J Antimicrob Chemother 2014; **69**: 200–210
doi:10.1093/jac/dkt342 Advance Access publication 12 September 2013

Journal of Antimicrobial Chemotherapy

Clinical and pharmacokinetic considerations for the use of daptomycin in patients with *Staphylococcus aureus* bacteraemia and severe renal impairment

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Received 22 April 2013; returned 22 June 2013; revised 22 July 2013; accepted 26 July 2013

Objectives: To support daptomycin dosing recommendations in patients with *Staphylococcus aureus* bacteraemia (SAB) and severe renal impairment using simulations from a population pharmacokinetic model for daptomycin.

Methods: A population pharmacokinetic model was developed using 4875 daptomycin plasma concentrations from 442 subjects. Daptomycin 24 h AUC and C_{max} were then simulated for subjects with a $CL_{CR} < 30$ mL/min [with or without haemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD)] for different dosing frequencies (every 24 h, every 48 h and three times weekly) with doses of 4 mg/kg and 6 mg/kg. These results were compared with efficacy and safety exposure references based on daily dosing to understand the implications of less frequent dosing (for example, higher exposures on day 1 versus day 2) and to evaluate the 4 mg/kg versus 6 mg/kg regimens.

Results: Substantially more patients with SAB and severe renal impairment were underexposed (24 h AUCs compared with an efficacy reference of 6 mg/kg/day, $CL_{CR} \geq 30$ mL/min, pivotal trial population) at 4 mg/kg every 48 h compared with 6 mg/kg. C_{max} results also favoured 6 mg/kg every 48 h over 4 mg/kg every 48 h. Both exposure metrics at 6 mg/kg every 48 h also stayed below the defined safety limits (based on 12 mg/kg/day, $CL_{CR} > 80$ mL/min, the highest dose in controlled clinical trials).

Conclusions: For patients with SAB and $CL_{CR} < 30$ mL/min, or receiving HD or CAPD, the dose recommendation of 6 mg/kg every 48 h provides appropriate daptomycin exposure for this indication; this will not be the case for patients receiving 4 mg/kg every 48 h.

Keywords: dosing, haemodialysis, continuous ambulatory peritoneal dialysis

Introduction

Daptomycin is an antibiotic active against a range of Gram-positive bacteria,[1] with greater bactericidal activity against methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* (MRSA) than nafcillin, vancomycin or any other currently approved anti-MRSA antibiotic.[2] This activity profile makes it a particularly valuable treatment option for serious infections, including those in immunocompromised patients,[3] such as patients with severe renal impairment (SRI) ($CL_{CR} < 30$ mL/min) undergoing dialysis.[4] It is notable that MRSA infections in patients receiving dialysis account for ~15% of MRSA infections, and patients with chronic kidney disease are 100 times more likely to develop MRSA infection than the general population.[4] Despite this epidemiology, there are limited pharmacokinetic (PK) and pharmacodynamic (PD) data to support antibiotic dosing regimens for patients with *S. aureus* bacteraemia (SAB) who have renal impairment.

Daptomycin has both a linear PK profile, which is dose-proportional between 6 mg/kg and 12 mg/kg when given once daily for up to 14 days,[5] and bactericidal activity that is concentration dependent.[6] The 24 h AUC and the C_{max} are the most relevant PK parameters that correlate with the efficacy of daptomycin *in vivo*.[6] Preclinical studies demonstrate that the AUC/MIC and C_{max}/MIC ratios are the parameters that best correlate with outcome.[6,7] The required AUC/MIC and C_{max}/MIC ratios for optimal killing vary according to the infecting pathogen and are generally higher for *S. aureus* than for *Streptococcus pneumoniae* or *Enterococcus faecium.* A dose of 6 mg/kg daptomycin is expected to result in exposure that readily exceeds the target ranges for *S. aureus* infections, resulting in efficacy.[6–8]

There is currently no PK parameter or exposure metric that reliably predicts clinically relevant daptomycin-related toxicity, although a clear relationship between the frequency of daptomycin dosing (rather than AUC or C_{max}) and muscular toxicity has been determined, with once-daily dosing minimizing the potential for skeletal muscle effects compared with more frequent dosing, even with administration of the same total daily dose.[9,10] Although it is plausible that the trough concentration (C_{min}) could be an indicator of toxicity, the C_{min} threshold that is clinically relevant has not been defined. Bhavnani *et al.*[11] demonstrated a potential correlation between a $C_{min} \geq 24.3$ mg/L and an increased probability of creatine phosphokinase (CPK) elevation, although this finding was based on a small sample size (six patients) and it should be considered that CPK elevations without any symptoms are not necessarily clinically relevant. In addition, post-marketing surveillance suggests that patients differ greatly in their susceptibility to muscle toxicity. A study with doses of daptomycin ≥8 mg/kg (patients in whom daptomycin C_{min} is likely to exceed ≥24.3 mg/L) found no significant correlation between dosage and the highest CPK levels observed.[12] CPK levels are, however, considered to be a sensitive marker of daptomycin-related muscle toxicity, and regular monitoring during therapy is currently recommended.[13]

Daptomycin is primarily eliminated by the kidneys: between 37% and 68% of a dose of daptomycin is recovered as unchanged drug in the urine.[5] Daptomycin PK remain linear in patients with renal insufficiency.[14] Daptomycin exposure is not markedly different between subjects with a CL_{CR} of 30–49 mL/min and subjects with a CL_{CR} of 50–79 mL/min or subjects with normal renal function. However, in patients on haemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD), systemic exposure to a given dose is 1.5–2 times greater than that in healthy volunteers with normal renal function.[14–17] Adjustments to the dosing scheme are necessary for patients with a CL_{CR} <30 mL/min in order to prevent overexposure and potential toxicity while maintaining efficacy. Reducing the dosage in HD/CAPD patients without changing the dosing interval is not the best approach.[18,19] The use of lower dosages will result in a lower C_{max}, which may result in suboptimal bacterial killing and lower efficacy rates.[13,19–21] In contrast, in patients with severe renal impairment, prolongation of the dosing interval from every 24 h to every 48 h correlates with daptomycin exposures similar to those simulated for patients with SAB/infective endocarditis (IE) who have a CL_{CR} ≥30 mL/min.[14]

