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Population Pharmacokinetics of Telavancin in Healthy Subjects and Patients with Infections

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A population pharmacokinetic model of telavancin, a lipoglycopeptide antibiotic, was developed and used to identify sources of interindividual variability. Data were obtained from healthy subjects (seven phase 1 studies), patients with complicated skin and skin structure infections (cSSSI; two phase 2 and two phase 3 studies), and patients with hospital-acquired pneumonia (HAP; two phase 3 studies). A two-compartment open model with zero-order input best fit the telavancin data from healthy individuals and patients with cSSSI or HAP. Telavancin clearance was highly correlated with renal function and, to a lesser extent, with body weight. Other covariates were related to at least one parameter in cSSSI (gender, bacterial eradication, and surgery) or HAP (age of ≥75 years) but did not markedly affect exposure. These analyses support current dosing recommendations for telavancin based on patient weight and renal function.

Telavancin is a bactericidal lipoglycopeptide antibiotic with activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) (12, 13). The antibacterial activity of telavancin results from a dual mechanism of action consisting of inhibition of bacterial cell wall synthesis and disruption of the bacterial membrane barrier function (11, 16). In the United States and Canada, telavancin is indicated for the treatment of adult patients with complicated skin and skin structure infections (cSSSI) due to susceptible Gram-positive pathogens, and in Europe, it is indicated for the treatment of nosocomial pneumonia, including ventilator-associated pneumonia, that is known or suspected to be caused by MRSA (1, 17, 20).

Pharmacokinetic (PK) and pharmacodynamic (PD) data for telavancin have been generated from several preclinical and clinical studies. For example, studies in mice have demonstrated that the 24-h area under the plasma concentration-time curve/MIC (AUC_{24}/MIC) ratio is the best predictor of telavancin efficacy (10). In the neutropenic mouse-thigh model, an AUC_{24}/MIC ratio of 219 resulted in a 1-$\log_{10}$ reduction in CFU/g against a MRSA strain with a MIC of 1 μg/ml (14). Studies in healthy volunteers have demonstrated that the PK of telavancin is linear at doses ranging between 0.25 mg/kg of body weight and 15 mg/kg (18, 24) and that telavancin is mostly excreted without metabolism via renal elimination (25). AUC values have been shown to increase with progressive renal impairment (6), and current product labeling indicates that the dosage, which is based on the patient's body weight, should be adjusted according to creatinine clearance (CL_{CR}) (1). The noncompartmental estimate of clearance from studies in healthy subjects is approximately 12 to 13 ml/h/kg or 0.9 to 1 liter/h in average-size adults (18, 24). The disposition of telavancin does not appear to be affected substantially by age, gender, or the presence of moderate hepatic impairment (7, 8, 24).

The objective of these analyses was to develop a population PK model of telavancin in healthy subjects and patients with cSSSI or hospital-acquired pneumonia (HAP) and to identify sources of interindividual variability in the PK of telavancin.

(Parts of these analyses were presented previously at the 47th ICAAC in Chicago, IL [2007], and the 20th annual ECCMID in Vienna, Austria [2010].)

MATERIALS AND METHODS

Subjects. All telavancin plasma concentration-time data were obtained from adult subjects including 236 subjects enrolled in seven phase 1 studies (2, 6–9, 18, 22, 24), 513 patients with cSSSI in two phase 2 (19, 21) and two phase 3 (20) studies, and 197 patients with HAP in two phase 3 studies (17). The phase 1 trials included healthy adults (including elderly subjects, ≥65 years of age), subjects with various degrees of renal function, and subjects with moderately impaired hepatic function. The phase 2 and 3 clinical trials were multicenter, randomized, active-controlled, parallel-group, multinational studies that included adult patients with various degrees of renal function and mild-moderate hepatic impairment. These patients also had a wide variety of underlying illnesses and were receiving multiple medications (17, 19–21).

Dosing and sampling procedures. Volunteers participating in phase 1 trials received single or multiple doses of telavancin at 0.25 mg/kg to 15 mg/kg administered once daily (q24h) by intravenous (i.v.) infusion over 30, 60, or 120 min. Rich sampling was employed at intervals up to 3 days following infusion.

