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Population Pharmacokinetic Analysis for a Single 1,200-Milligram Dose of Oritavancin Using Data from Two Pivotal Phase 3 Clinical Trials

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Oritavancin is a lipoglycopeptide antibiotic with activity against Gram-positive bacteria. Here we describe oritavancin population pharmacokinetics and the impact of patient-specific covariates on drug exposure variability. Concentration-time data were analyzed from two phase 3 clinical trials, SOLO I and SOLO II, in which oritavancin was administered as a single 1,200-mg dose to patients with acute bacterial skin and skin structure infections. A total of 1,337 drug concentrations from 297 patients (90% of whom had 4 or 5 pharmacokinetic samples) were available for analysis. A previously derived population model based on data from 12 phase 1, 2, and 3 oritavancin studies was applied to the SOLO data set. Alterations to the structural model were made, as necessary, based on model fit. Analyses utilized Monte Carlo parametric expectation maximization (S-ADAPT 1.5.6). The previous population pharmacokinetic model fit the data well ($r^2 = 0.972$), and population pharmacokinetic parameters were estimated with acceptable precision and lack of bias. Covariate evaluations revealed statistically significant relationships between central compartment volume and age and between clearance and height; however, these relationships did not indicate a clinically relevant impact on oritavancin exposure over the range of age and height observed in the SOLO studies. The mean (coefficient of variation [CV]) area under the plasma concentration-time curve from time zero to 72 h (AUC_{0-72}) and maximum plasma concentration (C_{max}) were 1,530 (36.9%) μg · h/ml and 138 (23%) μg/ml, respectively. The mean (CV) half-life at alpha phase ($t_{1/2\alpha}$), $t_{1/2\beta}$, and $t_{1/2\gamma}$ were 2.29 (49.8%), 13.4 (10.5%), and 245 (14.9%) hours, respectively. These analyses are the first to describe oritavancin pharmacokinetics following a single 1,200-mg dose. Covariate analyses suggested that no dose adjustments are required for renal impairment (creatinine clearance, >29 ml/min), mild or moderate hepatic impairment, age, weight, gender, or diabetes status.

Oritavancin is a novel, semisynthetic lipoglycopeptide with *in vitro* activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* and *Streptococcus pyogenes* (1, 2). Due to its *in vitro* spectrum of activity, its concentration-dependent bactericidal activity, and its long elimination half-life, oritavancin was developed clinically as a 1,200-mg single-dose therapy for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI). Based upon the results from two pivotal clinical trials, SOLO I and II, oritavancin recently gained approval by the U.S. Food and Drug Administration (FDA) (3, 4, 5).

Oritavancin is the first antibiotic approved by the U.S. FDA as single-dose therapy for the treatment of ABSSSI (3). A previous population pharmacokinetic (PK) model (6) was used to inform this unique dosing regimen, which was evaluated in two phase 3 studies, SOLO I and II (4, 5). Collection of PK data during the SOLO studies provided the opportunity to evaluate the disposition of oritavancin in the target patient population receiving a single 1,200-mg, once-only dose.

The objectives of the analysis described here were the following: (i) to characterize oritavancin plasma PK in patients enrolled in SOLO I and II by modifying the previously developed existing population PK model for oritavancin in order to obtain accurate estimates of oritavancin exposure for use in separate pharmacokinetic-pharmacodynamic (PK-PD) analyses for efficacy and (ii) to assess the impact of patient-specific demographic and disease characteristics on interindividual variability (IIV) for selected PK parameters.

MATERIALS AND METHODS

Study design. SOLO I and II were phase 3 randomized clinical studies in patients with ABSSSI, which employed identical designs (4, 5); the intent-to-treat population contained 968 patients in SOLO I and 1,019 patients in SOLO II. Patients in SOLO I and II were randomized to receive a single 1,200-mg dose of oritavancin, administered as a 3-hour intravenous (i.v.) infusion, or i.v. vancomycin (1 g or 15 mg/kg every 12 h) for 7 to 10 days. Within each study, patients at select sites participated in a PK substudy (termed the PK population). Plasma PK samples were obtained from each patient in the PK population at 3, 12, 24, 72, and 576 h after the start of the infusion of study drug. Only those patients randomized to oritavancin were included in the population PK analysis. The actual oritavancin dose administered and the infusion start-stop dates and times were recorded for each patient and used in these analyses, whenever available. When this information was not available, dose times and/or infusion durations were imputed according to the study protocol-specified directions.

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PK sample collection and processing. In each study, blood samples were collected into K_2EDTA-containing collection tubes at the protocol-specified times after the beginning of the infusion. The actual dates and times for dosing and PK sample collection were recorded on each case report form. Blood samples were immediately placed on ice. Within 60 min of collection, blood samples were centrifuged at 1,100 to 1,300 × *g* for 15 min at 4°C, and the separated plasma was stored at −80°C until the drug concentration assay was performed.

Drug concentration assay. Oritavancin plasma concentrations were determined using two possible liquid chromatography methods with tandem mass spectrometric detection (LC-MS/MS) (method on file; The Medicines Company). Method BTM-1379-R0 is an LC-MS/MS method for the determination of oritavancin in K_2EDTA-human plasma using TT99000808, a closely related oritavancin analog, as the internal standard. Method BTM-1379-R0 was fully validated with a calibration range of 12.5 to 1000 ng/ml. A second method for the determination of oritavancin in K_2EDTA-human plasma, BTM-1379H-R0, was developed based on method BTM-1379-R0; it has a higher assay range of 500 to 300,000 ng/ml. All samples were assayed using BTM-1379H-R0; 13 samples were reanalyzed using BTM-1379-R0, as in these samples oritavancin was below the limit of quantitation (BLQ) based upon BTM-1379H-R0.