Daptomycin is approved for use in complicated skin and soft-tissue infections (cSSTIs) at a dose of 4 mg/kg every 24 h in Europe and the USA.[13,18] In the USA, it is also approved for *S. aureus* bloodstream infections (i.e. SAB), including right-sided IE (RIE) at a dose of 6 mg/kg every 24 h,[18] whereas in Europe this indication is SAB with RIE or cSSTI and RIE due to *S. aureus*.[13] The same doses at a reduced frequency of every 48 h are recommended for patients with a CL_{CR} <30 mL/min (with or without HD or CAPD), with the suggestion to administer daptomycin immediately after dialysis when possible, owing to a variability in dialysis factors such as filter size, pressure and volume.[13]

We report here some modifications to a previously established population PK model for daptomycin,[22] updated with all relevant PK samples available from clinical trials sponsored by Novartis Pharma AG and Cubist Pharmaceuticals. The model was used as a tool to explore daptomycin dosing regimens through simulation. The simulation results, compared with efficacy and safety references from previous clinical trials, support dosing recommendations in patients with SAB and SRI.

Methods

Patients

PK data plus individual clinical and demographic covariate factors such as age, sex, race and renal function were collected in the 15 studies used by Dvorchik *et al.*,[22] who reported the first population PK analysis of daptomycin. Over the course of further development of the model, additional data from two Phase I studies of renally impaired subjects and three Phase III/IV studies (pivotal Phase III studies in SAB/IE and in cSSTIs, and a Phase IV study in patients with renal impairment and Gram-positive cSSTIs) were added to the PK database. Details of each of these studies are provided in Table 1. Subjects with normal renal function (CL_{CR} >80 mL/min), mild renal impairment (CL_{CR} 50–80 mL/min) and moderate renal impairment (30 to <50 mL/min) were pooled and categorized as CL_{CR} ≥30 mL/min ($n=374$). Further subject categories were defined as SRI (CL_{CR} <30 mL/min, not on dialysis; $n=11$), end-stage renal disease (ESRD) on HD every 48 h or three times weekly ($n=40$) and ESRD on CAPD ($n=14$). The majority of subjects on dialysis were dosed with daptomycin immediately after the end of dialysis.

Daptomycin assay

A validated HPLC method was used to analyse the plasma daptomycin concentrations in all but two of the studies. The lower limit of quantification for this was 3 mg/L and the inter-assay coefficient of variation was 3.51%.[16] For one study in healthy volunteers (DAP-00-04), a microbiological assay with a limit of quantification of 2 mg/L and an inter-assay coefficient of variation of 6.3% was used; the results of the assay correlated well with those of the HPLC assay and had a similar sensitivity. A validated liquid chromatography/tandem mass spectrometry method with a much lower limit of quantification of 0.1 mg/L was used for the other study (DAP-00-01) with healthy and renally impaired subjects.[22]

Population PK model

The established and validated model published by Dvorchik *et al.*[22] was updated with additional PK data, and simulations were conducted to explore daptomycin dosing regimens in patients with renal impairment. The model and database were updated in two stages. In stage 1, data from three studies (one Phase I study in subjects with renal impairment, and two Phase II studies in subjects with IE or bacteraemia and cSSTIs) were added to the Dvorchik *et al.*[22] database; the model parameterization was slightly modified (as described in the section on covariate analysis) and additional covariates were included. The final model in this step was evaluated using a posterior predictive check with the average concentration (C_{avg}) as the metric of interest. In stage 2, two additional studies in subjects with renal impairment (one Phase I and one Phase IV) were added to the database. The final model from stage 1 was found to sufficiently describe the new data, so no additional model modification or validation was carried out in this stage. Population parameter values were very similar to those from stage 1 but were updated to reflect the fit to the full database. Only the results of the final model with the full database are shown in this manuscript.

The Dvorchik model is a two-compartment linear disposition model parameterized in terms of total clearance (CL), central volume of distribution (V1), peripheral volume of distribution (V2), inter-compartmental clearance (Q) and duration of zero-order infusion (D1). Inter-individual variability for the parameters was described using an exponential error model. The residual error was described by an additive model with different parameters for the study that used a liquid chromatography/tandem mass spectrometry

Table 1. Study designs

Clinical Phase (ClinicalTrials.gov identifier)	Subject characteristic(s)	Dosing regimen	No. of subjects	No. of samples/ subject	Sample collection timepoints
I	subjects with ESRD on HD with low-flux and high-flux dialysis membranes	a single loading dose of 8 mg/kg on day 1, followed by eight additional doses of daptomycin (6 mg/kg) given after every dialysis on days 3, 5, 8, 10, 12, 15, 17 and 19 for a total of nine doses over 21 days	13	45	days 1, 8 and 17 (pre- and post-dose and at the EOI); days 3, 5, 10, 12, 15 and 19 (pre- and post-dose and 5 min prior to EOI)
I (NCT00490737)	non-infected subjects with ESRD on dialysis	6 mg/kg three times weekly (48 h–48 h–72 h) in patients undergoing HD; 6 mg/kg every 48 h in patients undergoing CAPD	16	28	days 1, 3 and 5 (pre- and post-dialysis and 0.5 h after EOI); days 1 and 5 (1, 2, 4, 6, 8, 12, 16 and 24 h post-dose); HD patients day 8 (pre- and post-dialysis); CAPD patients day 7 (pre- and post-dialysis)
III (NCT00093067)	patients with IE or bacteraemia caused by *S. aureus*	6 mg/kg every 24 h or conventional iv therapy [2 g of semi-synthetic penicillin every 4 h (nafcillin, oxacillin, cloxacillin or flucloxacillin) or 1 g of vancomycin every 12 h]	108	6	baseline and day 5 (pre-dose, 15–30 min after EOI, 60–90 min after EOI, 3–5 h after EOI and 9–12 h after EOI)
III	patients with cSSTIs caused by Gram-positive bacteria	4 mg/kg iv every 24 h over 30 min	15	7	day 4 (pre-dose and 0, 15 and 30 min and 3.5, 7.5 and 23.5 h post-dose)
IV (NCT00102947)	patients with renal impairment and cSSTIs caused by Gram-positive bacteria	group 1: CL_{CR} 30–50 mL/min, dose of 4 mg/kg every 24 h; group 2: CL_{CR} <30 mL/min, dose of 4 mg/kg every 48 h; group 4: ESRD and undergoing HD, dose 4 mg/kg every 48 h while an inpatient and 4 mg/kg three times weekly (48 h–48 h–72 h) with HD while an outpatient[a]	8	variable[b]	for outpatients, full PK sampling on day 1: within 0.5 h pre-dose; 0.5 h EOI; and 0.75, 1, 4, 8 and 24 h post-dose for group 1, plus 36 and 48 h for groups 2 and 4, and pre- and post-dialysis for group 4; limited sampling on days 3, 5, 7, 9, 11 and 13 for inpatients, full PK sampling on days 5, 9 and 13; limited sampling on days 3, 7 and 11