Patients participating in phase 2 and 3 trials were randomized to receive telavancin at 7.5 (phase 2 only) or 10 (phase 2 and 3) mg/kg q24h administered over 60 min. In patients randomized to receive 10 mg/kg q24h, the dosage of telavancin was adjusted in those with moderate renal impairment (CL_{CR} of 30 to 50 ml/min; 7.5 mg/kg q24h) or severe renal impairment (CL_{CR} of <30 ml/min; 10 mg/kg q48h). Up to seven plasma samples were collected from each patient, including peak and trough samples.

Telavancin assay. Plasma concentrations of telavancin were determined using fully validated techniques employing liquid chromatography with tandem mass spectrometric detection. Calibration curves for telavancin in human plasma ranged from 0.25 μg/ml to 100 μg/ml. The lower

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TABLE 1 List of demographics, baseline characteristics, and other selected covariates used in the population pharmacokinetic analysis of telavancin[a]

Parameter	Study				
	Phase 1, no infection	Phase 2, cSSSI	Phase 3, cSSSI	Combined phase 2 and phase 3, cSSSI	Phase 3, HAP
n (male, female)	236 (173, 63)	130 (72, 58)	383 (218, 165)		197 (123, 74)
No. of patients by race: W, B, H	189, 20, 22	64, 33, 0	306, 65, 4		172, 3, 0
No. of studies	7	2	2		2
Body wt, kg, median (range)	75.8 (45.40–119.8)	78.3 (44.0–167.7)	78.0 (38.6–314.0)		71.0 (33.6–171.2)
CL_{CR}, ml/min,[b] median (range)	112.8 (6.3–150.0)	100.3 (28.6–150.0)	105.6 (17.6–150.0)		71.0 (3.0–150.0)
Age, yrs, median (range)	28.0 (18.0–83.0)	44.1 (19.6–89.4)	44.0 (18.0–89.0)		67.0 (20–100)
Ht, cm, median (range)	174.8 (147.3–203.0)	170.0 (142.0–193.0)	170.2 (139.7–200.7)		169.6 (121.9–195.0)
Diabetes: 0, 1[c]	ND			414, 98	146, 51
Peripheral vascular disease: 0, 1[c]	ND			502, 11	187, 10
Infection: 0, 1, 2, 3, 4[d]	ND			293, 70, 132, 12, 6	ND
Surgery: 0, 1[c]	ND			322, 191	ND
Eradication: 0, 1, −1[e]	ND			53, 312, 122	25, 89, 83
Cure: 0, 1, 2[f]	ND			48, 434, 31	28, 128, 16
Metronidazole: 0, 1[c]	ND			290, 223	141, 56
Aztreonam: 0, 1[c]	ND			250, 263	73, 124
Narcotics: 0, 1[c]	ND			182, 331	143, 54
NSAID: 0, 1[c]	ND			359, 154	138, 59
Furosemide: 0, 1[c]	ND			467, 46	90, 107
Propofol: 0, 1[c]	ND			427, 86	160, 37

[a] Abbreviations: cSSSI, complicated skin and skin structure infections; HAP, hospital-acquired pneumonia; ND, not determined; NSAID, nonsteroidal anti-inflammatory drug; W, white; B, black; H, Hispanic.
[b] CL_{CR}, creatinine clearance, calculated using the Cockcroft and Gault equation (values > 150 ml/min were fixed to 150).
[c] 0, variable is not present; 1, variable is present.
[d] 0, major abscess; 1, wound infection; 2, deep/extensive cellulitis; 3, infected ulcer; 4, infected burn.
[e] 0, not eradicated; 1, eradicated; −1, missing.
[f] 0, not cured; 1, cured; 2, missing/undetermined.

limit of quantitation for telavancin in human plasma was defined as 0.25 μg/ml. Overall precision for the calibration standards and quality control samples, as measured by percent relative standard deviation, was always within 15%. All plasma concentrations below the limit of quantitation were removed from the population analysis.

