) | 24 (60) | 24 (60) | 23 (59) |
| Female | 17 (42.5) | 16 (40) | 16 (40) | 16 (41) |
| Race, N (%) | | | | |
| Caucasian | 19 (47.5) | 20 (50.0) | 22 (55.0) | 24 (61.5) |
| Black | 4 (10.0) | 5 (12.5) | 2 (5.0) | 3 (7.7) |
| Hispanic | 15 (37.5) | 12 (30.0) | 15 (37.5) | 8 (20.5) |
| Asian | 1 (2.5) | 1 (2.5) | 1 (2.5) | 3 (7.7) |
| Mixed | 0 | 2 (5.0) | 0 | 0 |
| Oriental | 1 (2.5) | 0 | 0 | 0 |
| Other | 0 | 0 | 0 | 1 (2.6) |
| Height, cm | | | | |
| Mean (SD) | 169.9 (9.26) | 170.7 (9.52) | 170.8 (9.27) | 171.4 (9.13) |
| Median | 171.3 | 170.7 | 170.5 | 171.0 |
| Min, Max | 152, 189 | 153, 188 | 152, 193 | 156, 189 |
| Weight, kg | | | | |
| Mean (SD) | 73.1 (13.24) | 75.7 (13.25) | 70.6 (10.01) | 73.0 (12.90) |
| Median | 73.5 | 75.3 | 71.7 | 71.1 |
| Min, Max | 51, 98 | 52, 104 | 50, 93 | 52, 101 |

### Statistical Analyses

## Primary Analysis

The primary method for calculating the corrected QT interval in this study was Fridericia correction (QTcF) defined as

$$QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$ ; where RR = the RR interval measured in ms

The PD analysis set included all subjects who were randomly assigned to treatments, received study drug and had at least one post baseline QT measurement, and provided ECG parameter information.

The null hypothesis tested was that the difference in mean QTcF between each dose of doripenem (Telavancin 7.5 mg and 15 mg)) and placebo is greater than or equal to 10 milliseconds, against the alternative hypothesis that the difference in mean QTcF between study drug and placebo is less than 10 milliseconds. The hypothesis will be tested at each time point of measurement.

The null hypothesis for Telavancin 15 mg dose vs. placebo will be tested first. If the null hypothesis for Telavancin 15 mg dose is rejected at every time point of measurement, it will be concluded that doripenem is non-inferior to placebo. The null hypothesis for Telavancin 7.5 mg dose vs. placebo will be tested only if the null hypothesis for 15 mg dose versus placebo is not rejected for at least one time point of measurement.

The primary analysis was based on a linear model (with factors for sex, treatment, and their interaction) applied to the data (change from baseline). A type III least squared means (using SAS PROC GLM) for each treatment comparison were computed. Student's t test was conducted for each treatment comparison in which mean square from the ANOVA model was used to estimate the variability. No adjustment for multiplicity was made. Two sided 90% confidence intervals for the difference between placebo least square mean and each active treatment least square mean were computed primary analysis was computed. Table 1 shows the summary of least square means from the linear model for comparison of mean ΔQTcF of the following pairs:

- Moxifloxacin versus placebo;
- Telavancin 7.5 mg versus placebo; and
- Telavancin 15 mg versus placebo.

**Table 8** shows the LS mean difference in change from time-matched baseline in QTcF values between drug and placebo at each time point of measurement in the study. It also shows the upper limit of the 90% confidence intervals for each comparison and p-values of the Student's t test for each comparison.

**Table 8: ICH E14 Analysis—Least-squares Mean Difference between Drug and Placebo of Change from Time-Matched Baseline QTcF values**

| | Moxifloxacin vs. Placebo | | | Telavancin 7.5 mg vs. Placebo | | | Telavancin 15 mg vs. Placebo | | |
|---|---|---|---|---|---|---|---|---|---|
| Time Point | LS Mean | P-value | Upper bound of Two-sided 90% CI | LS Mean | P-value | Upper bound of Two-sided 90% CI | LS Mean | P-value | Upper bound of Two-sided 90% CI |
| Pre | 5.9 | 0.052 | 11 | 0.3 | 0.917 | 5 | -0.6 | 0.848 | 5 |
| Post | 20.8 | <0.001 | 26 | 11.6 | <0.001 | 16 | 15.1 | <0.001 | 20 |
| 1h | 14.0 | <0.001 | 19 | 5.7 | 0.049 | 10 | 8.8 | 0.004 | 14 |
| 2h | 15.8 | <0.001 | 21 | 11.0 | <0.001 | 16 | 10.6 | 0.001 | 16 |
| 3h | 11.5 | <0.001 | 16 | 2.8 | 0.251 | 7 | 5.1 | 0.047 | 9 |
| 4h | 12.5 | <0.001 | 17 | 3.4 | 0.186 | 8 | 7.5 | 0.007 | 12 |
| 5h | 10.3 | 0.001 | 16 | 4.5 | 0.154 | 10 | 5.0 | 0.128 | 10 |
| 6h | 13.2 | <0.001 | 18 | 8.4 | 0.003 | 13 | 9.8 | <0.001 | 15 |
| 7 h | 9.3 | 0.002 | 14 | 3.4 | 0.232 | 8 | 7.0 | 0.021 | 12 |
| 8h | 9.6 | <0.001 | 14 | 2.2 | 0.407 | 7 | 3.3 | 0.237 | 8 |
| 9h | 5.6 | 0.063 | 11 | 3.5 | 0.243 | 8 | 0.1 | 0.974 | 5 |
| 10h | 4.9 | 0.061 | 9 | 2.5 | 0.337 | 7 | 3.1 | 0.250 | 8 |
| 11h | 7.3 | 0.012 | 12 | 1.5 | 0.594 | 6 | 2.4 | 0.427 | 7 |
| 13h | 6.8 | 0.009 | 11 | 3.9 | 0.127 | 8 | 2.2 | 0.407 | 7 |
| 15h | 1.4 | 0.641 | 7 | 0.4 | 0.906 | 5 | 0.4 | 0.909 | 6 |
| 17h | 5.0 | 0.173 | 11 | 4.8 | 0.190 | 11 | -0.5 | 0.902 | 6 |
| 23h | 3.3 | 0.337 | 5 | -0.5 | 0.879 | 5 | -2.0 | 0.587 | 4 |

