Population Pharmacokinetic Analysis of Dalbavancin, a Novel Lipoglycopeptide

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Dalbavancin is a lipoglycopeptide antibiotic in clinical development as a once-weekly treatment for serious infections. A total of 532 patients, consisting of 502 patients with skin and soft tissue infections requiring parenteral therapy and 30 patients with catheter-related bloodstream infections, was available for population pharmacokinetic analysis. The majority of patients (78.4%) received dalbavancin intravenously as a 1000-mg dose on day 1 and a single 500-mg dose on day 8. A 2-compartment model with first-order elimination provided the best fit to the data. The clearance of dalbavancin was influenced by body surface area and creatinine clearance, but together they described less than 25% of the interpatient variability. Body surface area was determined to be a predictor of the central volume of distribution. There was no evidence that the presence of metabolic substrates, inhibitors, or inducers of cytochrome P450 or selected concomitant medications influenced the clearance of dalbavancin.

Keywords: *Dalbavancin; population pharmacokinetics; lipoglycopeptide*

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Dalbavancin is a novel lipoglycopeptide antibiotic in late-stage clinical development for the treatment of serious infections, including skin and skin structure infections. Dalbavancin's method of action, like that of other glycopeptides, is the inhibition of cell wall peptidoglycan cross-linking by binding to the terminal of the D-alanyl-D-alaine pentapeptide chain in nascent peptidoglycan.[1] It has excellent in vitro activity against a broad range of gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and is generally more active than vancomycin.[2,3] Dalbavancin's minimum inhibitory concentration (MIC) values for staphylococci, including *S aureus* and coagulase-negative staphylococci of various species, range from ≤0.015 to 0.5 mg/L (MIC_{90} = 0.06 mg/L); dalbavancin MIC values for streptococci range from ≤0.015 to 0.25 mg/L (MIC_{90} = 0.03 mg/L).[2,4,5]

From Vicuron Pharmaceuticals, King of Prussia, Pennsylvania. Some of the data presented in this manuscript were presented as a poster at the 15th European Congress on Clinical Microbiology and Infectious Diseases (Abstract 1578), Copenhagen, April 2005. Online clinical study sites can be accessed from http://jcp.sagepub.com/cgi/content/full/45/11/1279/DC1/. Submitted for publication April 11, 2005; revised version accepted July 11, 2005. Address for reprints: Mary Buckwalter, MS, 455 South Gulph Road, King of Prussia, PA 19406; e-mail: mbuckwalter@vicuron.com.

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The pharmacokinetics of dalbavancin has been studied in healthy volunteers, renally impaired subjects, and hepatically impaired subjects. Maximum concentrations of dalbavancin (C_{max}) are achieved immediately following the end of infusion, and the drug initially distributes into a volume of approximately 8 to 12 L.[6,7] The eventual distribution of the drug, however, appears to be more extensive. A quantitative distribution study in rats showed that concentrations of drug-derived radioactivity in tissues, including skin, were comparable to those observed in plasma. Maximum tissue concentrations were observed within 24 hours after dose administration.[8,9] There is a linear dose-dependent increase in plasma concentrations and exposures of dalbavancin across dose levels, and the binding of dalbavancin to plasma proteins is reversible, concentration independent, and approximately 93%.[6,10]

Dalbavancin is not a substrate, inhibitor, or inducer of hepatic cytochrome P450 isoenzymes. In healthy volunteer studies, total clearance (CL) was estimated to be 0.04 L/h.[6] The drug is eliminated through renal and nonrenal routes, with the majority eliminated as intact drug.[8,11] A half-life of approximately 1 week characterizes the majority of drug distribution.[6] The effects of renal and hepatic insufficiency on the pharmacokinetics of dalbavancin were examined in otherwise healthy subjects. Concentrations and exposures of

dalbavancin do not increase with increasing degrees of hepatic impairment and were comparable to subjects with normal hepatic function.[12] Concentrations and exposures are slightly increased in subjects with renal impairment.[13,14]

The primary purpose of this analysis was to develop a population pharmacokinetic model to determine the significance of possible covariates on dalbavancin pharmacokinetic parameter values and to estimate the interpatient variability of these parameter values and the random residual error. The possible covariates examined included demographic factors and the use of concomitant medications.