Pharmacokinetic analysis. Population PK models were built using a nonlinear mixed-effect modeling approach using either first-order (cSSSI) or first-order conditional (HAP; without interaction) maximum likelihood estimation in the NONMEM program (double precision, version V, level 1.1; Icon, Ellicott City, MD) and NM-TRAN preprocessor (4). Data from the phase 1 studies were used for initial base model selection and preliminary covariate analysis. The resulting model was further developed using two separate data sets obtained by combining phase 1 data with PK data from patients with cSSSI or with HAP.

Base model selection. The PK mixed-effect model has two components: (i) a structural model that characterizes the concentration-time relationship and (ii) random-effect models, including interindividual variability in the PK parameters, and residual error, including intraindividual variability and measurement errors. One- and 2-compartment structural models with first-order elimination were fitted to the plasma concentration-time data.

An exponential interindividual variability error term, which assumes a log-normal distribution, was included on all the PK parameters in the model (equation 1), such that

$$P_i = P\exp(\eta_i^P) \quad (1)$$

where P_i is the true parameter value for individual i, P is the typical value (population mean) of the parameter, and η_i^P is the difference between the true value for individual i and the typical value for the population, with a mean of 0 and a variance of ω^2.

Additive, proportional, and combined additive and proportional error models were evaluated to estimate the residual variability. The combined additive and proportional error model is described in equation 2:

$$C_{ij} = C_{ij} \times (1 + \in_{1ij}) + \in_{2ij} \quad (2)$$

where C_{ij} is the jth measured observation (plasma concentration) for individual i, $\hat{C}_{ij}$ is the jth model predicted value (plasma concentration) for individual i, ε_{1ij} is the proportional residual error for the jth measurement for individual i and is normally distributed with a mean of 0 and a variance of σ_1^2, and ε_{2ij} is the additive residual error for the jth measurement for individual i and is normally distributed with a mean of 0 and a variance of σ_2^2. Assumptions about the base population model (1- versus 2-compartment and residual variability) were evaluated based on the objective function value, agreement between observed and predicted telavancin concentrations, and visual inspection of the distribution of the weighted residual plots.

Covariate analysis and final model selection. After selecting the base model, possible relationships between individual estimates of the PK parameters (obtained by Bayesian methodology) and covariates were explored graphically using the generalized linear models in S-PLUS. Covariates that were evaluated for the different data sets are listed in Table 1 and also Table S1 in the supplemental material.

These variables, selected as potentially influencing drug exposure, included demographics (e.g., age, sex, body weight, body mass index [BMI], and race), clinical covariates (disease outcome and underlying disease), blood and urine chemistry variables, and markers of renal function (CL_{CR} and serum creatinine). Creatinine clearance was estimated using the Cockcroft-Gault equation (5): $CL_{CR} = \{[(140 - \text{Age}) \times \text{WT}]/S_{CR}\} \times x$, where CL_{CR} is creatinine clearance (ml/min), Age = age in years, WT is actual body weight (kg), S_{CR} is serum creatinine (mg/dl), and $x = 1$ for males and 0.85 for females.

Additive models were used to include continuous covariates, whereas categorical covariates such as gender were incorporated as a power model as shown in equations 3 and 4, respectively:

$$P = \theta_1 + \theta_2 \times \text{COV} \quad (3)$$

TABLE 2 Population pharmacokinetic models of telavancin[e]

Pharmacokinetic parameter	No infection[a]	cSSSI[b]	HAP[b]
CL, liters/h	$0.68 + 0.00251 \times CL_{CR}$	$[0.286 + 0.00456 \times CL_{CR} + 0.0039 \times WT] \times GEND^{c} + 0.0847 \times ERAD$	$0.524 + 0.00238 \times CL_{CR} + 0.00317 \times WT$
V_1, liters	$2.17\text{-}0.0229 \times CL_{CR} + 0.0638 \times WT$	$1.64\text{-}0.0336 \times CL_{CR} + 0.0858 \times WT + 1.34 \times SURG$	$4.28\text{-}0.031 \times CL_{CR} + 0.0569 \times WT$
Q, liters/h	$3.6 + 0.0136 \times CL_{CR}$	$2.58 + 0.0419 \times CL_{CR}$	5.16
V_2, liters	$1.87\text{-}0.00514 \times CL_{CR} + 0.0514 \times WT$	$2.85 + 0.0498 \times WT$	$[1.35 + 0.0752 \times WT\text{–}0.0129 \times CL_{CR}] \times AGE^{d}$