Patient demographics. Subject demographic and laboratory data collected prior to administration of the study drug were used to characterize the analysis population and to evaluate the potential for patient descriptors to explain a portion of the IIV for selected PK parameters. Demographic information included age, height, weight, body surface area (BSA), body mass index (BMI), sex, and race. Body surface area was calculated using the method of Gehan and George (7). Body mass index was calculated as weight (in kilograms) divided by height (in meters) squared. The only laboratory information included in the analysis was serum creatinine. Creatinine clearance (CL_{CR}) was calculated from baseline serum creatinine, age, and body weight using the Cockcroft-Gault equation (8) and then normalized to BSA.

Handling of outliers and samples assayed as having BLQ oritavancin plasma concentrations. An outlier data point was defined as an aberrant observation that deviated substantially from the rest of the observations within an individual. Outliers were excluded owing to the potential for these observations to negatively impact the convergence and/or parameter estimates. As noted in the Food and Drug Administration guidance, including extreme values is not good practice with methods based on least-squares estimation or normal-theory estimation methods, as such outliers inevitably exert a disproportionate effect on the estimates (9).

Suspected outlier observations were identified during initial model development when the population PK model was fit to the data from each study separately. The potential outliers were then tested and, if justified, excluded, based on the procedure described below. Data for each subject were fit with and without the suspected outlier. A sample was suspected to be an outlier if the difference between the value of the fitted concentration and the observed concentration was at least three error standard deviations and the trajectory of the PK profile was significantly altered. In an instance when an improvement was seen in the fit of the remaining samples for that subject, then the observation was declared a significant outlier and excluded from the analysis. For cases in which data points were clearly outliers on visual inspection, these were not subjected to the process described above.

Concentration records with a BLQ result were flagged in the data set. The population analysis program then applied the Beal M3 method (10), such that the algorithm considered this BLQ value a normally distributed, random value somewhere between negative infinity and the limit of quantification. The Beal M3 method maximizes the probability that a concentration observed to be BLQ is also predicted to be BLQ.

Population PK analysis. All PK analyses were conducted using Monte Carlo parametric expectation maximization as implemented in the open-source software program S-ADAPT 1.5.6 (11). S-ADAPT analyses were performed on a Windows XP operating system and compiled using Intel FORTRAN 9.1. S-ADAPT (also called scriptable ADAPT) is a version of ADAPT II that contains an augmented interface as well as additional parameter estimation, simulation, and optimization abilities. The augmented portions of the S-ADAPT software were written by Robert J. Bauer. S-ADAPT uses the computational engine of ADAPT II release 4, developed by David D'Argenio and Alan Schumitzky, at the University of Southern California Biomedical Simulations Resources Department (11, 12, 13).

For each analysis, S-ADAPT computed an objective function value, a statistic that is proportional to minus the log likelihood of the data. In the case of hierarchical models, the change in objective function produced by the inclusion or deletion of a parameter is asymptotically distributed as chi-square with the number of degrees of freedom equal to the number of parameters added to or deleted from the model. S-ADAPT includes many options for the determination of the dispersion of mean PK parameters. The method chosen for this analysis calculated the standard error of the mean (SEM) using the full second derivative matrix and using third and fourth central moments (11).

Model selection criteria that were used to discriminate between candidate PK models included the following: (i) evaluation of individual and population mean parameter estimates and their precision (SEM); (ii) graphical examination of standard goodness-of-fit plots and plots of the observed versus individual predicted concentrations; and (iii) reduction in both residual variability (RV) and IIV and comparison of objective function for nested models, or Akaike's information criterion (14), for either nested or nonnested models.

The first step of PK model development involved the fitting of the population PK model developed using the data from 560 subjects and subjects from phase 1, 2, and 3 studies to the plasma concentration data from patients enrolled in SOLO I. The previous covariate relationships were removed from the model prior to fitting the model to the SOLO I data. If necessary to obtain an adequate fit, the SOLO I data were to be pooled with data from the previous studies which were used to develop the model (6). Alternative structural models were to be attempted only if severe model misspecification was identified. The outlier evaluation for SOLO I was conducted at this point in the analysis.

Interindividual variability was estimated for each structural population PK model parameter, where possible, using an exponential error model. Residual variability, which represents a composite of assay variability, intrasubject variability, model misspecification, errors in the timing of dose administration or PK sample collection, and other unexplained errors, was initially described using an additive plus proportional coefficient of variation error model. Other models for RV were to be explored if necessary.

Once the data from SOLO II were available, the structural population PK model was applied to the SOLO II data alone in order to identify influential outlier observations. The structural population PK model was then fit to the pooled data from SOLO I and SOLO II. If significant model misspecification was observed, alternative structural models were to be fit to the data at this point (i.e., prior to conducting the pooled covariate analysis).

Covariate analysis. Several demographic and disease characteristics were evaluated for their impact on the primary PK parameters. Demographic and disease characteristics evaluated included sex, race, age, weight, height, BSA, BMI, and normalized CL_{CR}. The potential importance of diabetes was evaluated as a *post hoc* analysis. Covariate exploration involved graphical examination of plots of PK parameters versus demographic and disease characteristics, followed by the creation of statistical models, which were used as the basis for the development of the covariate model using S-ADAPT.