METHODS

Study Design

A total of 532 patients from 3 phase II/III studies was included in the pharmacokinetic analysis. Subjects were studied at multiple sites listed in the appendix (available with the online version of this article), and the clinical studies were approved by those affiliated institutional review boards. The majority of patients (78.4%) were administered dalbavancin intravenously as a 1000-mg dose on day 1 and a single 500-mg dose on day 8. Patients administered dalbavancin intravenously as a 650-mg loading dose on day 1 and continuing with daily maintenance doses of 65 mg for up to 13 days (1.3%), as well as patients administered a single 1000- or 1100-mg dose on day 1 (20.3%), were also included in the analysis. Dalbavancin was administered intravenously over 30 minutes regardless of the dosing regimen. A total of 1668 blood samples was obtained for the determination of pharmacokinetics according to detailed sampling schemes. In general, samples were taken following the end of infusion on day 1, on day 4 (±24 hours), day 8 predose, postinfusion, and 5 hours postdose. Samples were also drawn at the end of treatment (within 3 days following the completion of study medication) and at test of cure visits (14 days ± 2 days after the completion of study medication). An average of 3 to 4 blood samples were collected per patient. The analysis population included 502 patients with skin and soft tissue infections with suspected or confirmed gram-positive bacterial pathogens and 30 patients with catheter-related bloodstream infections with suspected or confirmed gram-positive bacterial pathogens.

The clinical studies were conducted according to the Declaration of Helsinki and its amendments and were performed under good clinical practices regarding drug development. The rationale for the study, procedural details, investigational goals, and potential hazards involving adverse reactions were explained to the patients, and written informed consent was obtained from each patient prior to enrollment in the study.

Blood samples were drawn into heparinized tubes and centrifuged within 30 minutes after being collected. Plasma was separated and stored frozen at –20°C or below until time of assay. Plasma samples were assayed for dalbavancin using a validated method involving liquid chromatography coupled to tandem mass spectrometry (LC/MS/MS).

Plasma samples (0.05 mL) were fortified with an analog of dalbavancin (BI-K0098) as internal standard and deproteinized by addition of acetonitrile. The sample extracts were analyzed by LC/MS/MS using multiple reaction monitoring (MRM), monitoring the transition m/z 909 → 1429 for dalbavancin and m/z 923 → 1457 for BI-K0098. LC/MS/MS was performed either on a PE Sciex Model API III Plus or an API 3000 (Applied Biosystems, Foster City, Calif) tandem triple quadrupole mass spectrometer interfaced via a Sciex turbo ionspray probe to a liquid chromatograph. Chromatography was performed on either a Phenomenex Luna or Jupiter 5-μ C18 column (2.0 × 50 mm) with a C18 guard column using gradient elution and a flow rate of 0.3 mL/min. The method on the API III Plus used a step gradient from 95% A (10 mM ammonium formate, pH 2.5/2-propanol/acetonitrile, 80:10:10) to 100% B (10 mM ammonium formate, pH 2.5/2-propanol/acetonitrile, 20:40:40) over 4.5 minutes. The method used with the API 3000 employed a step gradient from 95% A (10% formic acid) to 90% B (2-propanol) over 3 minutes. The turbo ionspray probe on the API III Plus was operated at 500°C with nebulizing gas at 50 psi, auxiliary gas 8.0 L/min, and curtain gas 1.2 L/min. The conditions on the API 3000 were probe temperature 425°C, nebulizing gas setting 13, auxiliary gas 7.5 L/min, and curtain gas setting 10.

The LC/MS/MS method for dalbavancin in plasma was validated in the linear concentration range of 0.5 to 50 mg/L (API III Plus) or 1.0 to 128 mg/L (API 3000). The concentration limit was further extended with dilution. The assay demonstrated acceptable accuracy and precision, with an overall accuracy for the quality controls at concentrations 3.00, 10.0, 30.0, and 100 mg/L from 91.3% to 103% and an interassay coefficient of variation (%CV) that ranged from 5.2% to 13.2%.

A summary of potential covariates for inclusion in the dalbavancin population pharmacokinetic model is presented in Table I. These covariates included patient age, weight, gender, race, body surface area (BSA), screening creatinine clearance (CL_{CR}) as defined by the Cockcroft-Gault formula, and screening serum albu-

Table I Summary of Potential Covariates Examined in the Population Pharmacokinetic Analysis

Covariate		Median (Range) or Count (%)
Continuous variables		
Weight, kg	88	(42.8-320)
Age, y	46	(18-93)
Creatinine clearance, mL/min	120.6	(26-436)
Body surface area, m^2	2.05	(1.36-4.00)
Serum albumin, g/dL	3.6	(1.1-5.1)
Categorical variables		
Gender (male/female), n (%)	217	(41)/315 (59)
Race/ethnicity, n (%)		
White	350	(66)
Hispanic	103	(19)
Black	65	(12)
Other	9	(2)
Asian	5	(1)
Study, # of subjects/study (%)		
Phase II: Catheter-related bloodstream infections	30	(6)
Phase II: Skin and soft tissue infections	34	(6)
Phase III: Skin and soft tissue infections	468	(88)
Concomitant medication use, # of subjects (% total)		
Cytochrome P450 substrates	481	(90)
Cytochrome P450 inhibitors	265	(50)
Cytochrome P450 inducers	147	(28)
Acetaminophen	377	(71)
Aztreonam	87	(16)
Fentanyl	66	(12)
Metronidazole	69	(13)
Furosemide	79	(15)
Proton pump inhibitors	72	(14)
Midazolam	65	(12)
Simvastatin	37	(7)