[a] Phase 1 base model.
[b] Final population models.
[c] GEND = 1 for males, 0.907 for females.
[d] AGE = 1 for patients of ≥75 years of age, 1.41 for patients of <75 years of age.
[e] Abbreviations: AGE, patient age; CL, telavancin clearance; CL_{CR}, creatinine clearance; cSSSI, complicated skin and skin structure infections; ERAD, bacterial eradication; GEND, patient gender; HAP, hospital-acquired pneumonia; Q, intercompartment clearance; SURG, surgery; V_1, central compartment volume; V_2, peripheral compartment volume; WT, body weight; Y, additional covariate.

where P is the individual estimate of the parameter, θ_1 is the typical value of the parameter, θ_2 is the slope of the effect of the covariate on the parameter, and COV is the value of the covariate.

$$P = \theta_1 \times \theta_2^{IND} \quad (4)$$

where P is the individual estimate of the parameter, θ_1 is the typical value of the parameter when IND = 0, θ_2 is the effect of the covariate (IND = 1), and IND is an indicator variable, with a value of 0 or 1.

In cases where two covariates were significantly correlated with each other (such as body weight and height or CL_{CR} and serum creatinine), each covariate was evaluated separately for its influence on the PK parameters and only the more clinically relevant covariate was included in the final NONMEM model. Initially, age was to be included as a continuous variable in the model. However, a strong correlation between estimated CL_{CR} and age, but not body weight, was observed. Therefore, age was included as a categorical variable. Differences between subjects 65 years or older and subjects younger than 65 years of age were evaluated in the model. Similarly, an age cutoff of 75 years was also modeled.

A three-step approach was used to obtain the final population model. In the first step of the analysis, the statistical significance of each covariate-parameter relationship was screened individually in NONMEM. In the second step, significant covariates were added to the model in a stepwise fashion and their significance was tested. Hypothesis testing to discriminate among alternative hierarchical models was performed using the likelihood ratio test (α, $P = 0.05$). In the third step, a stepwise univariate deletion of covariates from the model (backward elimination) was performed. Only significant (α, $P = 0.001$) parameters were retained in the final model.

Model validation. The ability of the final population model to describe the observed data was investigated using bootstrap sampling technique and posterior predictive check using Monte Carlo simulation. For the bootstrap method, a total of about 200 resampling replicates were obtained from the original data set. The final population pharmacokinetic model, including final fixed-effect parameters and random-effect parameters (interindividual variability and residual error), was used to fit the replicates using the bootstrap option in the software package Wings for NONMEM (N. Holford, Auckland, New Zealand), and parameter estimates for each of the replicate data sets were obtained. The average values obtained using bootstrapping were compared with the parameter estimates from the final model. For the posterior predictive check, the final population pharmacokinetic model, including final fixed-effect parameters and random-effect parameters (interindividual variability and residual error), was used to generate 434 simulated data sets. The corresponding model parameters from the simulated data were compared with the parameter estimates of the data sets used for the final model building. Assuming that the model adequately describes the data, the pharmacokinetic parameters derived from either bootstrapping or the simulated data should be within the 5th and 95th percentiles of the parameter estimates using the observed data.

RESULTS

Data sets. The final data set for analysis for the cSSSI population PK model included 5,237 observations from 749 subjects (513 patients with cSSSI and 236 subjects without infection). The final data set for the HAP model included 3,675 observations from 433 subjects (197 patients with HAP and 236 subjects without infection). Demographics, baseline characteristics, and other selected covariates of the subjects are shown in Table 1. Most subjects in all studies were white. Subjects without infection had the highest median body weight and baseline CL_{CR} values and lowest median age, whereas patients with HAP had the lowest median body weight and CL_{CR} values and highest median age.