Based on the above analysis (Table 1), the sponsor concludes the following:

- The two-sided p-value for pairwise tests on the LS mean difference in change from time-matched baseline between the moxifloxacin treatment group and placebo was less than 0.10 at several time points of measurement post dose. This analysis confirms that moxifloxacin was a positive control in this study and the assay sensitivity is established.
- In both telavancin dose groups (7.5 mg and 15 mg), the upper bound of the two-sided 90% CI on the LS mean difference in change from time-matched baseline between Telavancin treatment group and placebo was not less than 10 ms at all time points of measurement post dose. Therefore, the effect of (both doses) on QT/QTc prolongation was not non-inferior to placebo within a margin of 10 ms.
- Therefore, this QTc study is positive; i.e., prolongation of the QTc by more than 10 ms due to administration of these doses of telavancin can not be excluded.

## Categorical Analysis

The sponsor also performed categorical analysis. No subject had an absolute QTcF value greater than 500 ms at any time point. One subject in the telavancin 15 mg/kg group had a change in QTcF from baseline > 60 ms at 17 hours after dosing, absolute QTcF at the time was 430 ms.

Table 9 shows the number of subjects with maximum changes from baseline in QTcF that were greater than or equal to 30 ms or 60 ms.

**Table 9: Number of Subjects with Maximum Changes from Baseline in QTcF Greater than or equal to 30 ms and less than 60 ms**

| Increase in QTcF | Placebo n/N (%) | Telavancin 7.5 mg n/N (%) | Telavancin 15 mg n/N (%) | Moxifloxacin n/N (%) |
|---|---|---|---|---|
| ≥ 30 & < 60 ms | 5/39 (13%) | 10/39 (26%) | 7/34 (21%) | 15/39 (38%) |

## Additional Analyses

The Sponsor conducted additional analyses similar to the primary analysis and categorical analysis using other correction methods for QT, namely, Bazett's correction, Population correction and Individual correction. The results with these correction methods were similar to the Fridericia's correction method used for the primary and categorical analyses.

### Safety Analysis

There were no deaths, syncope (one reported "vasovagal attack"), ventricular arrhythmias, or seizures reported in this study. There were a total of 302 AEs reported; 282 judged by the investigator as mild, 16 as moderate, 4 as severe. AEs were more frequent in the telavancin treated groups but most were injection site reactions, nausea and dysgeusia. 9 of the 12 moderate or severe AEs occurred in 15 mg/kg telavancin group and 2 of the 12 in the 7.5 mg/kg telavancin group but none of these events were cardiac nature. There was a SAE; one subject developed a kidney infection requiring hospitalization 16 days after completing the study. Nine subjects withdrew due to AEs; 6 of these were in telavancin treated subjects but all of these were due to pruritus and/or rash (telavancin is related to vancomycin and similar cutaneous reactions are seen). Two more subjects withdrew before being dosed; one withdrew consent due to family emergency and the other had frequent PVCs on a baseline ECG.

### Clinical Pharmacology

## Pharmacokinetic Analysis

Plasma samples were assayed for telavancin concentration and urine samples were assayed for telavancin, AMI-11352 (major metabolite) and AMI-999 (

b(4)

Concentration time profile following administration of telavancin 7.5 mg/kg or 15 mg/kg (once daily for 3 days) was presented in Figure 1 and Figure 2.