min. All demographic factors were recorded at baseline. Concomitant medications while on dalbavancin therapy were reviewed for each study to identify medications that are known to be cytochrome P450 substrates, inhibitors, or inducers. Identification of P450 substrates, inhibitors, or inducers was based on the current listing of "Drugs Metabolized by Known P450's," maintained by David A. Flockart, MD, PhD, at the Indiana University School of Medicine.[15] Other individual drugs that represented a significant amount of use in this population (>7%) were also examined on the model. This included acetaminophen, aztreonam, fentanyl, metronidazole, furosemide, proton pump inhibitors, midazolam, and simvastatin. A total of 79% of patients received some type of potentially interacting concomitant medication.

Pharmacokinetic Analysis

Mixed-effects models were evaluated using first-order (FO), first-order conditional estimation (FOCE), and first-order conditional estimation with interaction (FOCEI) maximum likelihood estimation in the NONMEM program (double precision, Version V, Level 1.1) and NM-TRAN preprocessor. Models were compiled using Compaq Visual Fortran (Version 6.6) and were run via PDx-Pop (Version 1.1j, GloboMax LLC) under the Windows 2000 Professional operating system. All figures were created using SPlus2000 for Windows (Insightful Corporation) or Sigma Plot 8.0 (SPSS, Inc).

Base Model Selection

The structural (compartmental) and statistical (variability) models were initially established without the inclusion of covariates. One-, 2-, and 3-compartment linear models were initially fit to the dalbavancin plasma concentration data. Selection of the appropriate base population pharmacokinetic model was based on a graphical evaluation of the plasma dalbavancin concentrations versus time and model diagnostic criteria, including a significant reduction in the objective function value ($P < .05$), a decrease in the residual error, randomness of the individual weighted residuals distribution against the predicted concentration and time, and randomness of the observed concentration distribution versus individual predicted concentration values across the identity line.

The population pharmacokinetic parameters were assumed to be log-normally distributed. Interpatient variability terms were initially included on all of the population model parameters. The importance of the variability parameters was evaluated during base model selection. A combined additive plus proportional residual error model was initially employed to allow the maximum amount of model flexibility.

Covariate Selection

The relationships between structural model-based Bayesian estimates of the pharmacokinetic parameters and individual covariates were explored graphically and via generalized additive modeling (GAM) analysis.[16] All of the covariates that were significant based on the Akaike information criterion (AIC) values from the GAM analysis or from the graphical evaluation were

evaluated in NONMEM. An additional exploratory analysis, which consisted of testing specific covariates against the final population model, was performed to investigate covariates of interest that may not have been detected by the GAM analysis.

Population Pharmacokinetic Model Building

Continuous covariates entered into the model according to the equation:

$$P = \theta_1 + \theta_2 \bullet (COV - \overline{COV}),$$

where P is the individual estimate of the parameter, COV is the value of the covariate, $\overline{COV}$ is the median value of the covariate in the study population, θ_1 represents the typical value of the parameter (when COV = $\overline{COV}$), and θ_2 represents the slope of the effect of the covariate on the parameter (eg, body weight or age).

Categorical covariates were included in the model using indicator variables, as shown in the following equation:

$$P = \theta_1 + \theta_2 \bullet IND,$$

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

The significance of each parameter was tested individually within NONMEM using a significance value of $P < .001$ (change in the minimum objective function [MOF] of 3.84 with 1 degree of freedom) by adding each covariate to the model, running the NONMEM estimation step, and recording the objective function. After all of the individual covariates were tested, the significant covariates were added to the base model in a forward selection manner.

Population Pharmacokinetic Model Evaluation

The ability of the final dalbavancin pharmacokinetic model to describe the observed data was investigated. Monte Carlo simulations in Crystal Ball 2000 (Decisioneering, Inc, Denver, Colo) using the final dalbavancin population pharmacokinetic model, including final fixed-effect parameters and random-effect parameters (interpatient variability), were used to create 10 000 replications of the observed pharmacokinetic data set. The simulated data were sorted by observation times, and the 95th, 90th, 75th, 50th (median), 25th, 10th, and 5th percentiles of the simulated data were calculated for each time point. The observed data were plotted against the percentiles of the pooled, simulated data to ensure that the majority of observed data fell within these boundaries. The results of these 10 000 simulations were used to provide evidence that the derived population pharmacokinetic model accurately described the observed data. Simulations were also used to examine the clinical significance and impact of the covariates in the final model.

RESULTS

Pharmacokinetic Analysis

Base Model

Initial model building indicated that a 2-compartment model parameterized in terms of clearance (CL), central volume of distribution (V1), intercompartmental clearance (Q), and peripheral volume of distribution (V2) gave the best fit. One-compartment models did converge, but the model residuals were biased. In addition, the change in the MOF from the 1- to the 2-compartment model indicated that the 2-compartment model was statistically better. Three-compartment models did converge, but interpatient variability could not be obtained for all parameters, and there was no improvement in model residuals. Therefore, a 2-compartment model with proportional interpatient variability was chosen as the base model.