Telavancin base population pharmacokinetic model. Plasma telavancin concentration-time data from phase 1 to 3 studies were adequately described by a two-compartment open model with first-order elimination. The base model consisted of four parameters: telavancin clearance (CL), volume of the central compartment (V_1), intercompartment clearance (Q), and volume of the peripheral compartment (V_2). CL was mainly influenced by renal function, and telavancin distribution was linearly correlated with body weight (Table 2).

Population PK parameters were estimated with good precision for both the cSSSI and the HAP data sets, as shown by percent relative standard errors (RSE) of 12% or less (Table 3). Values for CL and V_1 from the phase 1 base model were consistent with estimates from noncompartmental analyses (0.944 liter/h and 4.51 liters, respectively). Interindividual variability in the PK parameters ranged from 32% to 67%. All estimates of interindividual variability were associated with a precision RSE ranging from 11% to 52%.

Covariate analysis and final model evaluation. As in the phase 1 base model, the final models for cSSSI and HAP included renal function and body weight as significant influences on CL and telavancin distribution (Table 2). Both CL and V increased with increased body weight. Further, telavancin CL decreased and V increased as the renal clearance decreased, as evidenced in subjects with renal impairment (Table 4).

In the final model for cSSSI, gender and bacterial eradication were also significant covariates, as CL was approximately 10% higher in male patients than in female patients and was ≤10%

TABLE 3 Base model population estimated pharmacokinetic parameters[a]

Parameter	Value for data set			
	cSSSI		HAP	
Pharmacokinetic	Population value (% RSE)	Interindividual CV (% RSE)	Population value (% RSE)	Interindividual CV (% RSE)
CL (liters/h)	1.06 (3.3)	32 (11)	0.928 (2.5)	39 (24)
V_1 (liters)	5.01 (5.7)	48 (15)	5.00 (4.3)	44 (17)
Q (liters/h)	6.07 (12.1)	58 (52)	5.10 (5.3)	67 (28)
V_2 (liters)	6.63 (4.7)	42 (25)	7.38 (5.6)	64 (21)
Residual error	Estimate (% RSE)	Intraindividual error	Estimate (% RSE)	Intraindividual error
Additive	4.24 (65)	2.06 μg/ml	0.745 (66)	0.863 μg/ml
Proportional	0.019 (21)	14% CV	0.0107 (22)	10% CV

[a] Abbreviations: CL, telavancin clearance; cSSSI, complicated skin and skin structure infections; CV, coefficient of variation = (standard deviation/mean) × 100; HAP, hospital-acquired pneumonia; Q, intercompartment clearance; RSE, relative standard error; V_1, central compartment volume; V_2, peripheral compartment volume.

higher in patients in whom bacterial eradication was achieved. Surgery was also a significant source of interindividual variability in V_1 (Table 2). The average AUC_{24} calculated for subjects of ≥75 years of age ($n = 29$) was about 11% higher than that for patients of <75 years (780 ± 307 versus 698 ± 285 mg · h/liter, respectively). This was most likely attributable to the relationship between age and CL_{CR}. Despite a 50% increase in dose in obese patients (defined as subjects with a BMI of ≥35), the median telavancin AUC_{24} values were only about 34% higher in obese than in nonobese patients (838.0 [$n = 89$] versus 627.4 mg · h/liter [$n = 660$], respectively) and the median CL values were approximately 24% higher (1.34 [$n = 88$] versus 1.08 liter/h [$n = 660$], respectively).

In the final model for HAP, intercompartment clearance was independent of any covariate, but age was a significant covariate for V_2 (Table 2). The average AUC_{24} in patients of ≥75 years of age was only 6% lower than that in patients younger than 75 years (729 ± 318 [$n = 69$] versus 773 ± 397 mg · h/liter [$n = 364$], respectively).

With regard to body weight, as in the cSSSI population, despite a 55% increase in dose in obese over that in nonobese patients, the median AUC increased by only about 18% (810.1 [$n = 25$] versus 685.2 mg · h/liter [$n = 408$], respectively) and the median CL was about 27% higher (1.23 [$n = 25$] versus 0.97 liter/h [$n = 408$], respectively).