EOI, end of infusion; iv, intravenous(ly).
[a]No patients were evaluated in group 3; therefore, the data are not included.
[b]The number of samples per subject depended on the duration of hospital treatment.

assay owing to a much lower assay sensitivity compared with the HPLC and microbiological assays.[22] A proportional residual error component was also evaluated, but this addition caused under-prediction of the higher concentrations as well as unrealistic estimates for the length of daptomycin infusion, with no improvement in the diagnostic plots. Population PK analyses were conducted via non-linear mixed-effects modelling with NONMEM® (version VI Level 2.0)[23] using first-order conditional maximum likelihood estimation with eta–epsilon interaction.

Covariates

The covariates considered significant in the original model analyses by Dvorchik *et al.*[22] were retained for re-evaluation. The new data from subjects with ESRD on HD and patients with IE or bacteraemia suggested the investigation of two additional covariates: HD membrane type (low-flux or high-flux dialysis membranes) and final diagnosis by the Independent External Adjudication Committee (IEAC) (1 = left-sided IE, 2 = complicated RIE, 3 = uncomplicated RIE, 4 = complicated bacteraemia and 5 = uncomplicated bacteraemia) for patients with SAB/IE.[24]

Covariate analysis

The full covariate model was constructed based on exploratory graphics, scientific interest and mechanistic plausibility. Categorical covariates were modelled by indicator variables as in Dvorchik *et al.*,[22] but the continuous covariates were modelled using a normalized power model rather than a linear relationship, as shown in the equation below:

$$P_i = TH1 \cdot \left(\frac{COV}{\overline{COV}}\right)^{TH2}$$

where P_i is the individual estimate of the parameter, COV is the value of the covariate and $\overline{COV}$ is the median value of the covariate in the study population. TH1 and TH2 are the population values for the intercept and slope in the power model, respectively.

Model evaluation

The final daptomycin population PK model was evaluated in accordance with US FDA population PK guidance.[25] The final model and parameter estimates from stage 1 were investigated using a predictive check method, for which the basic premise is that a model and parameters (in this case, C_{avg}) derived from an observed dataset should produce simulated data that are similar to the original observed data. This type of model qualification is more practical and useful compared with approaches such as visual predictive check, considering that the PK database is built from multiple trials with diverse study designs and non-fixed sampling times in most of the Phase II/III trials.

Simulations

The final model (after stage 2) was used to perform simulations to estimate the systemic exposures to daptomycin resulting from different dosing regimens: 4 mg/kg every 48 h, 6 mg/kg every 24 h, 6 mg/kg every 48 h, and 4 and 6 mg/kg three times weekly (48 h–48 h–72 h, in HD only). Simulations with rich sampling were performed for each subject, based on their individual PK parameter values, to predict the daptomycin concentrations for 14 days. Steady-state PK metrics were estimated using the last dose data (analogous to steady state): the observed C_{max} at the end of infusion was recorded, and the AUC for each 24 h period of the last-dose profile was calculated using the trapezoidal rule for individual patients. The exposure metrics were summarized by the level of renal impairment or dialysis type: CL_{CR} ≥30 mL/min, SRI, HD and CAPD.

Reference efficacy exposure range and safety threshold

Based on the currently approved dose recommendations for daptomycin in SAB/IE, the reference range of drug exposure for efficacy was selected to be the IQR (between the 25th and 75th percentile) of the simulated steady-state AUC_{0-24} and C_{max} for patients with RIE and/or SAB with CL_{CR} ≥30 mL/min receiving 6 mg/kg every 24 h. This subset of patients was representative of and included patients who received daptomycin in the pivotal SAB/IE study by Fowler *et al.*,[24] the largest clinical trial ever performed in patients with SAB.

The 75th percentiles of the steady-state AUC_{0-24} and C_{max} for daptomycin reported in healthy volunteers with normal renal function who received a dose of 12 mg/kg every 24 h were used as the safety thresholds.[5] This choice is supported by the fact that 12 mg/kg every 24 h is the highest dose of daptomycin studied in controlled clinical trials, and a favourable safety and tolerability profile was observed.[5]

Results

A total of 442 adult subjects (consisting of healthy volunteers and patients with cSSTI, IE or bacteraemia) with 4875 daptomycin plasma concentration samples were analysed in the population PK model. A summary of the population demographics is presented in Table 2. CL_{CR} values calculated with the Cockcroft–Gault formula demonstrated the expected positive correlation with weight. High (>150 mL/min) values of CL_{CR} were truncated to 150 mL/min to ensure physiologically realistic values. ESRD subjects on dialysis represented 12.2% of the PK population.

Final population PK model

A validated model for daptomycin PK published by Dvorchik *et al.*[22] was chosen as the base model for the current analyses. The

Table 2. Subject demographics

Characteristic	Pooled analysis, *N* = 442
Body weight (kg), median (range)	76 (46–152.8)
Sex, *n* (%)	
male	258 (58)
female	184 (42)
Gram-positive bacterial infection, *n* (%)	
yes	256 (58)
no	186 (42)
Dialysis membrane, *n* (%)	
low flux	6 (1)
high flux	18 (4)
not available	418 (95)
IEAC diagnosis, *n* (%)	
LIE	8 (2)
complicated RIE	12 (3)
uncomplicated RIE	5 (1)
complicated bacteraemia	52 (12)
uncomplicated bacteraemia	31 (7)
missing	334 (76)
Body temperature (°C), median (range)	37.1 (35.1–40.1)

LIE, left-sided IE.

structural model adequately described the new data added to the database in both stages of subsequent model development, so no evaluation of other structural models was carried out. A graphical evaluation of covariate–parameter relationships supported retaining the previous covariates from the Dvorchik model in the model; no formal covariate search or backwards elimination step on previously included covariates was undertaken. These graphical evaluations also suggested that dialysis membrane and IEAC's final diagnosis should enter the model as covariates on CL.[22] The model evaluation results provided evidence that both the fixed and random effects components of the final model were reflective of the observed data as well (predictive check not shown).