The base model population pharmacokinetic parameter estimates for dalbavancin are presented in Table II. The typical values for CL, V1, Q, and V2 were estimated from the base model to be 0.0579 L/h, 4.03 L, 0.60 L/h, and 11.8 L, respectively. An interpatient variability term on each of the model parameters was also supported. Interpatient variability was below 34% for all pharmacokinetic parameters with the exception of the intercompartmental clearance (%CV = 92.8). Initially, a combined additive plus proportional residual error model was employed. However, the additive portion was not supported and dropped from the model; the proportional component (%CV) was estimated as 23.4%. All of the structural and statistical parameters were estimated with good precision, as evidenced by percent relative standard error range (%RSE) of 0.01% to 2.8% across the parameters.

Final Model

Exploratory graphical evaluation and GAM analysis indicated that CL_{CR}, weight, and BSA might be related to the clearance of dalbavancin. The effects of weight, BSA, and gender on the volumes of distribution were also examined for potential relationships. Weight and BSA appeared to explain the same amount of variabil-

Table II Dalbavancin Base Population Pharmacokinetic Parameter Estimates (FOCEI Method)

	Structural Model and Interpatient Variance Parameters	
Parameter	**Typical Value (%RSE)**	**Interpatient %CV (%RSE)**
CL, L/h	0.0579 (1.64)	23.7 (14.7)
V1, L	4.03 (1.90)	32.2 (21.1)
Q, L/h	0.600 (0.015)	92.8 (15.9)
V2, L	11.8 (2.81)	33.2 (28.5)
V_{ss}, L	15.9[a]	16.8[b]
$t_{1/2}$, days	8.5[a]	18.6[b]
Residual Error Parameter	**Estimate (%RSE)**	
$\sigma^2 1_{prop}$	%CV = 23.4 (15.0)	

%RSE is the percent relative standard error of the estimate = SE/parameter estimate • 100 (for variability terms, this is the %RSE of the variance estimate). FOCEI, first-order conditional estimation with interaction; CV, coefficient of variation; CL, clearance; V1, central volume of distribution; Q, intercompartmental clearance; V2, peripheral volume of distribution; V_{ss}, volume of distribution at steady state; $t_{1/2}$, terminal phase half-life; $\sigma^2 1_{prop}$, proportional component of the residual error model.

a. Calculated from individual parameter values: $t_{1/2}$ = Log(2)/(0.5 • ((K + K12 + K21) – SQRT((K + K12 + K21) – (4 • K • K21))), V_{ss} = V1 + V2.

b. Calculated as (standard deviation/mean) • 100.

Table III Dalbavancin Final Population Pharmacokinetic Model Parameter Estimates (FOCEI Method)

	Structural Model and Interpatient Variance Parameters	
Parameter	**Typical Value (%RSE)**	**Interpatient %CV (%RSE)**
CL, L/h	CL = θ1 + (BSA – MBSA) • θ5 + (CL_{CR} – MCL_{CR}) • θ6	18.0 (22.8)
θ1	0.0571 (1.55)	—
θ5	0.0109 (26.1)	—
θ6	0.000128 (12.5)	—
V1, L	V1 = θ2 + (BSA – MBSA) • θ7	24.5 (26.5)
θ2	4.15 (1.70)	—
θ7	2.70 (9.89)	—
Q, L/h	Q = θ3	86.3 (20.6)
θ3	0.476 (15.4)	—
V2, L	V2 = θ4	29.6 (37.3)
θ4	11.4 (3.75)	—
V_{ss}, L	15.7[a]	15.9[b]
$t_{1/2}$, days	8.5[a]	18.6[b]
Residual Error Parameter	**Estimate (%RSE)**	
$\sigma^2 1_{prop}$	%CV = 24.2% (12.9%)	

%RSE is the percent relative standard error of the estimate = SE/parameter estimate • 100 (for variability terms, this is the %RSE of the variance estimate). FOCEI, first-order conditional estimation with interaction; CV, coefficient of variation; CL, clearance; V1, central volume of distribution; Q, intercompartmental clearance; V2, peripheral volume of distribution; V_{ss}, volume of distribution at steady state; $t_{1/2}$, terminal phase half-life; $\sigma^2 1_{prop}$, proportional component of the residual error model; BSA, body surface area (m^2); MBSA, median BSA (2.05 m^2); CL_{CR}, creatinine clearance (mL/min); MCL_{CR}, median clearance (120.6 mL/min).

a. Calculated from individual parameter values: $t_{1/2}$ = Log(2)/(0.5 • ((K + K12 + K21) – SQRT((K + K12 + K21) – (4 • K • K21))), V_{ss} = V1 + V2.

