Model based dose identification of dalbavancin for long-term suppressive outpatient treatment of ventricular assist device-infections

Table S1: Structural model building.

	1-compartment	2-compartment	3-compartment
Parameterization	CL, V	CL, V1, V2, Qfixed	CL, V1, V2, V3, Q2, Q3
OFV (-2×log-likelihood)	373.08	316.94	317.09
AIC	383.08	330.36	343.09
BIC	385.9	334.31	350.44
BICc	389.12	338.60	357.95

Abbreviations: **BIC:** bayesian information criteria | **BICc**: corrected bayesian information criteria | **CL**: total body clearance for dalbavancin | **OFV**, objective function value | **Q**: inter-compartmental clearance | **V1**: central volume of distribution | **V2**: peripheral volume of distribution | **V3**: peripheral volume of distribution | **AIC:** Akaike information criteria.

Model based dose identification of dalbavancin for long-term suppressive outpatient treatment of ventricular assist device-infections

Covariate model building

Table S2: Pearson's correlation test of the random effect versus covariates.

Covariates	Eta_Cl		Eta_V1		Eta_V2	
	Coeff	p-value	Coeff	p-value	Coeff	p-value
Age	-0.29	3.29e-1	-0.13	6.77e-1	0.50	8.46e-1
Albumin	0.030	9.22e-1	-0.008	9.79e-1	-0.37	2.14e-1
BSA	0.065	8.32e-1	0.550	4.97e-2	0.34	2.5e-1
Creatinine-clearance	0.069	8.23e-1	-0.072	8.16e-1	-0.35	2.42e-1
Creatinine	0.14	6.40e-1	0.39	1.86e-1	0.15	6.31e-1
Weight	0.090	7.71e-1	0.58	3.65e-2	0.33	2.67e-1

The covariate with the highest correlation is considered for inclusion into the base structural model (forward inclusion).

For covariate modelling, continuous variables were log-transformed centered by the weighted mean using following equation using Body surface area (BSA) as an example:

$$\log(\theta_i) = \theta_{pop} + \beta_\theta \log\left(\frac{BSA_i}{BSA_{mean}}\right) + \eta_{\theta,i}$$

Where θ_i is the pharmacokinetic parameter for the ith individual and θ_{pop} is the population parameter estimate of the parameter θ. $\log\left(\frac{BSA_i}{BSA_{mean}}\right)$ is the log-transformed BSA of the ith individual normalized by the weighted mean of the population. $\eta_{\theta,i}$ is the deviation from the population value of θ for the ith individual and β_θ is a scaling exponent of the population value of θ.

Model based dose identification of dalbavancin for long-term suppressive outpatient treatment of ventricular assist device-infections

Table S3: Covariate model building.

	Base model	Covariate model	Covariate model	Covariate model
	CL, V1, V2, Qfixed	CL, V1, V2, Qfixed	CL, V1, V2, Qfixed	CL, V1, V2, Qfixed
Added covariate	-	logWeight on V1	logBSA on V1	logAge on V2
OFV (-2×log-likelihood)	316.94	311.25	311.76	312.39
AIC	330.36	327.25	327.76	328.39
BIC	334.31	331.77	332.28	332.9
BICc	338.60	336.06	336.57	337.2

Abbreviations: **BIC:** bayesian information criteria | **BICc**: corrected bayesian information criteria | **BSA:** body surface area | **CL**: total body clearance for dalbavancin | **OFV**, objective function value | **Q**: inter-compartmental clearance | **V1:** central volume of distribution | **V2:** peripheral volume of distribution| **V3:** peripheral volume of distribution | **AIC:** Akaike information criteria.

**Table S4:** Correlation test of individual parameter versus covariates.

	Statistics	p-value
Beta_V1_logtWeight	4.17	1.57e-3
Beta_V1_logtBSA	2.5	2.29e-2
Beta V2 logtAge	3.51	4.85e-3