The final model comprised separate equations (Figure 1), with some shared covariate effects, for CL in non-dialysis and dialysis patients; all other equations were applied to both populations.

The model successfully fitted the daptomycin concentration–time data, allowing an estimation of daptomycin PK parameters and the covariates affecting the PK properties of daptomycin. Plots of the observed versus predicted concentrations (both individual and population) and of the conditional weighted residuals and normalized prediction distribution errors versus time and versus predicted values were well centred, with relatively few outliers (Figure 2). These figures include only the subjects with SRI (CL_{CR} <30 mL/min) and those on dialysis, because all subsequent simulations for this analysis were based on this patient population and their individual PK parameters.

$$CL_{\text{DIALYSIS}_i} = \theta 1 \cdot \left\{\frac{TEMP\ (°C)}{37\ (°C)}\right\}^{\theta 9} \cdot \theta 8^{SEX[Female]} \cdot \theta 13^{DIAM[LowFlux]} \cdot \theta 14^{DIAM[HighFlux]} \cdot e^{\eta CL_i}$$

$$V1_i = \theta 2 \cdot e^{\eta V1_i}$$

$$Q_i = \theta 3 \cdot \left\{\frac{WT\ (kg)}{70\ (kg)}\right\}^{\theta 10} \cdot e^{\eta Q_i}$$

$$V2_i = \theta 4 \cdot \left\{\frac{WT\ (kg)}{70\ (kg)}\right\}^{\theta 11} \cdot \theta 12^{INFN[INFN1]} \cdot e^{\eta V2_i}$$

$$D1 = \theta 5$$

$$CL_{\text{NON-DIALYSIS}_i} = \theta 6 \cdot \left\{\frac{CLC0\ (mL/min)}{80\ (mL/min)}\right\}^{\theta 7} \cdot \left\{\frac{TEMP\ (°C)}{37\ (°C)}\right\}^{\theta 9} \cdot \theta 8^{SEX[Female]} \cdot \theta 15^{IEAC[IEAC1]} \cdot \theta 16^{IEAC[IEAC2]} \cdot \theta 17^{IEAC[IEAC3]} \cdot \theta 18^{IEAC[IEAC4]} \cdot \theta 19^{IEAC[IEAC5]} \cdot e^{\eta CL_i}$$

$$CP_i = \frac{A1_i}{V1_i}$$

Figure 1. Model for daptomycin clearance in non-dialysis and dialysis patients. η, NONMEM inter-individual error; θ, NONMEM fixed effect parameter; *A*1, amount in central compartment (mg); *CL*, clearance; CL_{DIALYSIS}, clearance in dialysis patients (L/h); $CL_{\text{NON-DIALYSIS}}$, clearance in non-dialysis patients (L/h); *CLC0*, creatinine clearance at baseline (mL/min); *CP*, concentration in the central compartment (mg/L); *DIAM*, dialysis membrane; *D*1, duration of zero order infusion (h); *i*, individual; *INFN*, presence of Gram-positive infection; *Q*, inter-compartmental clearance (L/h); *TEMP*, temperature (°C); *V*1, central compartment volume of distribution (L); *V*2, peripheral compartment volume of distribution (L); *WT*, weight at baseline (kg).

The parameter values for a 'typical' subject (70 kg male, normothermic, without an IEAC diagnosis) were: $CL_{\text{non-dialysis}}$ = 0.751 L/h (3%), assuming a CL_{CR} of 80 mL/min, CL_{dialysis} = 0.231 L/h (4%), V1 = 4.89 L (3%), Q = 3.64 L/h (4%), V2 = 3.19 L (3%) and D1 = 0.41 h (0.1%). These point (standard error) estimates of the parameters, and the estimates of unexplained inter-individual variability (coefficient of variation), were consistent with those from the previous population PK analysis[22] in healthy volunteers and in patients with cSSTIs. Consistent with previous results, renal function was the most significant covariate affecting daptomycin CL.[22] All final population model parameters are provided in Table S1 (available as Supplementary data at *JAC* Online).

Individual daptomycin PK parameters (CL and $t_{1/2}$) are summarized by renal function subgroup in Table 3. Overall, subjects with a CL_{CR} <30 mL/min (not undergoing dialysis) had a lower daptomycin CL, and therefore a higher exposure at the same dosing regimen, than subjects with CL_{CR} ≥30 mL/min.

Simulations

The reference efficacy exposure ranges (i.e. the IQR for the simulated steady-state exposure in SAB/IE patients with a CL_{CR} ≥30 mL/min on 6 mg/kg every 24 h) were determined to be an AUC_{0-24} of 465–761 mg·h/L and a C_{max} of 66–112 mg/L (Figure 3). The corresponding safety thresholds (75th percentile of exposure in subjects receiving 12 mg/kg every 24 h) were an AUC_{0-24} of 1422 mg·h/L and a C_{max} of 197 mg/L (Figure 3). Based on the individual PK parameter estimates, the exposure metrics at steady state (AUC_{0-24} and C_{max}) following daptomycin dosing at 4 mg/kg or 6 mg/kg are summarized for subjects with SRI, HD and CAPD in Figures 4 and 5 and compared with the references.

Discussion

Clinically robust, evidence-based definitions for the target concentrations in humans are currently available for few antibiotics. The present analysis used a validated population PK model for daptomycin and, to our knowledge, the most comprehensive clinical and PK information currently available. The reference thresholds for exposure were derived from relevant clinical trial data where daptomycin was shown to be effective and well tolerated. For efficacy exposure, this was the IQR of the exposure in patients representative of those in the pivotal SAB/IE study, the largest study in this indication to date.[24] Reference safety thresholds were derived from the PK of the highest dose tested in clinical trials, which was well tolerated.[5] These reference ranges, which are also in line with previously published ranges for microbiological targets,[6,7,20] are the basis for the dosing recommendations discussed below.