The final base covariate model was evaluated for any remaining bias in the residual variability models. A visual predictive check was used to evaluate the ability of the model to adequately describe the observed PK data (15).

TABLE 1 Summary statistics of the continuous subject demographic characteristics of the PK analysis population

Variable[a]	Mean (% CV), median (minimum–maximum)		
	SOLO I ($n = 110$)	SOLO II ($n = 187$)	Pooled ($n = 297$)
Age (yr)	48.2 (29.9), 48.0 (18.0–89.0)	44.6 (27.9), 45.0 (19.0–79.0)	45.9 (29.4), 47.0 (18.0–89.0)
Wt (kg)	83.1 (32.2), 78.0 (47.6–178)	77.9 (25.4), 74.8 (42.7–148)	79.9 (28.8), 75.6 (42.7–178)
Height (cm)	169 (6.70), 170 (129–196)	170 (6.56), 170 (125–203)	170 (6.59), 170 (125–203)
BSA (m^2)	1.93 (15.2), 1.89 (1.31–2.79)	1.88 (13.3), 1.89 (1.33–2.71)	1.90 (14.1), 1.89 (1.31–2.79)
BMI (kg/m^2)	28.9 (30.6), 27.0 (17.0–67.4)	26.9 (23.2), 25.5 (15.9–55.5)	27.7 (27.0), 26.2 (15.9–67.4)
CL_{CR} (ml/min/1.73 m^2)	102 (32.4), 102 (29.8–216)	108 (28.7), 109 (37.7–189)	106 (29.7), 106 (29.8–216)

[a] Abbreviations: BSA, body surface area; BMI, body mass index; CL_{CR}, creatinine clearance; CV, coefficient of variation.

Calculation of secondary PK parameters and exposure estimates. In order to generate appropriate oritavancin plasma exposure estimates (for example, the area under the plasma concentration-time curve from time zero to 24 h [AUC_{0-24}] and the maximum plasma concentration [C_{max}]) for oritavancin, it was necessary to perform a PK simulation using the final population PK model. In this simulation, the dosing history and *post hoc* PK parameter estimates for each patient were used to generate a PK profile from 0 to 576 h postdose after the start of drug administration. The AUC_{0-24}, AUC_{0-48}, AUC_{0-72}, and AUC_{0-576} were calculated by integrating the PK profile over time for the defined time interval. AUC_{0-72} was the primary AUC parameter of interest, as it represented the exposure measure used for PK-PD evaluations of efficacy based on the clinical data from SOLO I and II studies (16) and nonclinical data from the murine thigh infection models (17, 18). The evaluation of AUC_{0-72} best represented the period during which the pharmacodynamic effect was assessed for the analyses of nonclinical data and is consistent with the timing of the assessment of efficacy at early clinical evaluation in SOLO I and II, which occurred 48 to 72 h after start of therapy (4, 5). C_{max} values were obtained by simulating the concentration immediately following the end of the infusion.

The secondary PK parameter estimates for oritavancin were the three relevant half-life values for a drug exhibiting three-compartment behavior: half-life at alpha phase ($t_{1/2\alpha}$), half-life at beta phase ($t_{1/2\beta}$), and half-life at gamma phase ($t_{1/2\gamma}$). These were generated for each patient using the individual, *post hoc* parameter estimates and accepted equations (19).

RESULTS

Patient population. Summary statistics (mean with coefficient of variation [CV] and median with minimum and maximum) of the continuous subject demographic characteristics of the PK analysis population are presented in Table 1. The analysis population was predominantly male (67.7%) and Caucasian (76.4%) and had normal renal function (mean CL_{CR} of 106 ml/min/1.73 m^2). The mean (range) age was 45.9 (18 to 89) years. The mean (range) weight was 79.9 (42.7 to 178) kg. Note that the demographics of the PK population were consistent with the full population of oritavancin-treated patients in the SOLO studies ($n = 978$; mean age of 46 years, mean weight of 79 kg, 65% male, and predominantly [70%] with normal renal function). The full, pooled population PK data set across SOLO I and SOLO II contained 297 patients and 1,337 oritavancin plasma concentrations.

PK data description and outlier analysis. The full PK concentration data set from SOLO I contained 115 patients and 523 oritavancin plasma concentration records while that from SOLO II contained 197 patients and 871 oritavancin plasma concentration records. Three subjects were excluded prior to data set construction, as all of the blood samples for these patients were assayed as having oritavancin plasma concentrations BLQ. Eight subjects were subsequently removed from the data set because they had only one observed oritavancin concentration. The results of the outlier analysis were as follows: four patients were removed entirely from the data set due to completely irreconcilable PK profiles (17 concentration records were removed in total from these four patients), while a total of 24 individual concentration records from 14 separate patients were identified as significant outliers and excluded from the analysis.

Ultimately, the full, pooled population PK data set across SOLO I and SOLO II contained 297 patients and 1,337 oritavancin plasma concentrations. All subjects had at least two PK samples, and the majority had five; samples were spread throughout the postdose intervals in a manner consistent with the intended sampling schedules.

Population PK analysis. Initial structural model development involved the fitting of the previous population PK model (6) to the oritavancin concentration-time data from SOLO I alone. The only modification that was attempted was to alter the fixed portion of the RV (intercept/additive term for residual variability model for plasma concentrations [SD_{in}]) to test the sensitivity of the fit to this fixed value. Since lower values for SD_{in} did not result in a significant improvement in the fit of the model, the structure of the previous model was retained and the fixed SD_{in} value was maintained at 0.22.

