Pharmacokinetics of fixed dose telavancin in obese and non-obese adult subjects

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BACKGROUND

- The pharmacokinetics of telavancin have not been evaluated after administration of weight-stratified fixed doses in obese populations
- Total body weight (TBW)-based dosing of telavancin may not lead to bioequivalent exposure in obese patients compared to non-obese adults[1]
- A fixed dosing approach stratified by TBW is proposed to normalize exposure across the body weight continuum

OBJECTIVE

- To evaluate the single-dose pharmacokinetics of a weight-stratified fixed dose of telavancin in non-obese and obese subjects

STUDY DESIGN

- Phase I single-dose pharmacokinetics study in adult subjects conducted at the Clinical Research Center at the University of Illinois at Chicago (NCT02753855)
- Subjects eligible for enrollment were 18-50 years of age with normal renal and hepatic function and no significant medical comorbidities or potentially interacting medications
- Enrolled 32 subjects based on Body Mass Index (BMI) and TBW according to the scheme:

Table 1: Telavancin Enrollment and Dosing Scheme

Group	Category	BMI (kg/m^2)	TBW (kg)	Telavancin dose (mg)	n
A	Normal-overweight	18.5- 29.9	50- 74.9	500	4
			75- 99.9	750	4
B	Obese class I	30- 34.9	90- 99.9	750	4
			100- 115	1000	4
C	Obese class II	35- 39.9	105- 130	1000	8
D	Obese class III	≥ 40	≥ 120	1000	8

- Subjects in groups A/B were matched to subjects in groups C/D based on gender, age ± 10 years and serum creatinine ± 0.25 mg/dL
- Subjects received a single dose of telavancin as an intravenous infusion over 60 minutes
- Safety assessments included physical examination and laboratory tests (baseline and 48 hours), vital signs and adverse event monitoring

STATISTICAL & PHARMACOKINETIC ANALYSIS

- Plasma and urine samples were collected relative to the start of the intravenous infusion:
  Plasma: 0, 0.5, 0.95, 1.05, 1.25, 1.5, 2, 4, 6, 8, 12, 24, and 48 hours
  Urine: 0, 0-6, 6-12, and 12-24 hours
- Telavancin concentrations were determined by a validated LC/MS-MS method
- Urine creatinine concentrations were determined from an aliquot of the aggregated 24-hour urine volume to calculate measured creatinine clearance
- Noncompartmental analysis with Phoenix WinNonlin v 6.4 (Certara Corp, Princeton NJ) using the linear-up log-down trapezoidal method for area under the curve (AUC)
- Statistical comparisons of continuous data in dichotomous BMI groups with student t-test and Mann Whitney U test, as appropriate. Comparisons of observed and projected AUC by paired t-test within each obesity group.
- The projected $AUC_{0-\infty}$ based on TBW dosing was calculated by scaling the individual subject dose-normalized $AUC_{0-\infty}$ to the weight-based labelled dose

RESULTS

Table 2: Baseline Characteristics of Enrolled Subjects

Characteristic	Group A (n= 8)	Group B (n= 8)	Group C (n= 8)	Group D (n= 8)
Age (years)	30.8 ± 8.2	29.8 ± 9.0	28.5 ± 6.1	36.3 ± 8.5
Gender, male (%)	4 (50)	6 (75)	6 (75)	4 (50)
Total weight (kg)	72.2 ± 12.2	102.4 ± 8.9	110.0 ± 5.9	140.2 ± 9.8
BMI (kg/m^2)	24.4 ± 3.3	33.2 ± 1.4	36.8 ± 1.4	46.2 ± 2.5
$CrCl_{est}$ (mL/min)	91.5 ± 20.5	98.2 ± 18.2	97.7 ± 14.7	90.5 ± 7.9
$CrCl_{meas}$ (mL/min) (24 hour measured)	127.5 ± 16.2	175.9 ± 37.3	165.2 ± 36.0	151.1. ± 28.2

BMI= body mass index, CrCl= creatinine clearance, $CrCl_{est}$ by Cockcroft-Gault formula with ideal weight[2]
Numbers represent mean ± SD

Figure 1: Mean Concentration-time Profiles of Telavancin

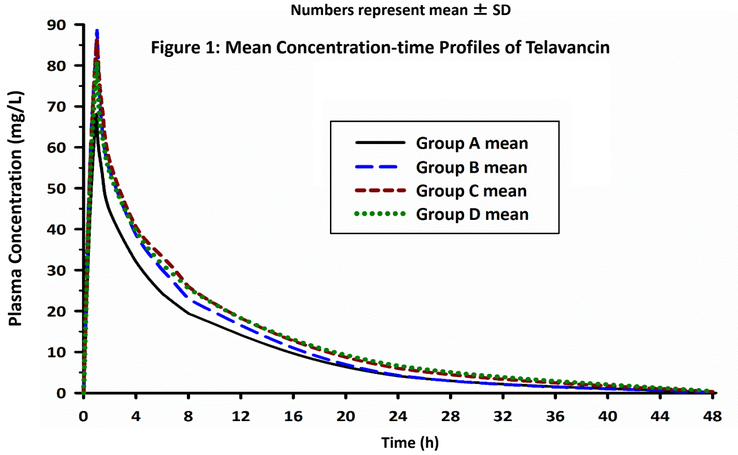


Table 3: Pharmacokinetic Parameters of Telavancin in Subjects < 35 and ≥ 35 kg/m^2