A large proportion of subjects with SRI treated with 4 mg/kg every 48 h will have insufficient 24 h AUCs on both the first and second days after dosing (Figure 4c) and the majority of subjects with SRI will not achieve the reference C_{max} (Figure 5c). In contrast, when treated with 6 mg/kg, insufficient AUC_{0-24} for efficacy will not be an issue on the first day, and on the second day a higher proportion of patients will achieve the reference exposure for efficacy as compared with the 4 mg/kg dose (Figure 4c). Most subjects with SRI will also achieve the reference C_{max} for efficacy with 6 mg/kg. Similarly for subjects on HD, with respect to AUC_{0-24}, the majority

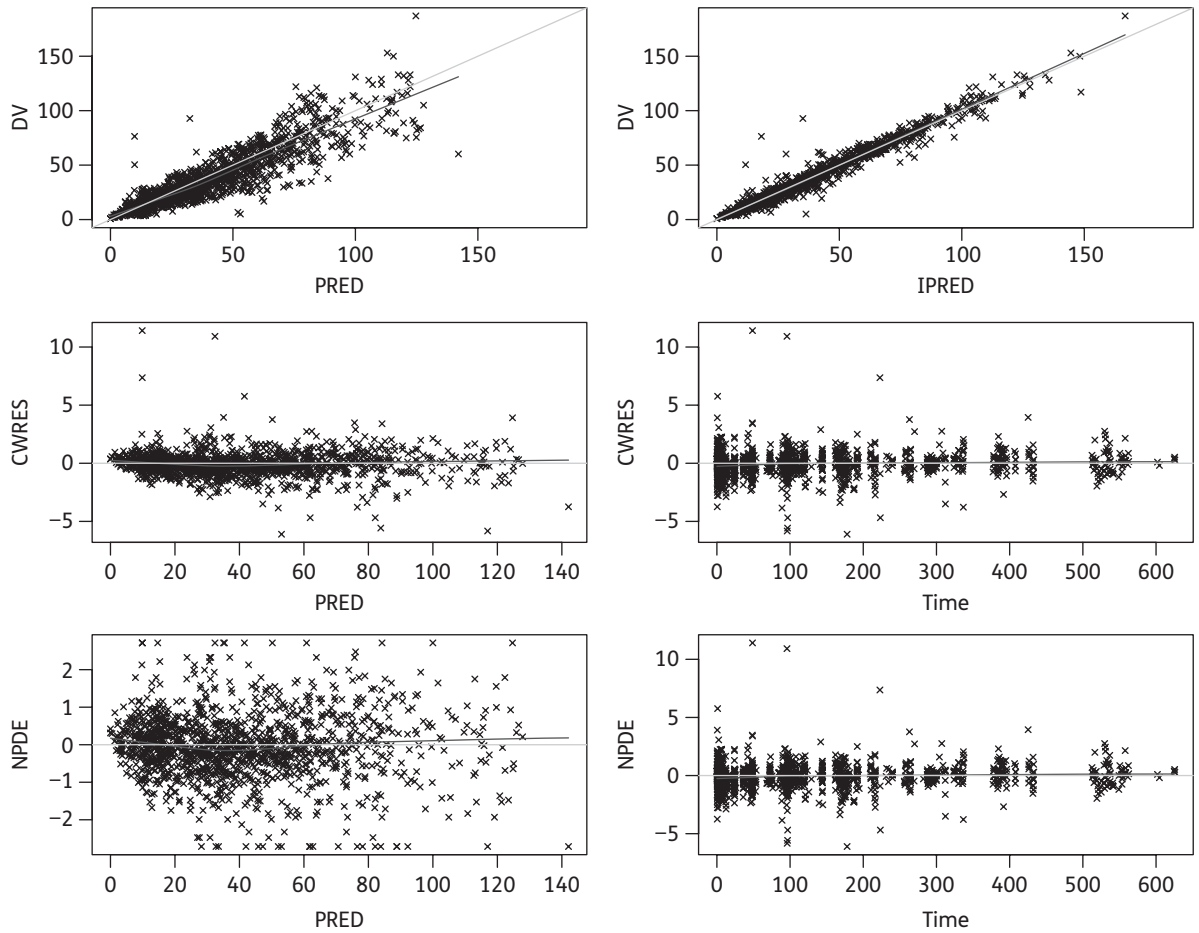

Figure 2. Goodness-of-fit diagnostic plots for subjects with SRI (CL_{CR} <30 mL/min) and those on dialysis. Top row (left to right): observations versus population predictions (PRED) and versus individual predictions (IPRED); middle row (left to right): conditional weighted residuals (CWRES) versus PRED and versus time; bottom row (left to right): normalized prediction distribution errors (NPDE) versus PRED and versus time. The grey line through the points in each plot is a local regression. DV, daptomycin concentrations (mg/L).

Table 3. Daptomycin PK parameters by renal function

	Mean (SD); %CV	
Renal function	$t_{1/2}$ (h)	CL (mL/h/kg)
Normal: CL_{CR} >80 mL/min (n=237)	9.08 (3.11); 34.3	11.4 (4.17); 36.5
Mild renal impairment: CL_{CR} 50–80 mL/min (n=97)	11.4 (8.05); 70.6	9.97 (3.51); 35.2
Moderate renal impairment: CL_{CR} 30 to <50 mL/min (n=40)	15.2 (5.76); 38.0	8.15 (3.09); 37.9
SRI: CL_{CR} <30 mL/min (n=11)	24.3 (8.01); 32.9	6.05 (2.84); 47.0
ESRD on HD (n=40)	31.2 (9); 28.9	3.43 (1.08); 31.5
ESRD on CAPD (n=14)	29.3 (8.34); 28.5	2.98 (0.92); 30.8

%CV, percentage coefficient of variation.
Three subjects were excluded from the analysis owing to unknown renal status.

will fall below the reference range every second day if dosed with 4 mg/kg every 48 h but within it if dosed with 6 mg/kg every 48 h (Figure 4a). The reference C_{max} is achievable in the vast majority of subjects on HD only if treated with 6 mg/kg (Figure 5a). All of the above comparisons show similar but less pronounced trends for subjects on CAPD (Figures 4b and 5b).