The model was then fit to the pooled data from SOLO I and SOLO II. The base structural model provided an excellent fit to the pooled data, and modifications to the structure were not required. The precision of the population mean parameters was universally high (maximum SEM of 9.02% for distributional clearance Q_3). In general, the magnitude of the IIV was relatively low (maximum of 50.0% for volume of distribution V_2) and consistent with the values seen in the original population PK analysis (6). Of note, the precision on the IIV in V_c was improved almost 2-fold (from 120% to 63.1% compared to the fit of the model to the SOLO I data alone). The IIV (slope/proportional term for residual variability model [SD_{sl}] of 21.6%) was not altered markedly.

The graphical examination of covariate relationships suggested several potential relationships between patient descriptors and PK parameters of interest, but none were remarkably strong. Based upon the relationships observed in the plots, all covariate relationships were modeled using power functions, which provide the flexibility to accommodate a linear relationship as necessary. Due to the high degree of covariance between V_c and V at steady state (V_{ss}), covariate relationships for V_{ss} were not evaluated.

In round 1 of forward selection, the most statistically significant covariate relationship was that between V_c and age, in which V_c decreased with increasing age. In round 2, the addition of the relationship between CL and patient height caused the most significant drop in objective function and was therefore added to the

TABLE 2 Final population PK model using pooled data from SOLO I and II[a]

Parameter[b]	Population mean		Magnitude of interindividual variability (% CV)	
	Final estimate	% SEM	Final estimate	% SEM
CL (liters/h)	0.445		27.2	21.6
V_c (liters)	5.79		34.3	24.5
Q_2 (liters/h)	0.469	3.68	50.7	15.7
V_2 (liters)	75.5	5.63	48.3	14.5
Q_3 (liters/h)	0.666	4.78	87.2	22.9
V_3 (liters)	6.29	5.61	62.4	15.7
V_c-age coefficient (liters)	5.54	3.98		
V_c-age power	−0.641	11.0		
CL-HTCM coefficient (liters/h)	0.446	2.57		
CL-HTCM power	0.695	84.8		
SD_{in}	0.22			
SD_{sl}	0.182	3.82		

[a] Minimum value of the objective function = 2,636.
[b] Abbreviations: Q_2 and Q_3, distributional clearances; V_2 and V_3, volumes of distribution of the peripheral compartments; HTCM, patient height (centimeters); SD_{in}, intercept additive term for residual variability model for plasma concentrations; SD_{sl}, slope proportional term for residual variability model; CV, coefficient of variation.

covariate model. No further covariate relationships were statistically significant in round 3.

Both of the relationships added into the model via forward selection remained significant based upon the more stringent statistical requirements of backward elimination (5.92-unit increase in the objective function value [OFV] with removal of the relationship). Removal of the V_c-age relationship resulted in a 42-unit increase in OFV, while removal of the CL-height relationship resulted in a 10-unit increase in OFV.

The final population PK model for the pooled data from SOLO I and II was a three-compartment model with zero-order infusion and first-order (linear) elimination. The population PK parameter estimates and associated standard errors for the model are provided in Table 2. In general, the magnitude of the IIV was relatively low (maximum of 62.4% for V_3), with the exception of Q_3, which had an IIV of 87.2%. These results are consistent with the values seen in the original population PK analysis (6). The precision on the IIV estimates was universally high (maximum of 24.5% for the IIV on V_c). The intrasubject variability, which is approximated by the SD_{sl}, was less than 20%, which is similar to variability measures reported in other phase 3 studies (6, 20, 21).

Standard goodness-of-fit plots showed excellent fits to the data. The overall r^2 values based on observed versus individual fitted concentrations and based on observed versus population fitted concentrations were 0.972 and 0.825, respectively. The relatively high r^2 for the observed versus population fitted concentrations is consistent with the relatively low IIV seen in the population PK model. In general, the residual plots showed consistent scatter about zero, indicating that there were no significant biases in the fit of the data across the range of fitted concentrations or over time. Of note, the fit of the model was similar between the two studies, as would be expected given that the studies employed nearly identical designs. Plots of the mean oritavancin concentration over time, overlaid upon the observed concentrations, are provided in Fig. 1.

A visual predictive check was conducted and is provided in Fig. 2. The majority of the observed data fall within the 90% confidence interval (CI) of the simulated data, with 17% of the observed concentrations outside that CI. The numbers of observed concentrations above and below the CI were consistent (103 below and 127 above); the number of samples outside the 90% CI across time since start of infusion was also consistent.

Oritavancin exposure and secondary PK parameter estimates. The summary statistics for oritavancin plasma exposure and secondary PK parameters are provided in Table 3. The mean V_{ss} of nearly 100 liters suggests that oritavancin is widely distributed after i.v. administration. The half-lives associated with the three-compartment nature of oritavancin PK indicate a rapid initial distribution (mean $t_{1/2\alpha}$ of 2.29 h) followed by a slower secondary distribution phase (mean $t_{1/2\beta}$ of 13.4 h) and a slow terminal elimination (mean $t_{1/2\gamma}$ of 245 h). Note that the exposure-related parameters (C_{max}, minimum plasma concentration [C_{min}], and area under the plasma concentration-time curve [AUC]) were obtained from the fitted profile, while the half-life estimates were obtained using the individual, *post hoc* parameter estimates and accepted equations (19).