Parameter	Group A & B (BMI < 35 kg/m^2)	Group C & D (BMI ≥ 35 kg/m^2)	*P* value
C_{max} (mg/L)	80.0 ± 19.8	83.2 ± 11.7	0.184
C_{max}/dose (mg/L/mg)	0.110 ± 0.029	0.083 ± 0.012	0.001
$AUC_{0-\infty}$ (mg-h/L)	510.5 ± 80.8	615.5 ± 101.7	0.003
$AUC_{0-\infty}$/dose (mg-h/L/mg)	0.704 ± 0.144	0.616 ± 0.012	0.032
CL (L/h)	1.47 ± 0.25	1.66 ± 0.25	0.032
CL_{renal} (L/h)	1.09 ± 0.18	1.18 ± 0.19	0.218
V_d (L)	12.38 ± 2.17	15.65 ± 2.42	< 0.001
$t_{1/2}$ (h)	5.96 ± 0.54	6.53 ± 0.87	0.035

C_{max}= maximum concentration, AUC= area under the concentration-time curve, CL= clearance, V_d= volume of distribution, $t_{1/2}$ = elimination half-life; numbers represent mean ± SD

Figure 2: Observed Telavancin AUC by Study Group and Dose

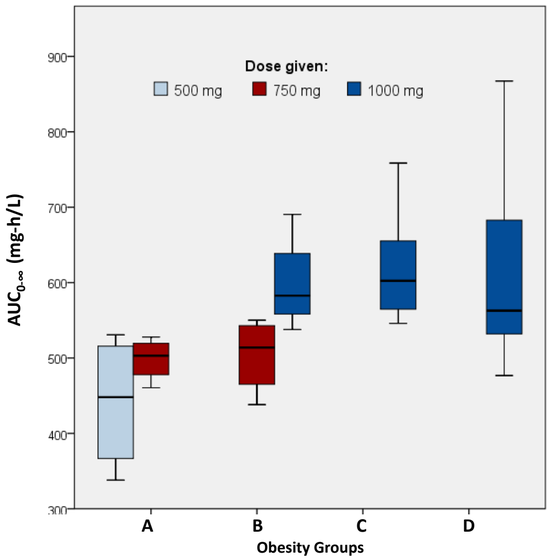
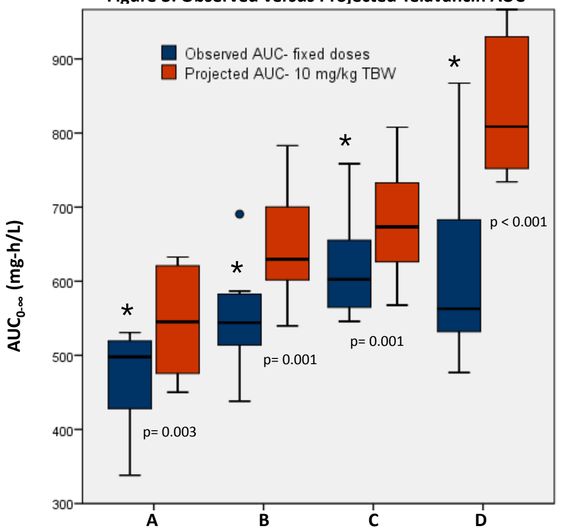


Figure 3: Observed versus Projected Telavancin AUC



* Statistically significant difference between observed and projected AUC
Dot represents individual subject outlier

DISCUSSION

- Volume of distribution and total clearance of telavancin were higher in obese class II-III subjects than those with a lower BMI and TBW.
- Linear projections of the $AUC_{0-\infty}$ indicate that TBW-based dosing could lead to supratherapeutic exposure in obese patients, particularly those above 120 kg, relative to normal weight patients.
- $AUC_{0-\infty}$ in group A subjects administered 500 mg was lower than previously reported values in volunteers who received 10 mg/kg, suggesting that the 500 mg fixed dose may not be optimal for the entire 50-74.9 kg TBW range.[3]

CONCLUSIONS

- Alternatives to TBW-based dosing strategies of telavancin appear to be needed in obese patients
- A fixed dosing scheme with a maximum dose of 1000 mg in this study led to more uniform pharmacokinetic exposure across the weight continuum than would be expected with TBW-based dosing.

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