The greater risk of failure to achieve the reference AUC_{0-24} for efficacy on the second day, and/or failure to achieve the reference

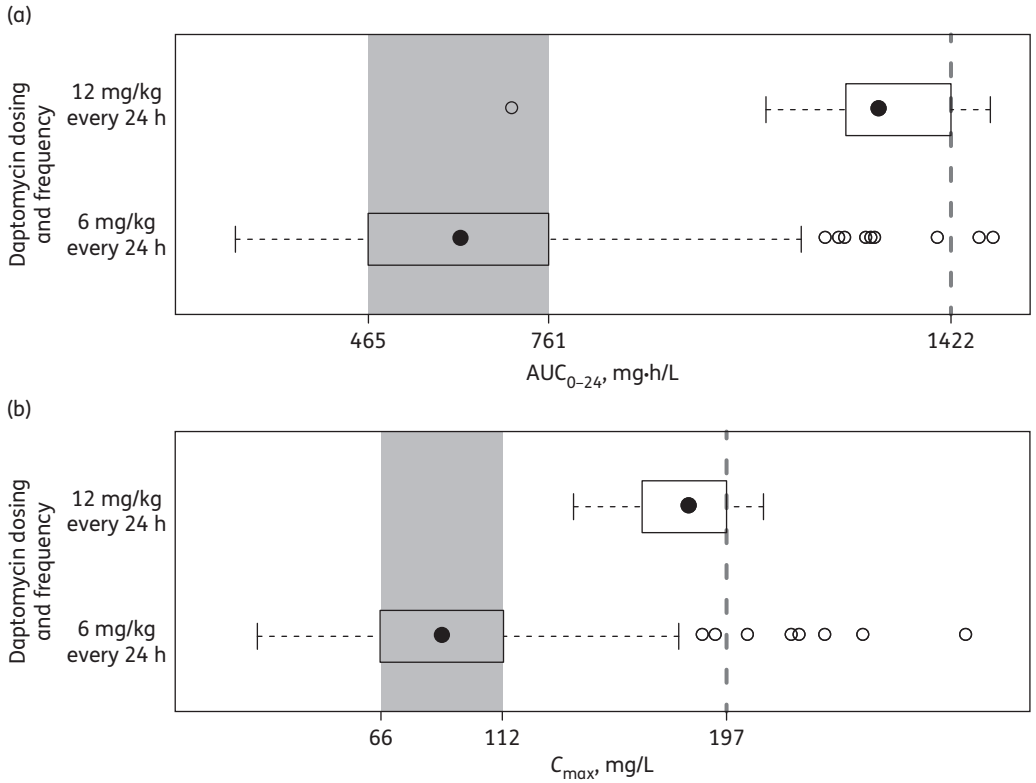

Figure 3. Reference daptomycin exposure ranges and safety thresholds. Simulated steady-state AUC_{0-24} (a) and C_{max} (b) are shown for a dose of 6 mg/kg every 24 h in patients with RIE and/or SAB and $CL_{CR} \geq 30$ mL/min and for a dose of 12 mg/kg every 24 h in healthy volunteers with a $CL_{CR} > 80$ mL/min. The box boundaries mark the 25th and 75th percentiles, the filled circles the mean, the whiskers the range up to 1.5 times the IQR below the 25th percentile and above the 75th percentile, and the open circles the outlier values. The reference exposure ranges are indicated by the shaded IQRs, and the safety thresholds by the broken lines.

C_{max} with dosing of 4 mg/kg every 48 h compared with 6 mg/kg every 48 h, is likely to be detrimental to patient outcomes. In the pivotal SAB/IE trial, it was shown that MRSA bacteraemia may persist for more than 1 week.[24] Therefore, underexposure on any day during the first week of treatment may have serious consequences such as treatment failure, development of resistance and metastatic infections. Despite the availability of antimicrobial therapy, the mortality rates of patients with SAB/IE are high, varying from 20% to 37%.[26–29] Several studies have demonstrated that patients on dialysis are at higher risk of treatment failure in SAB/IE than non-dialysis patients.[26,27] In addition, it is notable that ~85% of patients on dialysis have an invasive device or catheter fitted at the time of infection,[4,30] and these are commonly associated with biofilms that, in turn, raise the risk of suboptimal concentrations of antibiotics at the site of infection and the development of resistance. Antimicrobial therapy for HD-associated infections is one of the factors increasing the prevalence of antimicrobial resistance, especially if patients are exposed to suboptimal concentrations of antibiotics. Accordingly, we conclude that, for subjects with SRI or on HD or CAPD, dosing with 4 mg/kg daptomycin every 48 h is inferior to dosing with 6 mg/kg every 48 h and should not be used in the treatment of SAB/IE. The use of doses <6 mg/kg every 48 h in SAB patients with SRI or on dialysis, which had been reported before the regulatory approval of daptomycin 6 mg/kg every 48 h, is to be avoided.[13,31]

Conversely, it can be argued that the association of 6 mg/kg every 48 h with exposures higher than the reference range on the first day can be beneficial, especially given that the safety threshold is generally not exceeded by the vast majority of subjects. Higher exposure is predicted to enhance the bactericidal activity of daptomycin,[16] a property of particular clinical importance in patients with IE and/or SAB. The potential advantages of daptomycin doses ≥6 mg/kg every 24 h in achieving both greater efficacy and suppressing the emergence of resistance have been demonstrated in various *in vitro* and animal models of endocarditis.[32–34] Recent treatment guidance recommends the use of higher daptomycin doses (up to 10 mg/kg every 24 h),[35–39] although there is no specific consideration for patients with SRI. Clinical studies, including those reported by Figueroa *et al.*[40] (2009), Bassetti *et al.*[41] (2010) and Kullar *et al.*[12] (2011), although not specifically in patients with SRI, demonstrate a good safety profile for daptomycin doses ≥8 mg/kg.[41,42] It should be noted that experience with daptomycin doses ≥8 mg/kg in patients with SRI is very limited and the 48 h dosing interval should be observed in these patients, regardless of the daptomycin dose, in order to avoid muscular toxicity. These patients should also be monitored more frequently for any increase in CPK level, which is the most relevant safety measure for potential exposure-related toxicity. Monitoring daptomycin C_{min} levels in patients with SRI is not necessary in clinical practice as CPK monitoring is the most reliable laboratory parameter to ensure that daptomycin is used safely.