**Figure 1: Concentration time profile (Mean ± SD) following administration of telavancin 7.5 mg/kg (once daily for 3 days)**

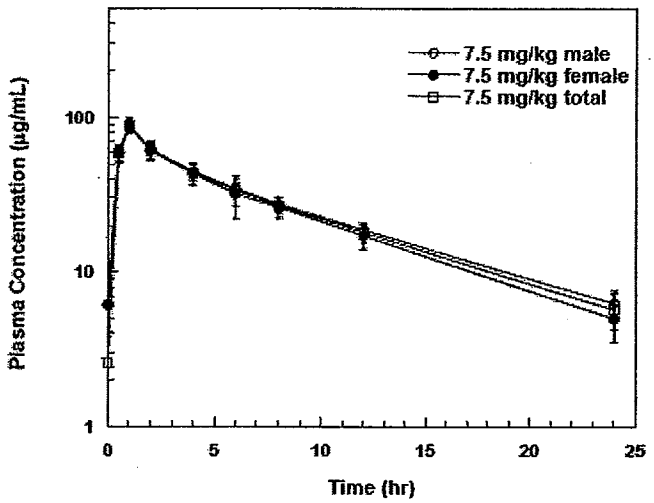
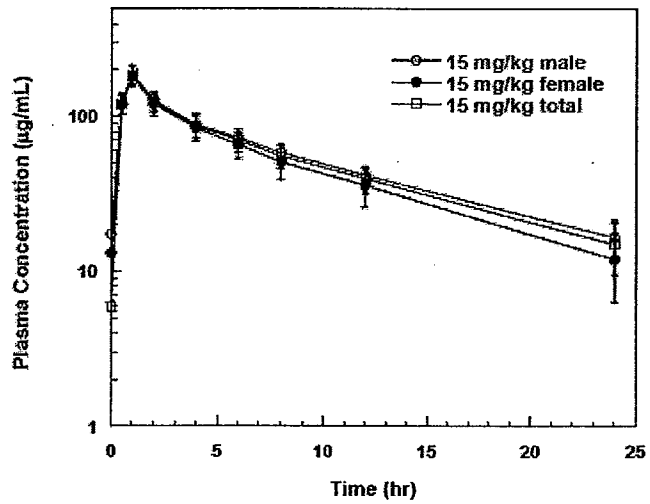



**Figure 2: Concentration time profile (Mean ± SD) following administration of telavancin 15 mg/kg (once daily for 3 days)**




## Exposure-Response Analysis

The sponsor did not conduct exposure-response analysis.

# REVIEWERS' ASSESSMENT

## Statistical Assessments

The Statistical Reviewer used the following data set submitted in the NDA to carry out some of the independent analyses for statistical evaluation of the results: \\cdsesub1\n22110\N_000\2007-01-31\ECG.XPT . This dataset is described in the\\cdsesub1\n22110\N_000\2007-01-31\ define.pdf.

The Statistical Reviewer's evaluation is based on a linear model with the PD parameter of ΔQTcF (the change of QTcF value from baseline) as the dependent variable, and the independent variables being treatment and gender.

### *Inferential Analysis*

Note that the Sponsor reported the primary analysis results based on a linear model with the PD parameter of ΔQTcF as the dependent variable, and the independent variables being treatment, gender and treatment by gender interaction. The Sponsor's analysis was based on a single (later) observation although there were two observations available after predose timepoints. The Statistical Reviewer performed analyses based on a linear model with the PD parameter of ΔQTcF as the dependent variable, and the independent variables being treatment, gender and treatment by gender interaction using day 3 observation. However, this reviewer has used time matched QTCF at Day 0 as baseline whereas the sponsor defined baseline as the Day 0 mean, regardless of the Day 3 analysis variable.

1. Change from baseline (predose) in Fridericia-corrected QTc values were calculated for each subject at each time point of measurement for each of the treatment groups, Telavancin 7.5 mg, Telavancin15 mg, moxifloxacin 400 mg, and placebo. This is $\Delta QTcF(t,i)$, where $t$ is the time point of measurement and $i$ is the index for $i^{th}$ subject.
2. Difference of change from time-matched baseline in QTcF for each dose of telavancin, or moxifloxacin vs. change from time-matched baseline QTcF values for placebo was calculated. This is $\Delta\Delta_{D\text{-}P}QTcF\ (t,i) = \Delta_D QTcF(t,i) - \Delta_P QTcF(t,i)$, where $D$ refers to the drug and $P$ refers to Placebo.

Table 10 shows the mean difference in change from time-matched baseline in QTcF values between drug and placebo at each time point of measurement in the study.

**Table 10: LS Mean Difference between Drug and Placebo of Change from Time-Matched Baseline QTcF values**

| | Moxifloxacin 400 mg vs. Placebo | | Telavancin 7.5mg vs. Placebo | | Telavancin 15mg vs. Placebo | |
|---|---|---|---|---|---|---|
| **Time Point** | **LS mean difference** | **Lower bound of 2-sided 90% CI** | **LS mean difference** | **Upper bound of 2-sided 90% CI** | **LS Mean Difference** | **Upper bound of 2-sided 90% CI** |
| Post Infusion | 24.04 | 17.74 | 13.95 | 20.23 | 17.86 | 24.47 |
| 1h | 12.91 | 6.9 | 5.50 | 11.48 | 8.48 | 14.77 |
| 2h | 13.61 | 7.03 | 13.54 | 20.08 | 15.11 | 21.99 |
| 3h | 14.10 | 8.39 | 4.20 | 9.86 | 8.53 | 14.49 |
| 4h | 12.42 | 6.73 | 4.39 | 10.05 | 8.51 | 14.46 |
| 5h | 10.89 | 4.57 | 4.40 | 10.68 | 5.21 | 11.84 |
| 6h | 13.18 | 7.18 | 8.81 | 14.77 | 6.94 | 13.22 |
| 7h | 5.03 | -1.02 | 0.94 | 6.11 | 7.25 | 13.55 |
| 8h | 9.49 | 4.47 | 2.49 | 7.47 | 2.21 | 7.46 |
| 9h | 5.16 | -0.68 | 5.19 | 10.18 | 2.31 | 7.57 |
| 10h | 6.62 | 1.60 | 2.25 | 8.06 | .29 | 6.41 |
| 11h | 9.84 | 3.5 | 3.36 | 9.69 | 5.93 | 12.60 |
| 13h | 4.48 | -1.51 | 5.06 | 11.01 | -0.55 | 5.72 |
| 15h | 3.22 | -2.62 | -1.16 | 4.64 | -.21 | 6.31 |
| 17h | 5.9 | -1.34 | -1.39 | 5.8 | -5.77 | -1.8 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 23h | 2.66 | -3.79 | 1.37 | 5.04 | -4.08 | 2.66 |