b. Calculated as (standard deviation/mean) • 100.

ity, and only BSA was carried forward in the covariate model testing. This decision was consistent with findings from a previous population pharmacokinetic analysis of dalbavancin in a healthy subject population.[17]

The final population pharmacokinetic model contained effects of BSA and CL_{CR}. The equations describing the relationships between the significant covariates and dalbavancin clearance and central volume of distribution were determined to be the following:

$$CL\ (L/h) = 0.0571 + 0.0109 \bullet (BSA - 2.05\ m^2) + 0.000128 \bullet (CL_{CR} - 120.6\ mL/min),$$

$$V1\ (L) = 4.15 + 2.70 \bullet (BSA - 2.05\ m^2),$$

where CL is dalbavancin clearance, V1 is dalbavancin central volume of distribution, BSA is the body surface area, and CL_{CR} is creatinine clearance. The intercompartmental clearance was estimated to be 0.476 L/h, and volume of the peripheral compartment was estimated as 11.4 L. The volume of distribution at steady state derived from the model was 15.7 L. Terminal half-life values were calculated from the individual parameter estimates for each patient. This yielded a mean terminal half-life of 8.5 days.

The inclusion of other covariates (gender, race, age, serum albumin, weight, and concomitant medications) was not supported in the model. For the concomitant medication categories (substrate, inducer, inhibitor, acetaminophen, aztreonam, fentanyl, metronidazole, furosemide, proton pump inhibitors, midazolam, and simvastatin), there were adequate numbers of patients (>7%) to see any clinically meaningful changes.

The final population pharmacokinetic parameter estimates are listed in Table III. The population pharmacokinetic parameters for dalbavancin were estimated with good precision. The percent relative standard error for all of the fixed-effect parameters was below 20%

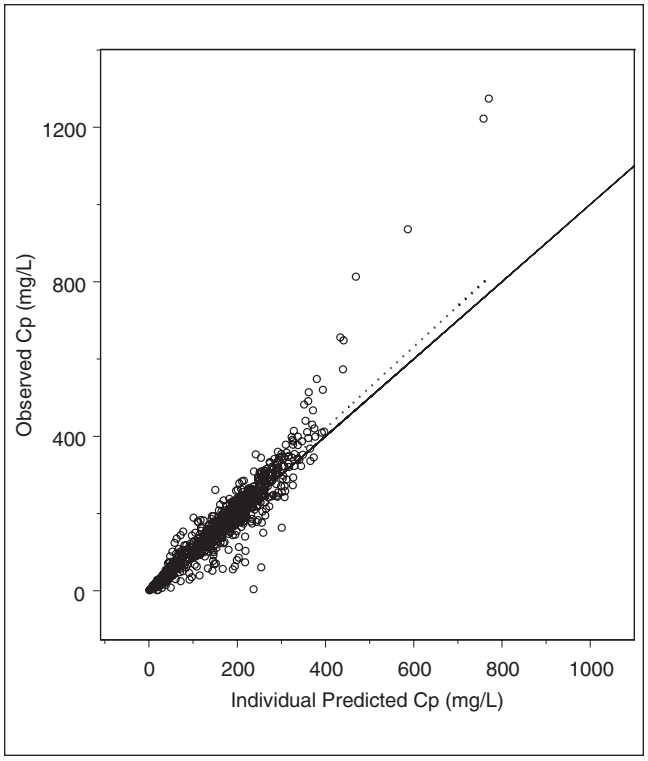

Figure 1. Observed versus predicted dalbavancin plasma concentrations (Cp). Observed dalbavancin plasma concentrations versus individual (empirical Bayes) predictions, using the final model and first-order conditional estimation with interaction (FOCEI) method and a local regression method (LOESS) smooth of the data (dotted line), are presented. The line of identity (solid) is included as a reference.