Graphical depictions of various relationships between oritavancin exposure and patient demographic characteristics are provided in Fig. 3. Despite the statistically significant relationship between age and V_c, C_{max} is not predicted to increase significantly in elderly patients (Fig. 3, second row, left panel). The only body size measure to have an impact on oritavancin PK was height, which influenced oritavancin CL to a greater extent than body weight or BSA. However, height explains a relatively small amount of the IIV in oritavancin CL, and the magnitude of the relationship is such that oritavancin clearance would be predicted to increase by only 28% over a range in height of 140 to 200 cm. As shown in Fig. 3 (second row, right panel), the resultant impact on the AUC_{0-72} is minimal compared to the overall variability. Similarly, neither gender, renal function, race, nor diabetes is expected to have a clinically significant effect on oritavancin exposure (Fig. 3, middle and lower panels).

DISCUSSION

The objectives of these analyses were 2-fold. The first objective was to apply the previously established population PK model for oritavancin to the PK data from SOLO I and SOLO II in order to obtain accurate estimates of oritavancin exposure to facilitate the conduct of separate PK-PD analyses for efficacy. The plan allowed for modifications to this model as necessary to obtain an adequate fit to the data. The second objective was to identify any patient factors associated with the IIV in oritavancin population PK parameters.

The results of these analyses indicate that the previous population PK model structure (three-compartment, linear elimination) was appropriate for the PK data collected from SOLO I and SOLO II; precise estimates of the population PK parameters were obtained, and the fit of the model to the individual patient concentration-time data was robust. Statistically significant relationships were identified between the IIV in oritavancin CL and V_c and patient height and age, respectively. However, these covariates explained less than 5% of the variability in these parameters, such that oritavancin dose adjustments are not warranted based upon patient height or age. Given that none of the other covariates that were explored were related to the IIV in oritavancin PK, dose

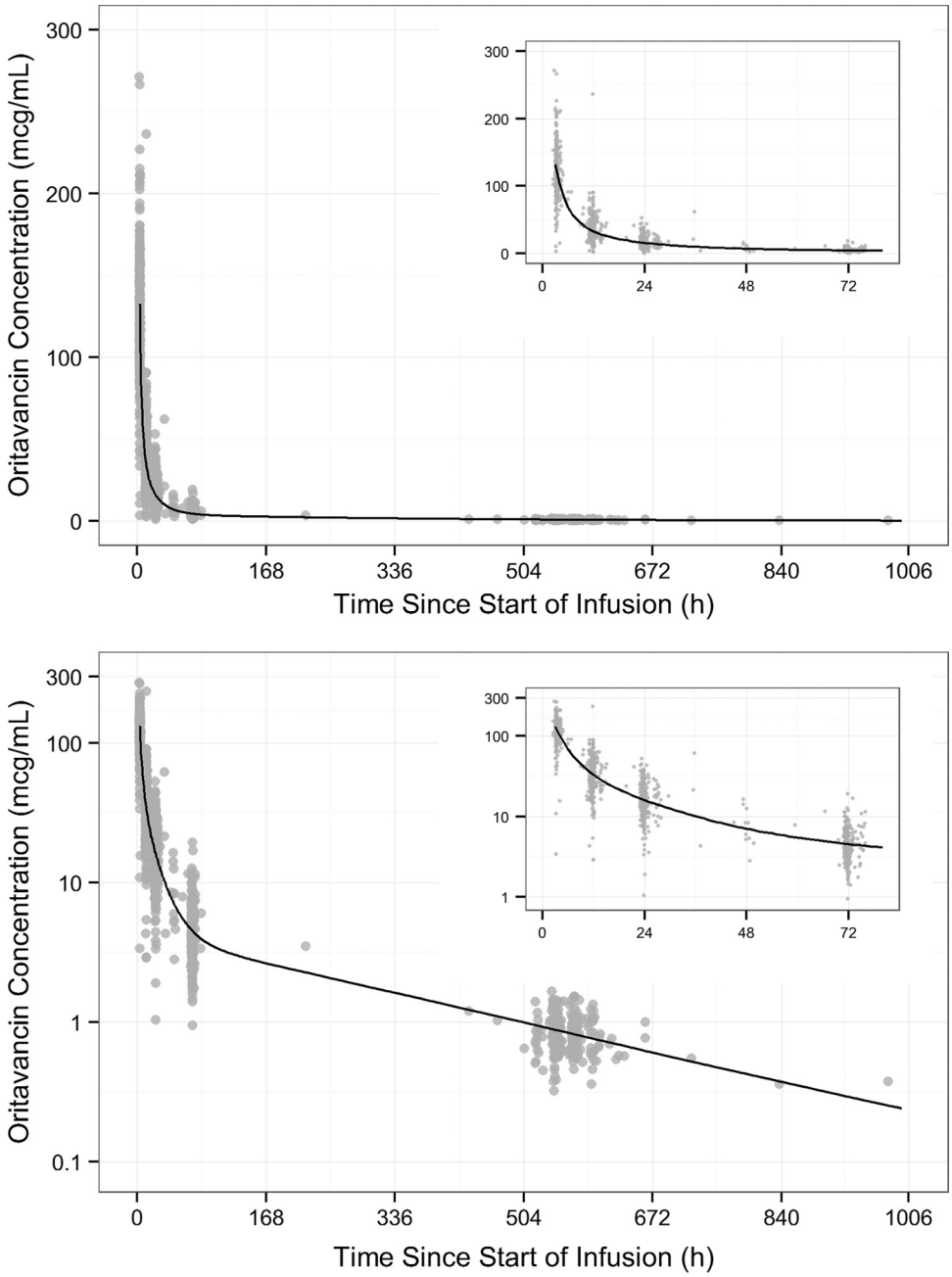

FIG 1 Population mean concentration-time profile following a single oritavancin dose of 1,200 mg i.v. administered over 3 hours, overlaid upon the observed concentration-time data. Top, linear scale; bottom panel, semilog scale. The insets show the first 80 hours of the postdose period. The solid lines through the data are the population mean predicted oritavancin concentration-time profiles.