Based on the above analysis (8), the Statistical Reviewer makes the following conclusions:

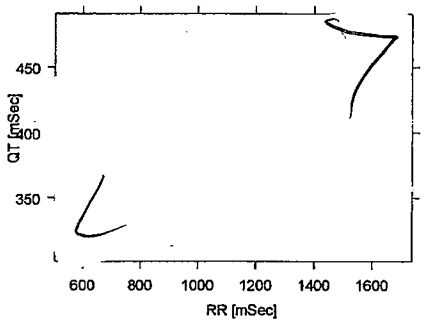
- Telavancin at a dose of 7.5 mg as well as at 15 mg prolongs the QT interval.
- In both Telavancin dose groups (7.5 mg and 15 mg), the upper bound of the 2-sided 90% CI based on LS mean difference in change from time-matched baseline between Telavancin treatment group and placebo was greater than 10 ms (the level identified as the threshold of regulatory concern in ICH E14) at several time points for both Telavancin doses.
- The lower bound of the 2-sided 90% Confidence Interval on the mean difference in change from time-matched baseline between the moxifloxacin treatment group and placebo was higher than 5 ms at several time points (1 hr (5.86), 2 hr (7.69), 3 hr (9.25), 4 hr (7.11) and 6h (7.19)). Note that we did not perform a multiple endpoint adjustment.
- The lower bound of the 2-sided 90% Confidence Interval on the LS mean difference in change from time-matched baseline between the moxifloxacin treatment group and placebo was higher than 5 at post dose, 1h, 2h, 3h, 4h, and 6h. This analysis confirms that moxifloxacin was a positive control in this study and assay sensitivity is established.

## Clinical Pharmacology Assessments

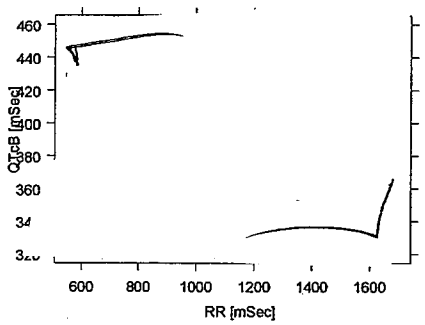
### *QT Interval Correction*

The observed QT values are presented in Figure 3 A. Two different heart-rate correction methods (Fridericia's and Bazett's correction) were performed. The results were illustrated in Figure 3 B and C. The Bazett's correction (QTcB) overcorrects at elevated heart rates and undercorrects at low heart rates. As shown in Figure 3 C), Fridericia's correction (QTcF) is sufficient, and thus was employed for this concentration QTc analysis.

**Figure 3: QT / QTc (QTcF and QTcB) versus RR at baseline**

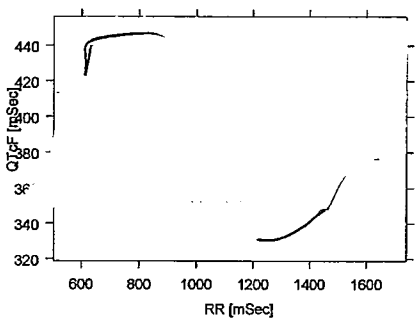



A.) QT versus RR




B.) QTcB versus RR

b(4)




C.) QTcF versus RR

Note: The red line is the lowest smooth line.

*ΔΔQTcF and Concentration Time Profiles*

The ΔΔQTcF (baseline and placebo corrected QTcF) versus telavancin concentration is plotted in Figure 4. The highest ΔΔQTcF was observed at the time to the peak of telavancin concentration ($t_{max}$). There was no evidence of hysteresis (Figure 5).