Diagnostic plots (Fig. 1) showed a good fit of the final models to telavancin plasma concentrations. No bias was observed among the different study phases. In addition, parameter estimates from the population estimates were similar to those obtained with Monte Carlo simulation and bootstrap replicates (Table 5).

TABLE 4 Summary statistics with selected demographic variables (final model) of estimated pharmacokinetic parameters in patients with complicated skin and skin structure infections or hospital-acquired pneumonia according to status of renal function[a]

Population and degree of renal impairment (n)[b]	Mean (SD)			
	CL (liters/h)	V_1 (liters)	V_{SS} (liters)	CL_{CR} (ml/min)
cSSSI				
Severe (16)	0.59 (0.15)	8.62 (4.02)	14.89 (4.44)	17.40 (7.07)
Moderate (36)	0.82 (0.23)	7.57 (2.53)	14.17 (3.45)	41.28 (5.34)
Mild (122)	1.00 (0.24)	6.43 (2.81)	13.06 (3.95)	67.54 (8.79)
None (575)	1.22 (0.32)	5.28 (2.41)	11.87 (3.47)	117.27 (19.86)
HAP				
Severe (26)	0.64 (0.22)	8.19 (2.53)	15.64 (3.76)	17.73 (7.49)
Moderate (48)	0.91 (0.24)	6.77 (2.11)	13.68 (3.61)	39.63 (5.89)
Mild (88)	1.03 (0.26)	7.17 (4.07)	14.11 (5.23)	64.92 (8.25)
None (271)	1.10 (0.35)	5.74 (5.70)	11.47 (6.78)	118.25 (20.15)

[a] Abbreviations: CL, telavancin clearance; CL_{CR}, creatinine clearance; cSSSI, complicated skin and skin structure infections; HAP, hospital-acquired pneumonia; V_1, central compartment volume; V_{SS}, steady-state volume.

[b] Degree of renal impairment was classified as follows: severe, CL_{CR} of <30 ml/min and including patients on dialysis; moderate, CL_{CR} of <50 ml/min to ≥30 ml/min; mild, CL_{CR} of <80 ml/min to ≥50 ml/min; none, CL_{CR} of ≥80 ml/min.

DISCUSSION

This is the first report describing the population PK of telavancin in distinct populations, including subjects without infection, patients with cSSSI, and patients with HAP. A two-compartment open model was adequate to fit the plasma concentration-time data from either combined phase 1, 2, and 3 (cSSSI) or phase 1 and 3 (HAP) studies and proved useful to evaluate the potential contribution of covariates to differences between individuals in PK parameters.

Given the differences between demographics and baseline characteristics of the cSSSI and HAP patient populations, separate analyses were conducted to control for possible differences in the PK of telavancin. The population model was generally consistent across the two patient populations with some subtle differences, perhaps due in part to differences in the disease characteristics. The population model estimates of CL (0.93 to 1.1 liter/h) for patients with cSSSI and HAP, respectively, are virtually identical to the model-independent estimates derived from studies in healthy subjects (18, 24). Given that telavancin is cleared mainly by renal elimination (24), it may not be surprising that telavancin CL was influenced primarily by renal function. Telavancin CL decreased in parallel with CL_{CR}. Although values were comparable in subjects with normal renal function (CL_{CR} of >80 ml/min) and subjects with mild renal dysfunction (50 < CL_{CR} <80 ml/min), the average telavancin CL in subjects with moderate and severe renal impairment was 15 to 30% and 35 to 50% lower, respectively. The reduction in telavancin CL in subjects with moderate and severe renal impairment supports current dosing recommendations in the approved product labeling based on renal function (1). This conclusion was further supported by Monte Carlo simulation conducted across various categories of renal dysfunction (15). The AUC_{24}/MIC ratio was maintained above the PD target