adjustments are also not warranted on the basis of patient body size, BMI, race, gender, renal function, or the presence of diabetes.

In general, the population PK parameter estimates from the fit of the model to the pooled SOLO data were comparable to those obtained previously (6). However, the volume of distribution was about 50% lower in the patients from the SOLO studies than in those from the previous clinical trials. It is important to note that SOLO I and SOLO II are the only clinical studies to date that involved exclusive use of the 1,200-mg single dose of oritavancin and, perhaps more importantly, a 3-hour i.v. infusion. The differences seen in the population mean volume parameters (versus those for patients in previous phase 2/3 trials) may be a consequence of this unique aspect of the SOLO studies.

The results of the pooled population PK model also differ from those of the previous population PK analysis in terms of predicted oritavancin $t_{1/2}$ values. The mean $t_{1/2\beta}$ and $t_{1/2\gamma}$ values for the patients from SOLO I and SOLO II were substantially lower than those observed in the patients from the previous phase 2/3 studies (6). The mean $t_{1/2\beta}$ in the 297 patients from SOLO I and SOLO II included in this analysis was 13.4 h, compared to a mean of 31.2 h

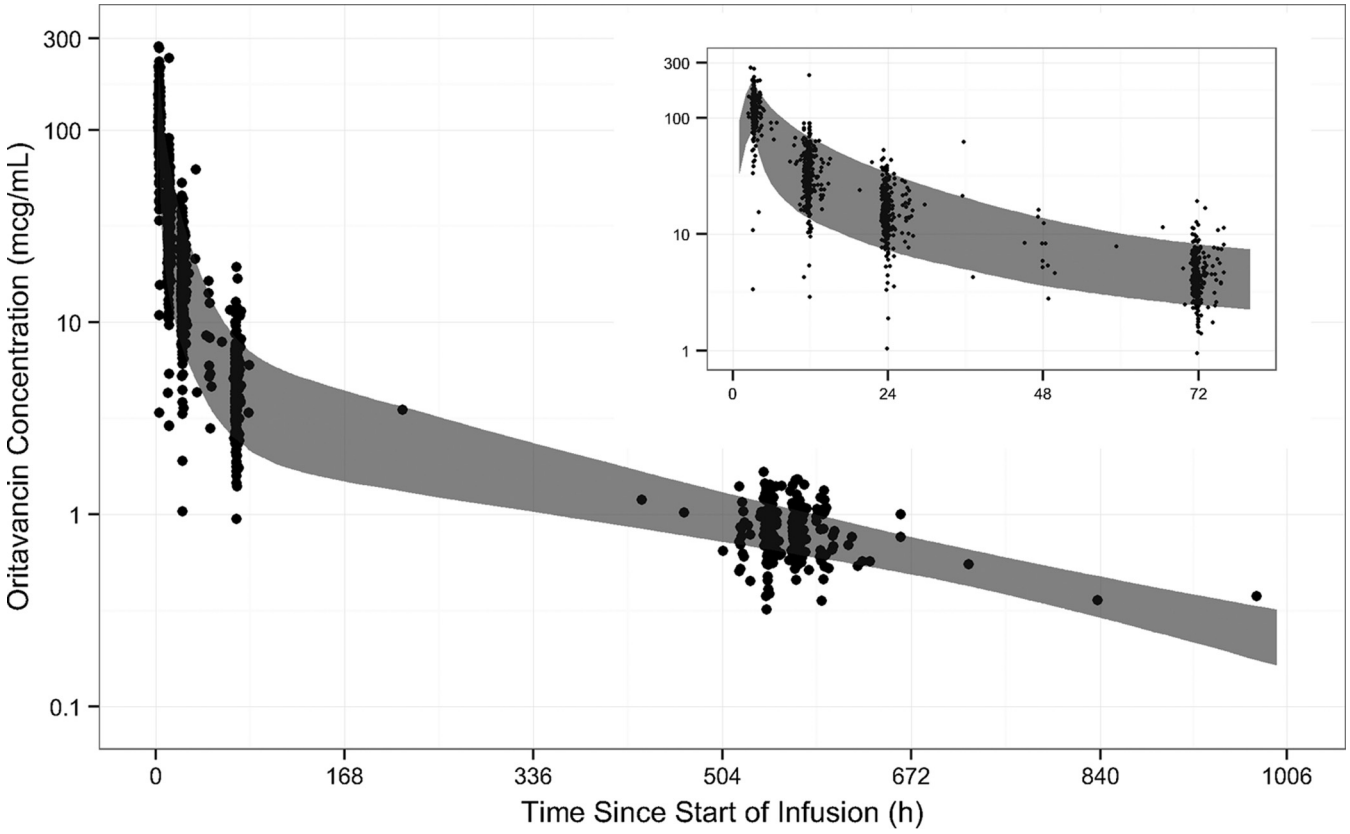

FIG 2 Visual predictive check for the final oritavancin population PK model using pooled data from SOLO I and II ($n = 1{,}337$ oritavancin concentrations). Black dots represent the observed oritavancin concentrations; grey band is the 90% confidence interval for the simulated concentrations from the visual predictive check.