**Figure 4: Mean Telavancin Concentration and Mean ΔΔQTcF Time Profile**

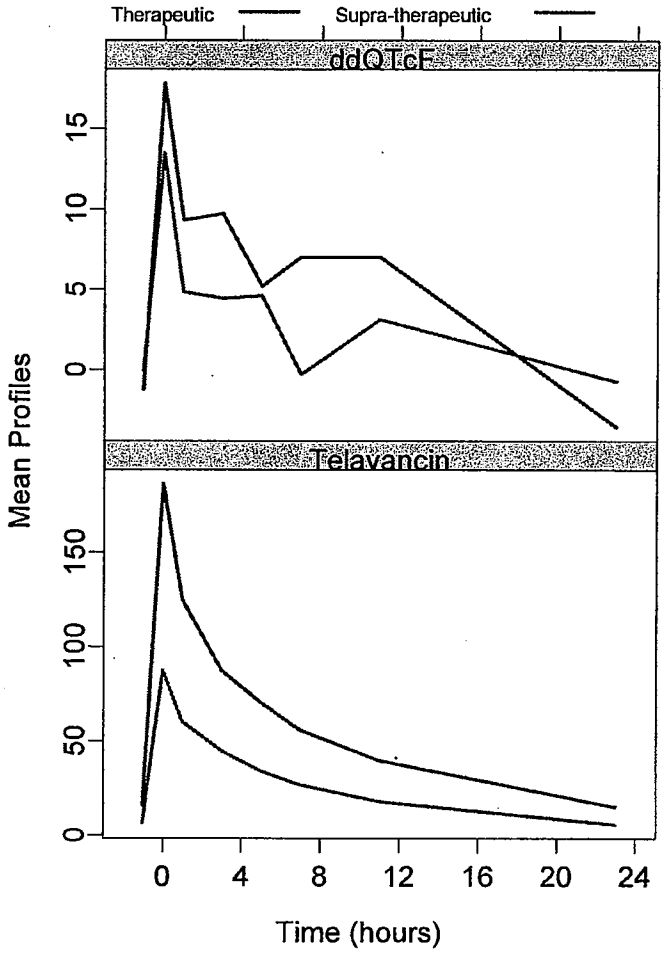
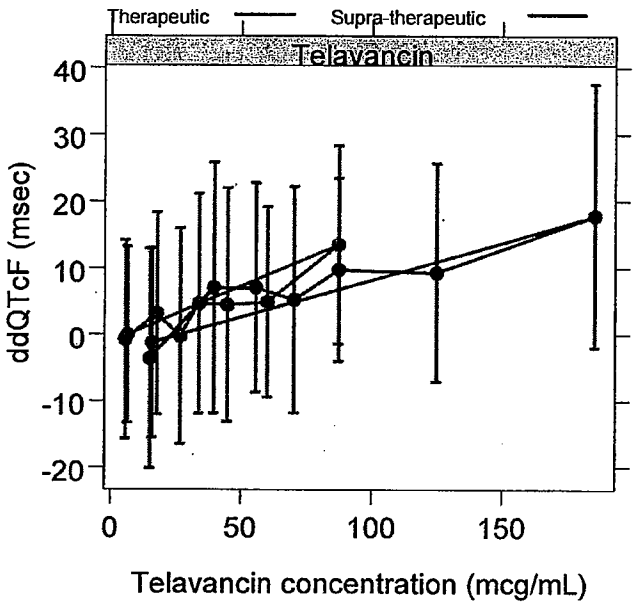


**Figure 5: Concentration-Effect Relationship with Observations Connected by Time**




*Exposure-Response Modeling*

Due to the overlapping ΔQTcF values for the 7.5mg/kg and 15 mg/kg dose groups (Figure 6), a step-wise linear model was used to describe the exposure-response relationship. Model parameters from the data obtained in 7.5 mg/kg and 15 mg/kg are shown in Table 11 respectively and goodness-of-fit plots in Figure 7 to Figure 8. Furthermore, the model predicted distribution of QTc interval prolongation was compared with the bootstrapped QTc interval prolongation. The results were presented in Figure 9.