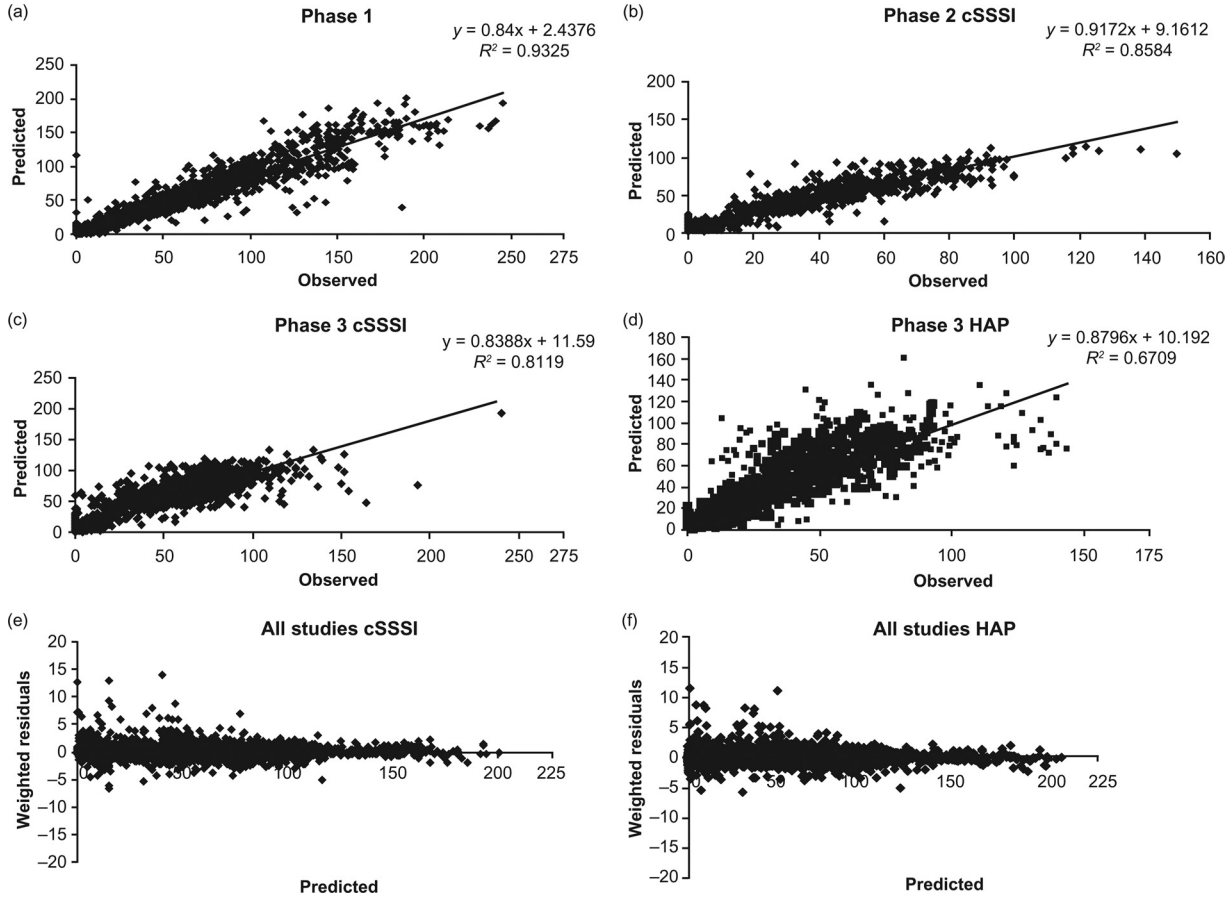

FIG 1 Population predicted versus observed plasma concentrations of telavancin for pharmacokinetic final model in subjects without infection from phase 1 studies (a); patients with cSSSI from phase 2 (b) and phase 3 (c) studies; patients with HAP from phase 3 studies (d); and weighted residuals versus predicted telavancin plasma concentrations for all cSSSI studies (e) and HAP studies (f).

of 219 for susceptible organisms throughout the dosing interval in more than 90% of the patients, regardless of their renal function.

The volume of distribution was inversely proportional to CL_{CR}, suggesting that subjects with impaired renal function have a higher volume of distribution. Impaired renal function is often associated with edema and water retention, resulting in an increase in extracellular fluid and hence an increase in telavancin volume of distribution.