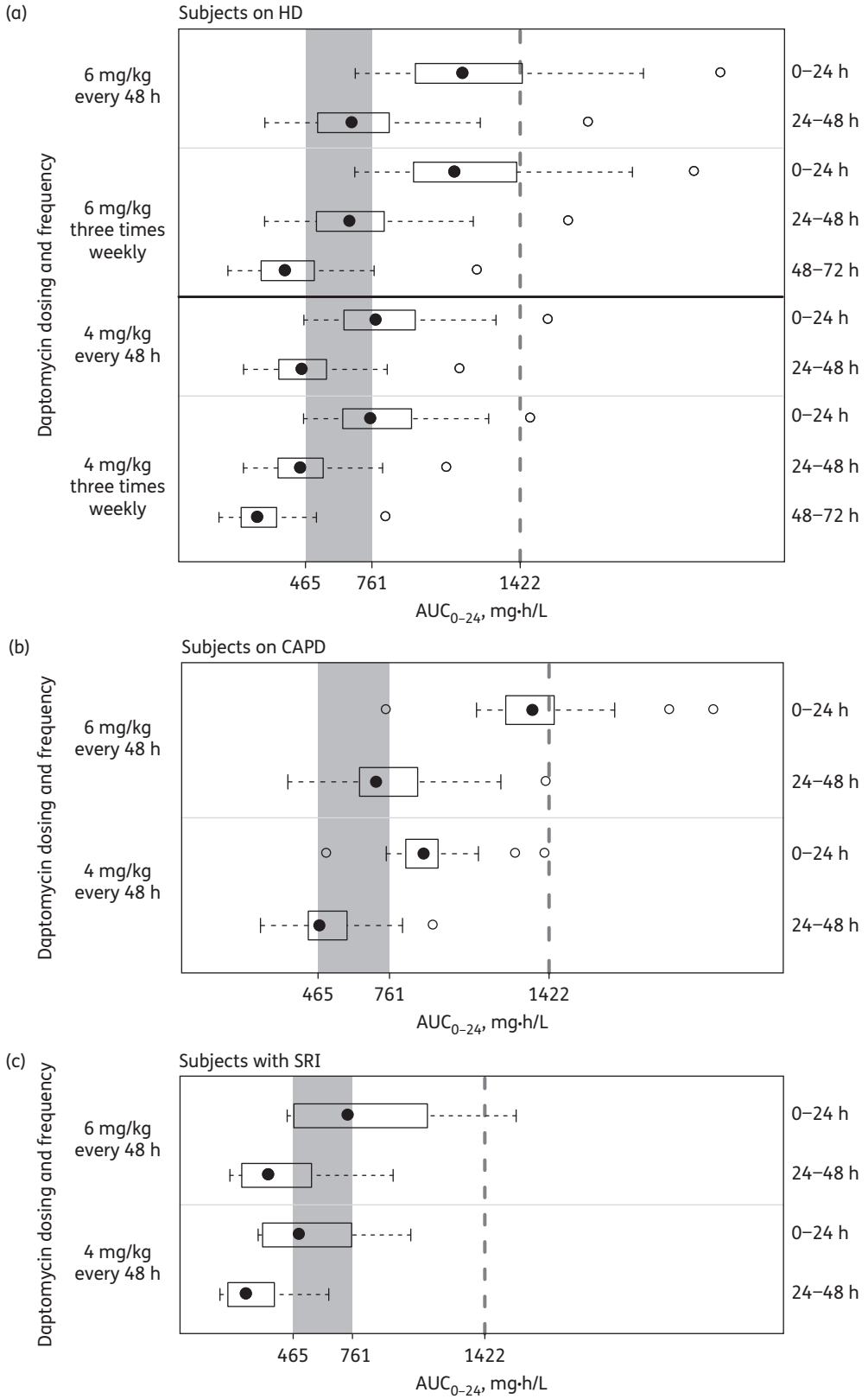

Figure 4. Simulated AUC exposure over 24 h. The box boundaries mark the 25th and 75th percentiles, the filled circles the mean, the whiskers the range up to 1.5 times the IQR below the 25th percentile and above the 75th percentile, and the open circles the outlier values. The reference exposure ranges from Figure 3 are indicated by the shaded IQRs, and the safety thresholds by the broken lines.