**Figure 6: Boxplots of Post-Infusion ΔQTcF (at 0 hour on Day 3) Stratified by Treatment**

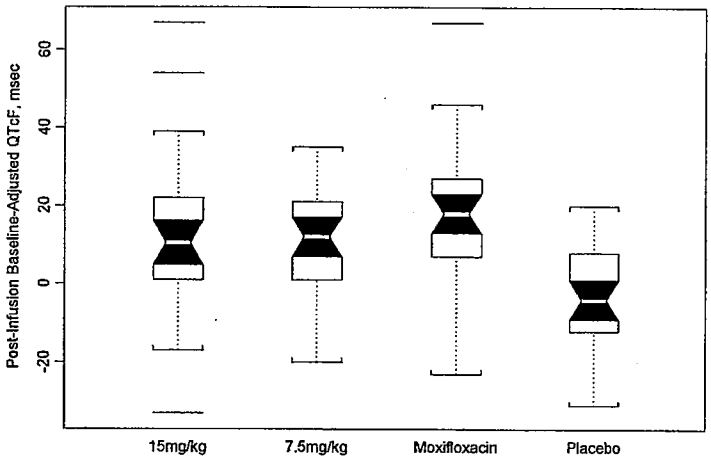
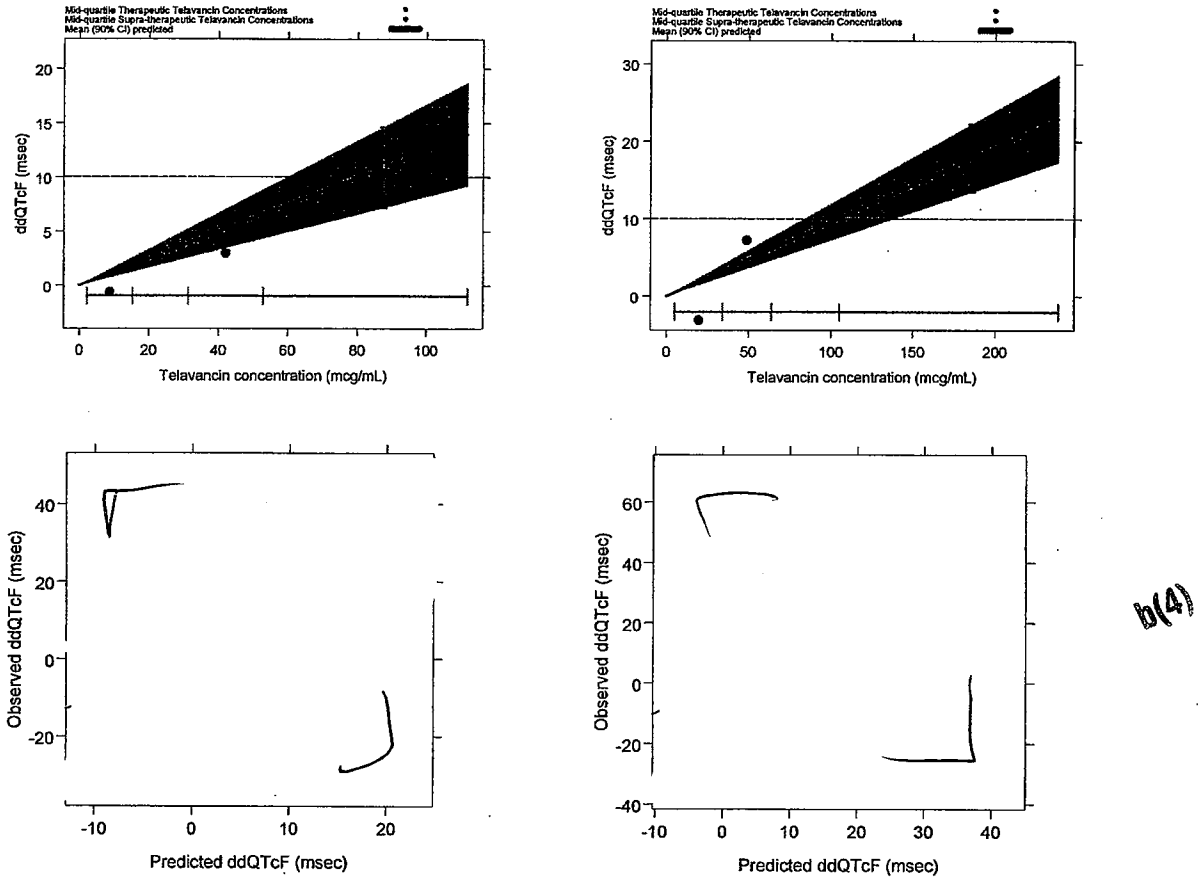
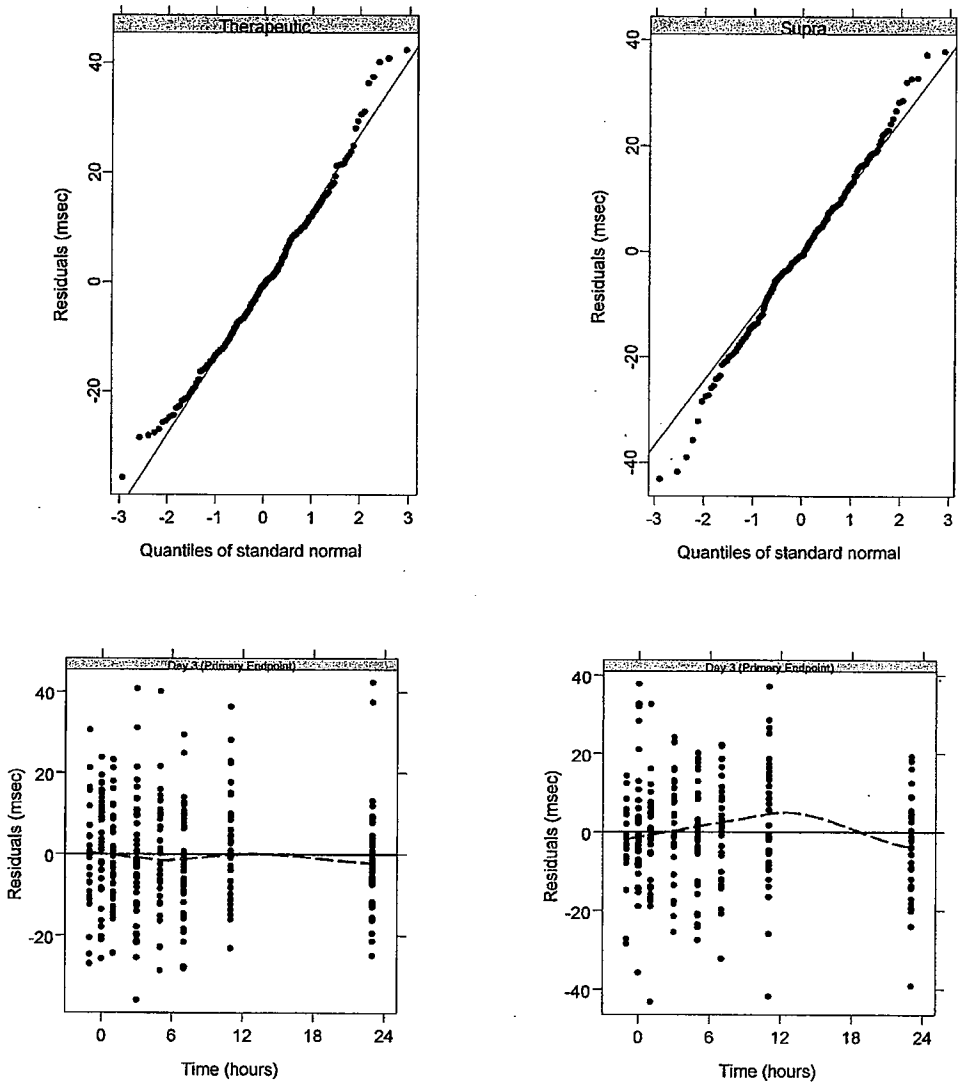