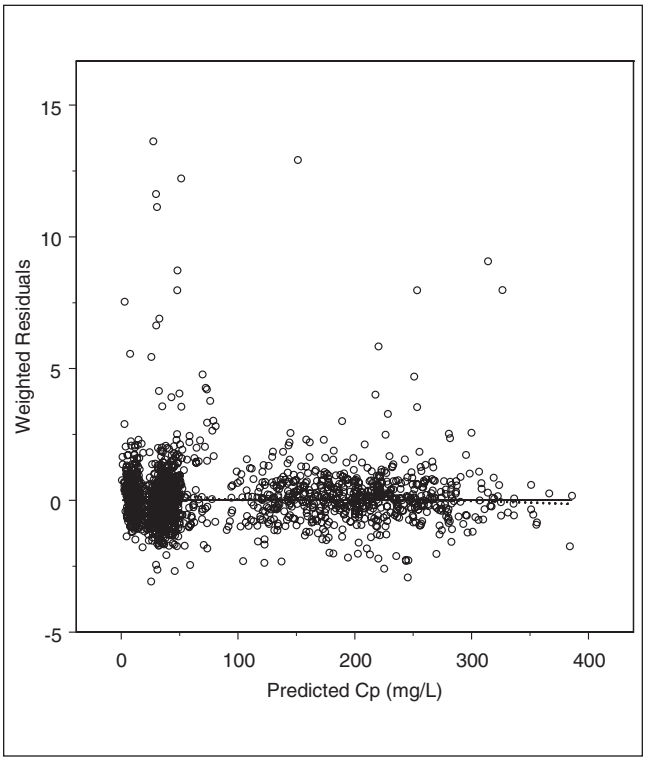

Figure 2. Weighted residuals versus predicted dalbavancin plasma concentrations (Cp). Weighted residuals versus final model (first-order conditional estimation with interaction [FOCEI] method) predicted dalbavancin plasma concentrations and a local regression method (LOESS) smooth of the data (dotted line). A line at y = *0 (solid) is included as a reference.*

with the exception of BSA on CL (%RSE = 26.1%). The random-effect parameter was also estimated with good precision (%RSE = 12.9%). The diagnostic plots shown in Figures 1 and 2 for the final population pharmacokinetic model are additional evidence that the model adequately predicted the observed dalbavancin concentrations. There was some possible bias observed with a small number of concentrations that were greater than 400 mg/L. However, most of the concentrations were below 400 mg/L, and it is not known if this was an artifact due to sampling.

Model Evaluation

The ability of the final model to describe the observed data was evaluated via Monte Carlo simulations. Ten thousand data sets were simulated using the fixed-effect and random-effect (interpatient variability) parameters from the final population model. The random residual component of the model was set to 0 in the simulation. Data were simulated for the single 1000-mg and 1000/500-mg dosing regimens. The simulated data were sorted by observation times elapsed from the first dose, and the 95th, 90th, 75th, 50th, 25th, 10th, and 5th percentiles of the simulated data were calculated for each time point. The observed data for the single 1000-mg and 1000/500-mg dosing regimens, representing 95.5% of the sampled population, were plotted against the percentiles of the pooled, simulated data. The results of the model evaluation are shown graphically by dosing regimen, with the observed data in Figure 3. No corrections are made in the plot for patients receiving a second dose prior to or after the protocol scheduled time. Approximately 70% of the observations are within the 10th and 90th percentiles when correcting for the time of dose, providing evidence that the derived population pharmacokinetic model accurately described the observed data.

Additional simulations (10 000 profiles/simulation) were performed using the model parameters from the final population pharmacokinetic model to examine the impact of the model covariates. Simulated populations included a population with a higher distribution

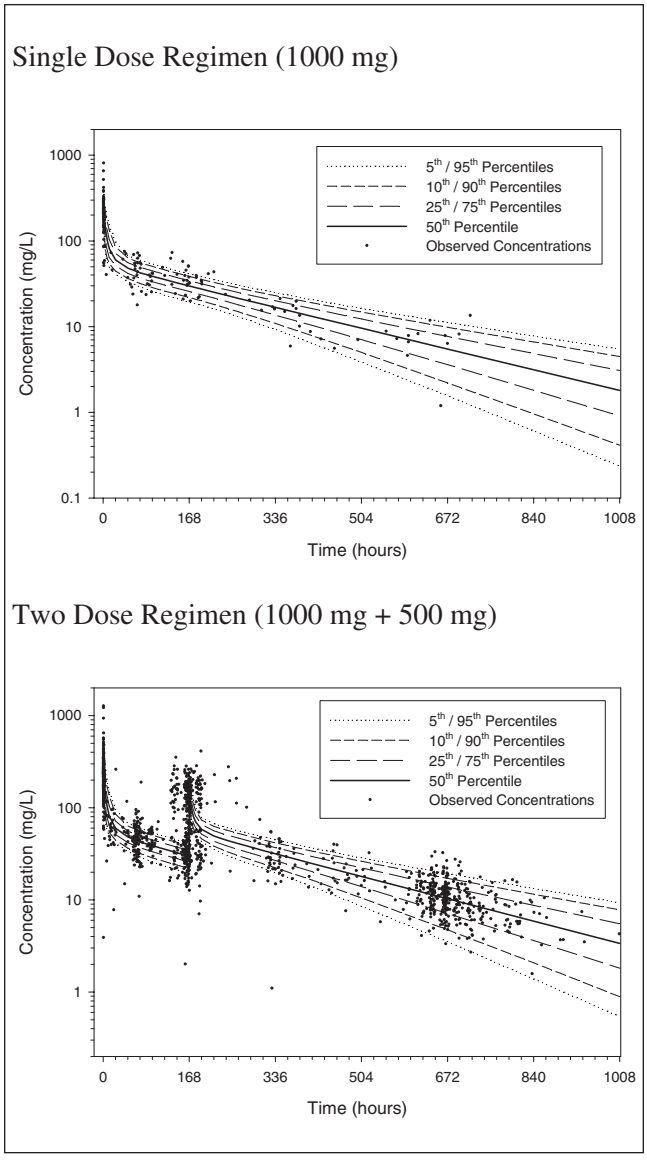

Figure 3. Monte Carlo simulation of the final population pharmacokinetic model. A total of 10 000 simulations are summarized by percentiles. For observed concentrations, no corrections for individual dose administration times are made in the plot; data are plotted by times of sample collection relative to individual dosage administration times.