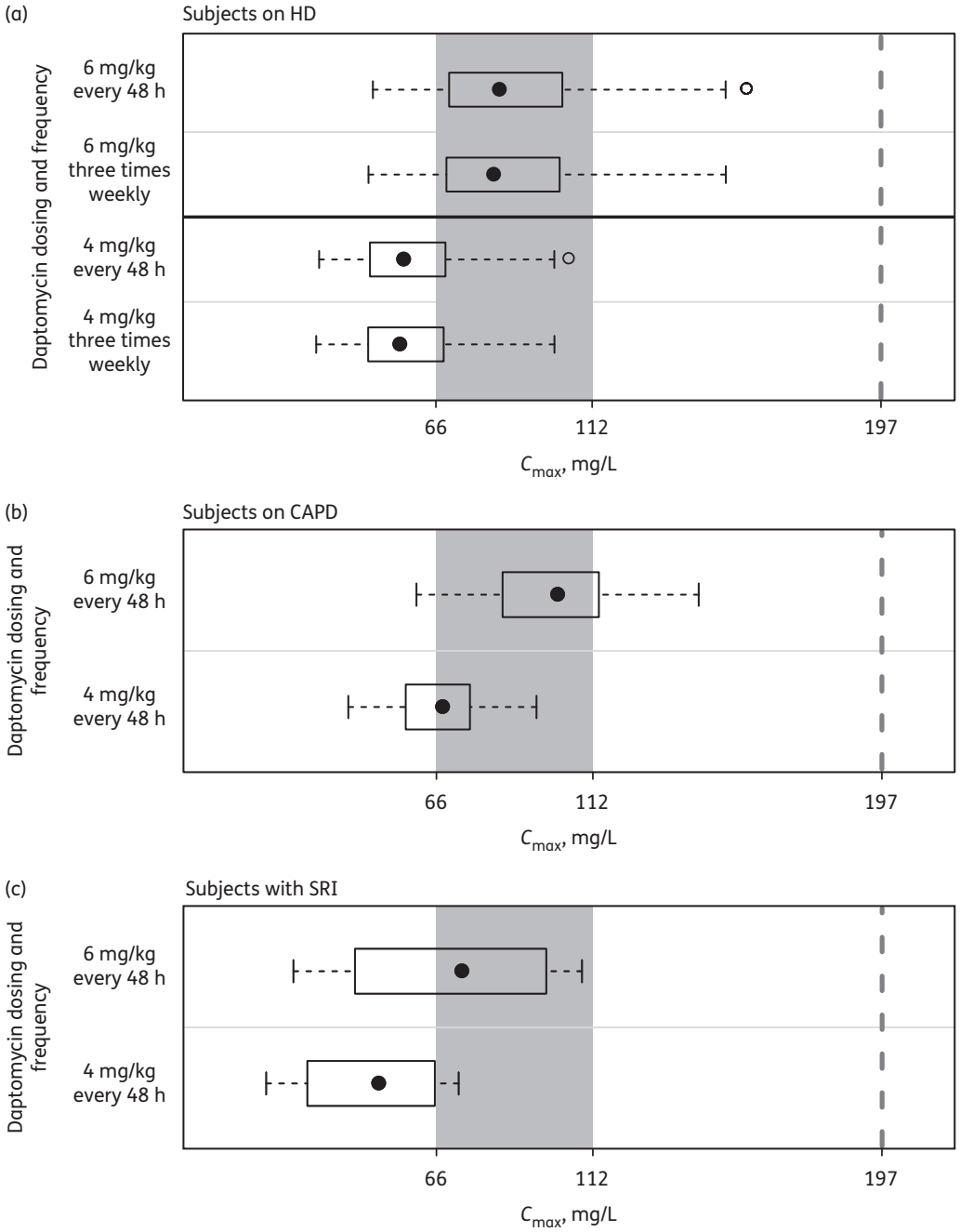

Figure 5. Simulated maximum plasma concentrations. The box boundaries mark the 25th and 75th percentiles, the filled circles the mean, the whiskers the range up to 1.5 times the IQR below the 25th percentile and above the 75th percentile, and the open circles the outlier values. The reference exposure ranges from Figure 3 are indicated by the shaded bars, and the safety thresholds by the broken lines.

For subjects on HD, our analysis also included three times weekly dosing (48 h–48 h–72 h) because this regimen is common practice in dialysis centres in Western countries. The AUC_{0-24} profile for daptomycin 6 mg/kg three times weekly is similar to that for 6 mg/kg every 48 h, except on the third day of the 72 h interval when the values are more similar to those achieved on the second day of a 4 mg/kg every 48 h dosing regimen (Figure 4a). Therefore, patients treated with 6 mg/kg three times weekly will be exposed to suboptimal concentrations for 1 day per week. This may be of concern owing to higher risks of treatment failure. Accordingly, Patel *et al.*[19] suggest a dosing schedule of 6 mg/kg–6 mg/kg–9 mg/kg for patients undergoing dialysis while receiving three times weekly dosing (the 9 mg/kg dose to be given only for the 72 h interval, once a week). However, there is probably a greater risk of dosing errors with this approach, because it is not usual clinical practice to use different

dosages for consecutive administrations of antibiotics. This approach could lead to the administration of 9 mg/kg three times weekly as a predictable medical error, which would result in drug exposure above the safety limits defined in this manuscript. To our knowledge, robust clinical data to support the safety of this level of daily drug exposure are currently not available.

Several accounts of post-marketing experience support the use of a dose of 6 mg/kg daptomycin every 48 h in patients on dialysis. Benziger *et al.*[43] reported acceptable safety and PK results in non-infected patients receiving 6 mg/kg three times weekly on HD and 6 mg/kg every 48 h on CAPD. Reports from the European Cubicin® Outcomes Registry and Experience (EU-CORE^{SM}) have demonstrated that daptomycin has a good safety profile dosed at 6 mg/kg every 48 h in patients with a CL_{CR} <30 mL/min (with or without dialysis).[44] A recent study by Cardone *et al.*[14] also supported the use of daptomycin at 6 mg/kg every 48 h in patients with SAB/IE undergoing CAPD.

The results presented and discussed in this analysis refer to outpatient dialysis (HD and CAPD). Patients undergoing continuous renal replacement therapy or extended dialysis in intensive care units have not been included in our analyses, but it is clear that they will have different daptomycin clearance profiles and, accordingly, different dosing recommendations will be relevant.

The analysis presented supports the current daptomycin dosing recommendations in Europe and the USA for patients with *S. aureus* RIE or SAB associated with cSSTIs or RIE with renal impairment: 6 mg/kg every 48 h provides appropriate daptomycin exposure for patients with CL_{CR} <30 mL/min and for patients undergoing HD or CAPD in this indication, whereas 4 mg/kg every 48 h does not. Daptomycin should be administered immediately after the completion of dialysis. The availability of daptomycin as a 2 min intravenous injection, in addition to the 30 min infusion, makes dosing after completion of HD both convenient and time efficient.

Acknowledgements

Some of the data discussed in this manuscript were presented as a poster at the Fiftieth Interscience Conference on Antimicrobial Agents and Chemotherapy, Boston, MA, USA, 2010 (A1-1365).

We would like to acknowledge Bill Knebel, Principal Scientist, Metrum Research Group LLC, for earlier work contributing to the PK model. We would also like to acknowledge Fiona Woodward of Chameleon Communications International, who provided medical writing assistance.

Funding

This work was supported by Novartis Pharma AG, Basel, Switzerland. The medical writing assistance provided by Fiona Woodward of Chameleon Communications International was also funded by Novartis Pharma AG, Basel, Switzerland.

Transparency declarations

R. L. C. is an employee of Novartis Pharma AG and owns stock options with the company. A. C. is an employee of Novartis Pharmaceuticals Corp. and owns stock within the company. D. B. is an employee of Cubist Pharmaceuticals and owns stock options with the company. S. T. is an employee of Astellas Pharma Global Development and was formally an employee of Novartis Pharma AG.

Fiona Woodward of Chameleon Communications International provided medical writing assistance. This encompassed assembly of the first draft under the direction of the authors and help with referencing, preparing tables and figures, and incorporating authors' revisions. At all stages, the authors had full control over the content of this manuscript, for which they have given final approval and take full responsibility. Novartis Pharma AG enforces a 'no ghost-writing' policy.

Supplementary data

Table S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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