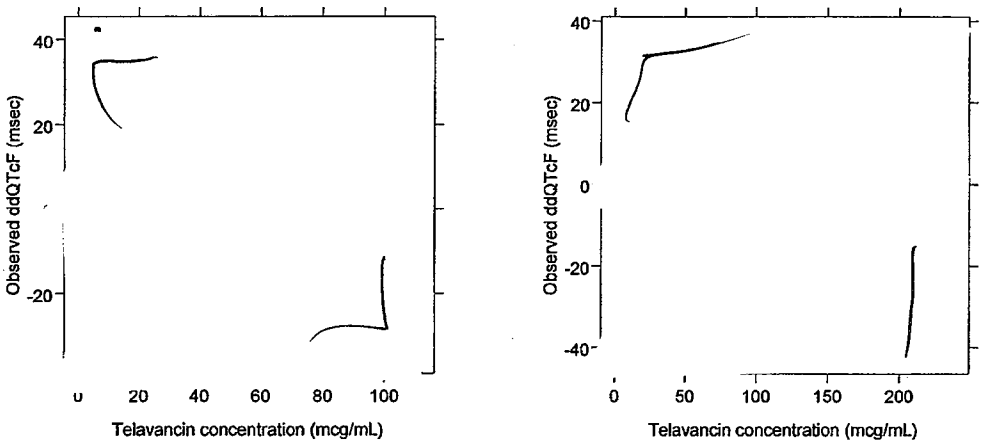
**Figure 7: Goodness-of-Fit Plots for Step-wise Linear Model (Left Panel: Model Developed from 7.5mg/kg Dose Group, Right Panel: Model Developed from 15 mg/kg Dose Group)**




b(4)

**Figure 8: Residual Plots for the Step-wise Linear Model (Left Panel: Model developed from 7.5 mg/kg Dose Group, Right Panel: Model developed from 15 mg/kg Dose Group).**



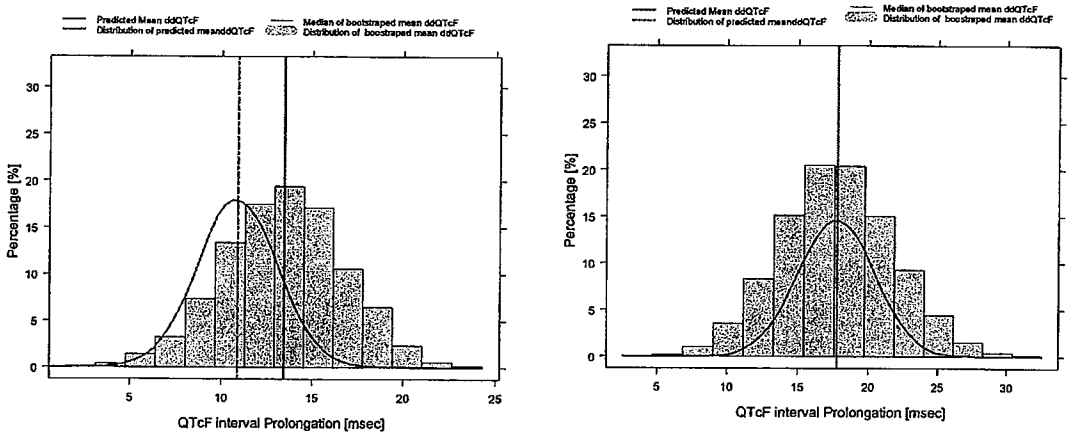



b(4)

**Table 11: Exposure-response Analysis of Telavancin Using Step-wise Linear Model**

| | Estimate (90% CI); p-value | Between-subject variability (SD) |
|---|---|---|
| Model 1 is developed based on the concentration and QT observation from 7.5 mg/kg dose group<br>**Model1: ΔΔQTcF = Intercept + slope*concentration** | | |
| Intercept, msec | 0 | 6.26 |
| Slope, msec per mcg/mL | 0.1246 (0.083, 0.166)<br><0.0001 | 0.040 |
| Residual Variability, msec | 14 | --- |
| Model 2 is developed based on the concentration and QT observation from 15 mg/kg dose group<br>**Model 2: ΔΔQTcF = Intercept + slope*concentration** | | |
| Intercept, msec | 0 | 6.89 |
| Slope, msec per mcg/mL | 0.096 (0.073, 0.120)<br>< 0.0001 | <0.001 |
| Residual Variability, msec | 14.43 | --- |