in the 360 patients from the phase 2/3 trials included in the previous analysis (6). The mean $t_{1/2\gamma}$ values were 245 and 393 h in the pooled SOLO studies and in the previous phase 2/3 studies (6), respectively. The mean $t_{1/2\alpha}$ values were similar (2.29 h in the current analysis and 2.04 h in the previous analysis). While the exact cause of the differences in $t_{1/2}$ is not known, it is important to note that there were substantial differences in study design between the SOLO studies and the previous clinical studies (6). As mentioned above, all of the patients in the SOLO studies who were randomized to oritavancin received a single 1,200-mg dose, while the majority of the patients in the previous studies received daily dosing at lower doses (the majority at 200 or 300 mg/day, with a maximum of 10 mg/kg/day). The duration of infusion was also longer in the SOLO studies (3 h) than in the previous phase 2/3

TABLE 3 Summary statistics for individual, model-derived oritavancin plasma exposure and secondary PK parameters for all patients included in the PK population ($n = 297$)

Parameter[a]	Value							
	Mean (% CV)	Median	Minimum	5th percentile	25th percentile	75th percentile	95th percentile	Maximum
V_{ss} (liters)	97.8 (56.4)	90.2	15.1	47.3	69.1	115	158	615
C_{max} (μg/ml)	138 (23.0)	135	11.1	93.9	120	154	187	319
AUC_{0-24} (μg · h/ml)	1,110 (33.9)	1,050	109	686	885	1,300	1,720	4,060
AUC_{0-48} (μg · h/ml)	1,390 (36.5)	1,310	172	836	1,080	1,630	2,160	5,370
AUC_{0-72} (μg · h/ml)	1,530 (36.9)	1,430	223	910	1,190	1,790	2,420	5,900
AUC_{0-576} (μg · h/ml)	2,510 (31.4)	2,350	607	1,590	2,000	2,920	3,750	7,750
$AUC_{0-\infty}$ (μg · h/ml)	2,800 (28.6)	2,640	832	1,860	2,270	3,200	4,070	8,070
$t_{1/2\alpha}$ (h)	2.29 (49.8)	2.01	0.0192	1.01	1.55	2.78	4.43	6.97
$t_{1/2\beta}$ (h)	13.4 (10.5)	13.1	7.75	12.0	12.6	14.0	16.2	20.3
$t_{1/2\gamma}$ (h)	245 (14.9)	242	139	192	222	262	308	435

[a] Abbreviations: V_{ss}, steady-state volume of distribution; C_{max}, maximum plasma concentration; AUC_{0-24}, area under the plasma concentration-time curve from time zero to 24 h; AUC_{0-48}, area under the plasma concentration-time curve from time zero to 48 h; AUC_{0-72}, area under the plasma concentration-time curve from time zero to 72 h; AUC_{0-576}, area under the plasma concentration-time curve from time zero to 576 h; $t_{1/2\alpha}$, half-life at alpha phase; $t_{1/2\beta}$, half-life at beta phase; $t_{1/2\gamma}$, half-life at gamma phase; CV, coefficient of variation.