Body weight was a significant factor influencing telavancin volume of distribution in all populations. Telavancin is distributed by diffusion into the extracellular fluids, the volume of which increases with body weight (3, 23); thus, the estimated increases in the volume of distribution of telavancin with increased body weight are consistent with the physicochemical properties of telavancin and the physiological effects of weight.

The linear relationship between body weight and telavancin CL

TABLE 5 Final estimates for the population pharmacokinetic parameters from the NONMEM model, Monte Carlo simulation, and 201 bootstrap replicates[a]

	cSSSI						HAP					
	NONMEM model		Monte Carlo simulation		Bootstrap replicates		NONMEM model		Monte Carlo simulation		Bootstrap replicates	
Parameter	Estimate	SE	Estimate	SE	Mean	95% PI[b]	Estimate	SE	Estimate	SE	Mean	95% PI[b]
CL, liters/h	0.286	0.104	0.304	0.063	0.275	0.084–0.467	0.524	0.153	0.659	0.113	0.493	0.285–0.700
V_1, liters	1.64	1.04	1.11	0.718	1.51	−0.350–3.38	4.28	1.40	5.02	0.110	3.28	1.34–5.21
Q, liters/h	2.58	0.965	2.91	0.409	3.46	1.104–5.808	5.16	0.447	5.31	0.247	5.12	4.20–6.04
V_2, liters	2.85	0.922	2.60	0.818	2.42	0.648–4.20	1.35	1.01	1.40	0.627	1.43	−0.38–3.23

[a] Abbreviations: CL, telavancin clearance; cSSSI, complicated skin and skin structure infections; HAP, hospital-acquired pneumonia; PI, prediction interval; Q, intercompartment clearance; SE, standard error; V_1, central compartment volume; V_2, peripheral compartment volume.

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

supports telavancin dosing on a mg/kg basis. This relationship was explored further by comparing obese and nonobese patients. The increases in absolute doses in obese patients over those in nonobese patients were accompanied by only modest increases in both telavancin CL and exposure. Telavancin CL might also be affected by gender, as a slightly higher clearance was observed in male subjects independent of body weight and renal function, although this difference was statistically significant only in the cSSSI analysis. However, the magnitude of this gender influence was small (~10%), and therefore, it was unlikely to be of any clinical relevance.

No age-related differences were observed for telavancin CL and volume of distribution of the central compartment. A significant effect of age was observed in the peripheral volume of distribution in the HAP analysis. However, this effect did not result in any significant differences in the systemic exposure of telavancin and was therefore considered clinically irrelevant. As expected, patients with HAP had a much higher mean age than did those with cSSSI or those without infection. This may explain these slight differences between the two patient populations.

None of the disease-specific covariates were significant in the HAP population. However, in patients with cSSSI, telavancin CL was higher in patients achieving bacterial eradication, and the central compartment volume of distribution increased in patients who underwent surgery. The greater extent of bacterial eradication in patients with higher clearance values (lower exposure) is unexpected. Likewise, the effect of surgery is not easily interpreted, especially because the timing of the surgery with respect to the PK sampling (before or after sampling) is not known in all cases. Due to the small differences observed (<10%), these covariates should be of little clinical consequence, and the observed effect is likely confounded by other factors.

The possibility of drug interactions as covariates was also explored, but that could not be ascertained using the population approach for the following reasons: (i) concomitant medications were present only in patients from phase 2 and 3 studies and, therefore, any estimated interactions might be confounded with other, possibly unmonitored, patient-related differences; (ii) the substantial overlap between patients receiving different combinations of the concomitant medications precluded any meaningful assessment of specific interactions, if any; and (iii) significant correlations were observed between patients receiving certain drugs and other tested covariates (e.g., use of propofol in patients having surgery and furosemide use in patients with renal impairment).

In conclusion, the results from these population PK analyses demonstrate the similarity of the PK of telavancin in the three populations and the consistency with the noncompartmental analysis results obtained in phase 1 studies. The analyses support the dose adjustment based on renal function implemented in phase 3 studies and included in dosing recommendations in the approved product labeling (1).

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