## Figure 9: Predictive Check for the Step-wise Linear Model.




Note: Distribution form model prediction was obtained using predicted mean and standard error under normality assumption. Distribution for the mean ΔΔQTcF was obtained by bootstrapping the ΔQTcF for treatment group and the placebo group 5,000 times. Then take the mean difference. Note: Left Panel Represents the Predictive Check for 7.5 mg/kg and Right Panel Represents the Predictive Check for 15 mg/kg.

## Table 12: Predicted Change of ΔΔQTcF Interval at Mean Cmax

| Dose Group | Predicted change in ΔΔQTcF interval (msec) Mean | 90% Confidence Interval |
|---|---|---|
| **7.5 mg/kg qd (steady-state)** | | |
| Mean Cmax ( 87.5 μg/ml) | 10.90 | (7.37, 14.42) |
| **10 mg/kg (steady-state)** *1 | | |
| Mean Cmax (121.6 μg/ml) | 15.15 | (10.24, 20.05) |
| 10 mg/kg | | |
| Mean Cmax 121.6 μg/ml) *2 | 11.7 | (8.9, 14.5) |
| **15 mg qd (single dose)** | | |
| Mean Cmax (186.2 μg/ml) | 17.9 | (13.6, 22.1) |

*1: Steady-state mean Cmax 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 Cmax 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.

### Medical Assessments

No adverse events suggestive of torsade de pointes occurred in this study.

# 2 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-* 2

## Table of Study Assessments

| Activities | Pre-Study Screen | Admission (Day 0) | Day 1 | Day 2 | Day 3 | Day 4 | Discharge (Day 5) |
|---|---|---|---|---|---|---|---|
| Explain Study/Sign ICF | X | | | | | | |
| Confinement to Phase 1 Clinic | | X | X | X | X | X | |
| Medical History | X | X[a] | | | | | |
| Vital Signs[b] | X | X | X | X | X | | X |
| Physical Examination | X | | | | | | X |
| Hematology/Serum Chemistry | X | X | | | | X | X |
| Urinalysis | X | X | | | | X | |
| Urine Drug Screen | X | X | | | | | |
| Hepatitis and HIV Screen[c] | X | | | | | | |
| Coagulation Tests[d] | X[i] | | X | X | | | |
| Urine Protein[e] | | | | | X | | |
| Serum Pregnancy Test (females only) | X | X | | | | | |
| D5W Infusion | | X | | | | | |
| Study Medication Administration | | | X | X | X | | |
| Electrocardiogram (12-lead)[f] | X | X | X | X | X | X | |
| Pharmacokinetic Plasma Samples[g] | | X | | | X | X | X |
| Pharmacokinetic Urine Samples[h] | | X | | | X | X | X |
| Adverse Events | | X | X | X | X | X | X |

[a] Medical history updated, if applicable.
[b] Supine systolic and diastolic arterial BP determined by sphygmomanometry, supine HR by palpation, and oral temperature by digital thermometer. Measurements obtained at screening, admission, prior to each infusion, at the end of each infusion, and at discharge from the clinic. Temperature measured at screening and admission only.
[c] Includes hepatitis B (Hbs-Ag), hepatitis C (Hep C Ab), and HIV antibody.
[d] Plasma samples for coagulation tests performed on first and last 40 subjects randomized. Samples obtained prior to and 5 minutes and 23 hours following the end of the Day 1 and Day 3 infusion. Coagulation tests on Day 1 (first 40 subjects) included: PT/aPTT, ACT, WBCT (Lee and White), and bleeding time and on Day 3 (last 40 subjects) included the Stachrom Heparin test, FDP and D-dimer.
[e] A urine aliquot from the 0–6 hour urine collection collected for urine protein assays.
[f] A 12-lead ECG obtained at screening and as follows: Days 0 and 3 (pre-infusion and 16 ECGs at the following time points relative to the end of the 60-minute infusion: immediately post-infusion, and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 15, 17, and 23 hours. Day 1 (immediately post-infusion) and Day 2 (pre-infusion and immediately post-infusion).
[g] Plasma samples for PK analysis collected at admission and on Day 3 pre-infusion and at the following time points, relative to the start of the infusion on Day 3: 30 min, 1, 2, 4, 6, 8, 12, 24, 36, and 48 hours.
[h] Urine samples collected at admission and on Day 3 pre-infusion, and then cumulative collections following the Day 3 infusion at the following times: 0–6 hours, 6–12 hours, 12-24 hours, 24–36 hours and 36–48 hours. All times relative to the start of the study medication infusion.
[i] Plasma for PT/aPTT collected at screening for all subjects.

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/s/

Jeffrey Tworzyanski
10/4/2007 12:46:23 PM
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Charles Bonapace
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BIOPHARMACEUTICS

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