of BSA (2.25-3.0 m^2), a population with a lower distribution of CL_{CR} (20-50 mL/min), and a population with a lower CL_{CR} (20-50 mL/min) and lower BSA (1.4-1.7 m^2). The selected populations were compared to a normal population (CL_{CR} = 80-180 mL/min, BSA = 1.5-2.25 m^2) and statistically tested. The results are presented in Table IV. Higher BSA resulted in lower maximum concentrations (~34% decrease) but did not have any significant effect on clearance. Lower CL_{CR} did not result in a significant change to maximum concentrations, but a slight difference was detected for clearance (~21% decrease). The pairing of low CL_{CR} with low BSA resulted in higher maximum concentrations (~30% increase) and lower clearance estimates (~27% decrease).

Table IV Statistical Comparison of Dalbavancin Clearance (CL) and Maximum Concentration (C_{max}) Determined From Simulations of Different Patient Populations

Simulation Parameter	Geometric Least Squares Means		Ratio Test/ Reference	90% Confidence Interval
	Reference	Test		
Higher BSA				
C_{max}, mg/L	258.3	171.3	66.3	65.9-66.7[a]
CL, L/h	0.0557	0.0638	114.5	114.0-115.0
Lower CL_{CR}				
C_{max}, mg/L	258.3	259.3	100.4	99.7-101.0
CL, L/h	0.0557	0.0443	79.5	79.2-79.9[a]
Lower CL_{CR} and lower BSA				
C_{max}, mg/L	258.3	335.3	129.8	129.0-130.6[a]
CL, L/h	0.0557	0.0406	72.9	72.6-73.2[a]

Parameters estimated using linear mixed-effects modeling. Log-transformed parameters tested by bioequivalence testing. Simulations include (1) a population with a higher distribution of body surface area (BSA; 2.25-3.0 m^2), (2) a population with a lower distribution of creatinine clearance (CL_{CR}; 20-50 mL/min), and (3) a population with a lower CL_{CR} (20-50 mL/min) and lower BSA (1.4-1.7 m^2). Simulations are compared to a normal population (reference; CL_{CR} = 80-180 mL/min, BSA = 1.5-2.25 m^2).

a. The 90% confidence interval does not fall completely within the 80% to 125% bioequivalence interval.

DISCUSSION

The final pharmacokinetic model for dalbavancin was a 2-compartment model with interpatient variability described on all the parameters. After the pharmacokinetic structure was determined, the effects of covariates on interpatient variability were evaluated. There was a significant linear relationship between dalbavancin clearance and BSA and CL_{CR}. In addition, there was a significant linear relationship between BSA and the central volume of distribution. Patient weight was also significant and described a similar amount of variability as BSA, and so it was dropped from the analysis in favor of BSA. The inclusion of covariates lowered the interpatient variability in dalbavancin clearance