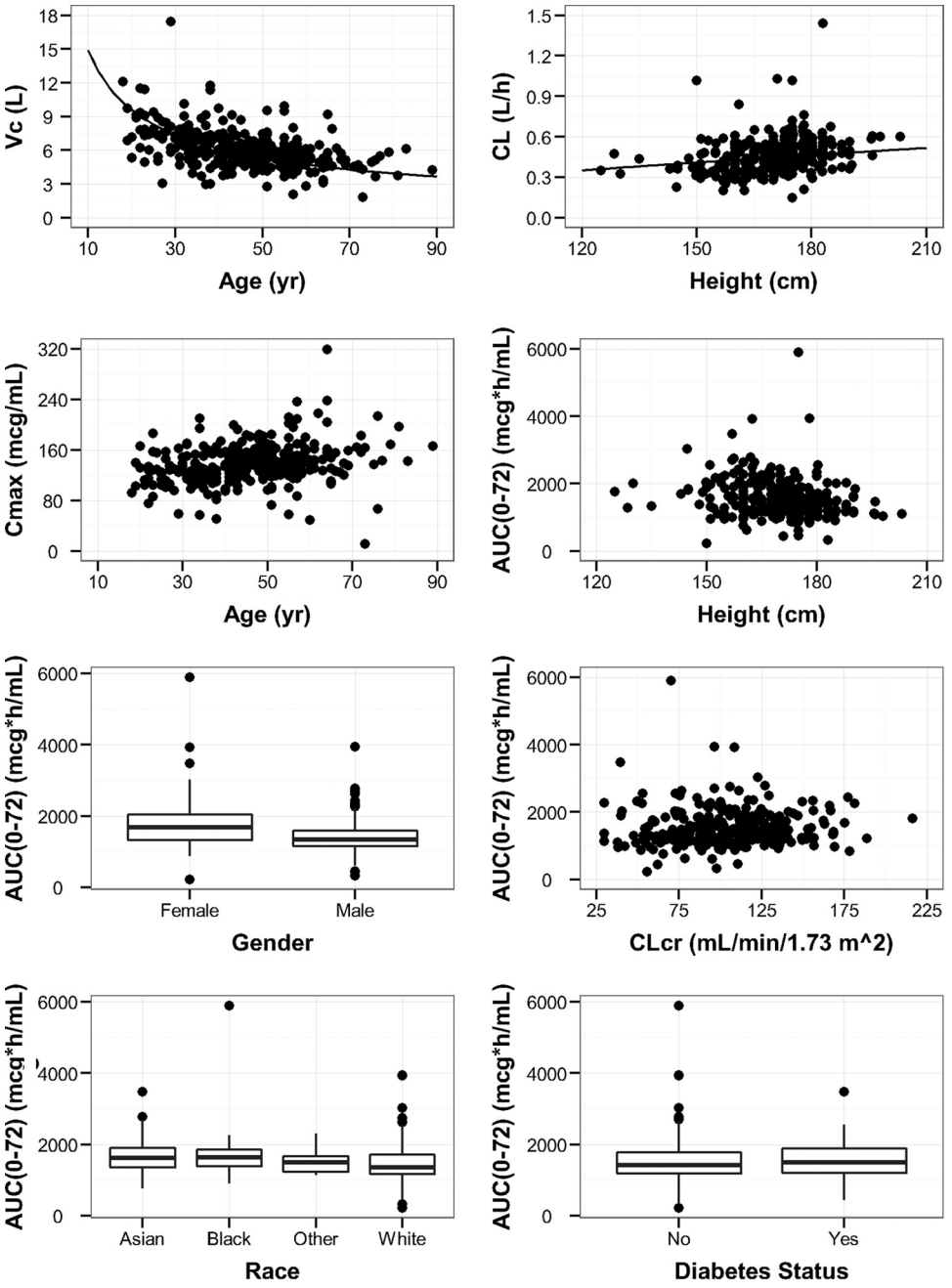

FIG 3 Graphical depictions of various relationships between oritavancin exposure and patient demographic characteristics. Solid lines in the top two panels show the population mean relationship between the covariate on the *x* axis and the PK parameter on the *y* axis.

studies (0.5 to 1 h). There were also differences in the PK sampling schemes among the studies. Generally, the duration of sampling was shorter (typically 24 h) and more frequent (10 samples per patient) than in the SOLO studies (sampling duration of at least 24 days; 5 samples per patient). All of these factors may have contributed to the observed differences in $t_{1/2}$ values between the two analyses. Note that, despite the extremely long $t_{1/2\gamma}$, 60% of the overall exposure ($AUC_{0-\infty}$) is achieved within 3 days after the start of i.v. infusion, and over 90% is achieved in the first month. Thus, the oritavancin exposure is maximized in the first few days of therapy, which is likely to maximize the antibacterial effect (22).

Traditional covariate model building techniques were employed to identify those patient descriptors (age, body, size, renal function, etc.) that were associated with the IIV in oritavancin PK. This process led to the identification of two statistically significant relationships: a relationship between age and V_c in which V_c decreased with increasing age and a relationship between height and CL in which CL increased with increasing height. These relationships explained a relatively small amount of the IIV in oritavancin PK parameters but were retained in the model as they aided in reducing the correlation between CL and V_c and provided for an increased precision in the fitted parameters as a whole. This fact,

combined with the modest impact of these relationships on oritavancin plasma exposures of interest (C_{max} or AUC_{0-72}) indicates that the dose of oritavancin does not need to be modified on the basis of age or height. Furthermore, none of the other patient descriptors included in the analysis (body weight, BSA, BMI, race, gender, diabetes, and renal function) were related to the IIV in oritavancin PK. Thus, the results of the analysis indicate that the recommended clinical dose (1,200 mg oritavancin administered over 3 h as an i.v. infusion) is appropriate regardless of differences in patient age, body size, gender, race, renal impairment, or presence of diabetes.

It is important to recognize some of the limitations of this analysis. Given that the PK data were collected as part of two large, multinational phase 3 studies, it was necessary to employ a sparse sampling scheme. Furthermore, the sites that enrolled patients in the SOLO studies were not universally experienced in the collection of PK data. Two factors help mitigate the importance of these potential issues. First, extensive population PK analyses had been conducted prior to the design of the SOLO studies (6); the knowledge gained in these analyses was used to design an optimal sampling scheme for these studies in order to optimize the information content from the minimum number of PK samples. A second limitation is that, despite the number of patients included in the data set, there are a relatively limited number of patients at the margins of the demographic distributions. Thus, the results of the analyses are applicable to the range of covariates observed in the SOLO trials (e.g., height ranging from 129 to 203 cm, CL_{CR} of >29 ml/min/1.73 m^2, etc.).

In conclusion, the population PK of oritavancin in patients enrolled in the SOLO studies were best described using a three-compartment model with linear elimination. Patient height was significantly associated with the interindividual variability in CL, while patient age was significantly associated with the interindividual variability in V_c. The excellent individual fits obtained using population PK methods indicate that the primary objective of the analysis was met. A robust description of the plasma PK of oritavancin in these patients was achieved such that the derived measures of oritavancin exposure are expected to be both accurate and precise. These measures of exposure were indexed to drug potency and were subsequently used to conduct separate PK-PD analyses for antimicrobial efficacy observed in SOLO studies (16).

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