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

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Background: Total body weight (TBW)-based dosing of telavancin may lead to higher exposure in obese compared to non-obese adults. A fixed-dosing approach stratified by TBW has the potential to normalize exposure across the body weight continuum. The objective of this study was to evaluate the single-dose pharmacokinetics of telavancin in obese and non-obese subjects who received a TBW-stratified fixed dose.

Materials/methods: This was an open-label pharmacokinetic study in healthy adult subjects (NCT02753855). Subjects were classified into groups (n= 8) based on both body mass index (BMI) and TBW to avoid potential height-related misclassification of obesity as described in Figure 1: (A) normal-overweight, (B) obese class I, (C) obese class II, (D) obese class III. Subjects from groups A and B were matched to subjects from groups C and D by age ± 10 years, gender, and serum creatinine ± 0.25 mg/dL. Telavancin was administered as a 60-minute infusion according to the dosing scheme: 500 mg for 50-74.9 kg (Group A1), 750 mg for 75-99.9 kg (Groups A2 and B1), and 1000 mg for ≥ 100 kg (Groups B2, C, and D). Plasma concentrations were assessed at 0, 0.5, 0.95, 1.05, 1.25, 1.5, 2, 4, 6, 8, 12, 24, and 48 hours after the start of infusion via a validated LC/MS-MS method. Pharmacokinetic parameters were determined by noncompartmental analysis. Statistical comparisons of continuous data between matched groups were conducted with student t-test and Mann Whitney U-

test as appropriate. The predicted $AUC_{0-\infty}$ for the approved 10 mg/kg dosing regimen was calculated for each subject by linear transformation of individual subject dose-normalized $AUC_{0-\infty}$ for comparison.

Results: The 32 subjects had a mean (range) age 31.3 (20-49) years, weight 106.2 (56.9-154) kg, BMI 35.1 (20.2-51.5) kg/m^2, and calculated creatinine clearance (Cockcroft-Gault with ideal body weight) 94.5 (69.2-132.4) mL/min. With fixed dosing, there was a 20.5% increase in arithmetic mean $AUC_{0-\infty}$ in groups C/D (615.5 vs 510.5 mg•h/L, p= 0.003), 26.4% increase in mean volume of distribution (15.65 vs 12.38 L, p < 0.001), and a 13% increase in mean clearance (1.662 vs 1.467 L/h, p= 0.032) compared to groups A/B. The observed $AUC_{0-\infty}$ with a fixed dosing scheme was lower than predicted with TBW-based dosing, particularly among obese class III subjects (Figure 1).

Conclusions: Telavancin mean volume of distribution and clearance are marginally higher in obese class II/III subjects compared to non-obese and obese class I subjects. A stratified fixed telavancin dosing regimen may lead to more uniform pharmacokinetic exposure in obese patients compared to TBW-based dosing.