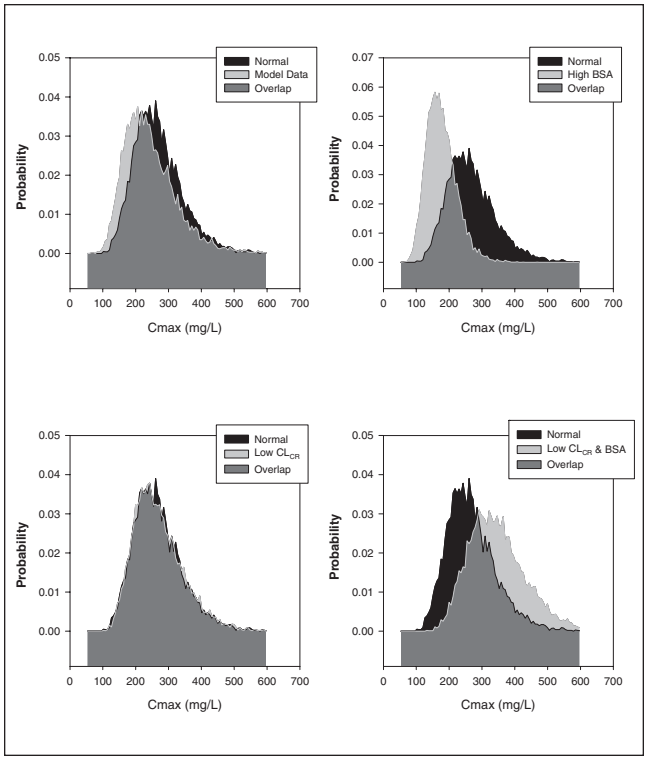

Figure 4. Distribution of C_{max} across simulations of different populations. Simulations of final population pharmacokinetic model include the following: Normal: creatine clearance (CL_{CR}) = 80 to 180 mL/min; body surface area (BSA) = 1.5 to 2.25 m^2. Model data: Covariate distributions of model-building data. High BSA: BSA = 2.25 to 3.0 m^2. Low CL_{CR}: CL_{CR} = 20 to 50 mL/min. Low CL_{CR} and BSA: CL_{CR} = 20 to 50 mL/min; BSA = 1.4 to 1.7 m^2.

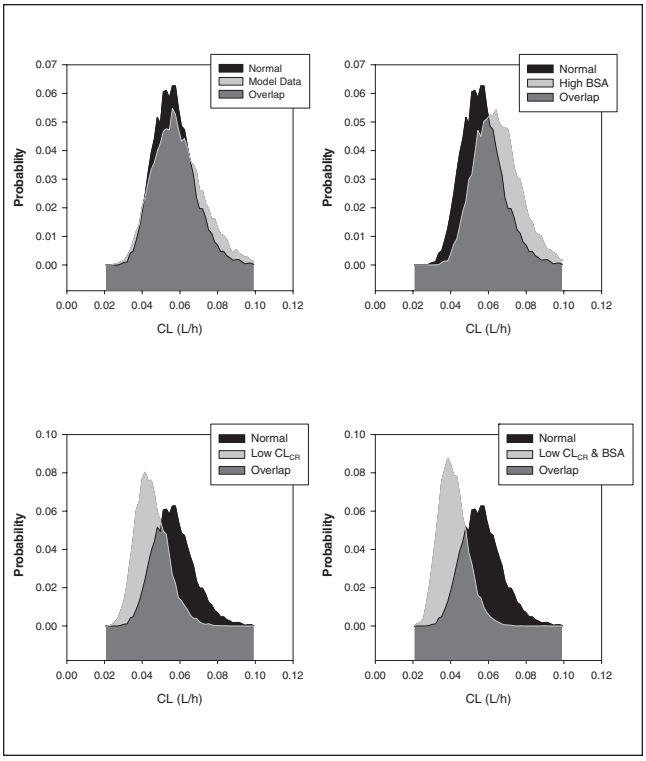

Figure 5. Distribution of clearance (CL) across simulations of different populations. Simulations of final population pharmacokinetic model include the following: Normal: creatine clearance (CL_{CR}) = 80 to 180 mL/min; body surface area (BSA) = 1.5 to 2.25 m^2. Model data: Covariate distributions of model-building data. High BSA: BSA = 2.25 to 3.0 m^2. Low CL_{CR}: CL_{CR} = 20 to 50 mL/min. Low CL_{CR} and BSA: CL_{CR} = 20 to 50 mL/min; BSA = 1.4 to 1.7.

from 23.7% to 18.0%. The inclusion of covariates also lowered the interpatient variability about the central volume of distribution from 32.2% to 24.5% (a 23.9% decrease). The final model was similar to a model developed with healthy subjects.[17]

Simulations of the final model demonstrate that patients with higher BSA have a lower C_{max} but have no significant differences in CL. Patients with lower CL_{CR} will have a lower CL. Although these differences are considered to be statistically significant, considerable overlap between the distributions exists, as demonstrated by simulations (Figures 4 and 5). Typical CL values for patients with either a low CL_{CR} or extreme BSA are still within 20% to 30% of a typical patient with normal CL_{CR} and BSA. Patients with both low CL_{CR} and low BSA, the most extreme outlying population, will have a higher C_{max} and a lower CL. However, even for this group, there is considerable overlap in the distributions compared to the "normal" population.

The presence of cytochrome P450 substrates, cytochrome P450 inhibitors, cytochrome P450 inducers, or selected concomitant medications had no clinically significant effect on the clearance of dalbavancin. The screening of individual concomitant medication was limited in that it included only those medications that had significant use in this population. In addition, other tested parameters such as age, gender, and race, as well as serum albumin, had no effect on the pharmacokinetics of dalbavancin.

In conclusion, a 2-compartment model with first-order elimination provided the best fit to the data. The clearance of dalbavancin was influenced by BSA and CL_{CR}. There was also a significant linear relationship between BSA and the central volume of distribution. Secondary parameters of $t_{1/2}$ and V_{SS} were 8.5 days and 15.7 L, respectively, and were similar to observed parameters in phase I studies. In the final model, accounting for fixed effects, the interpatient variability in clearance was low and estimated to be 18%. Although BSA and CL_{CR} were identified as sources of variability on clearance, together they described less than 25% of the interpatient variability.

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