Model based dose identification of dalbavancin for long-term suppressive outpatient treatment of ventricular assist device-infections
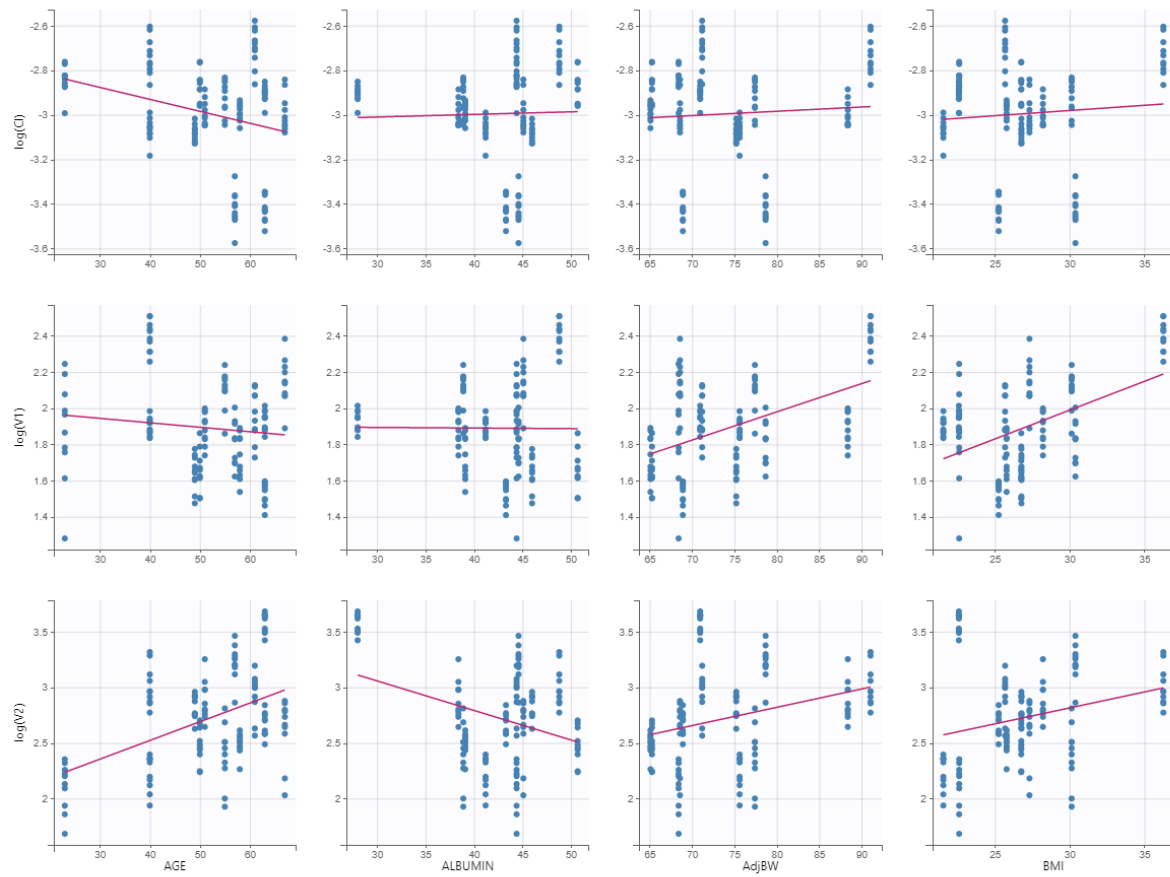
Figure S1: Correlation of covariates and estimates of the final model

Model based dose identification of dalbavancin for long-term suppressive outpatient treatment of ventricular assist device-infections
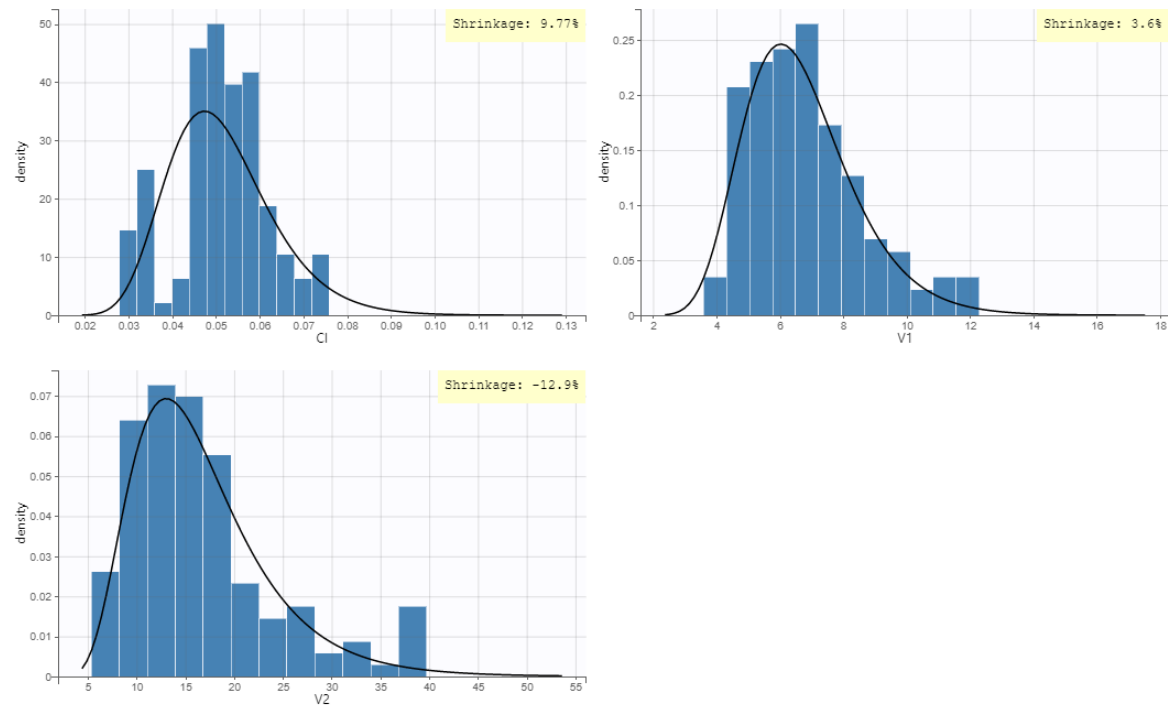
Figure S2: Conditional distribution of the parameter estimates including low shrinkage values.

Model based dose identification of dalbavancin for long-term suppressive outpatient treatment of ventricular assist device-infections

Table S5: Pharmacokinetic properties of dalbavancin of the respective patients

Patient number	CL (L/h)	V1 (L)	V2 (L)	MIC (mg/L)	Protein binding (%)	$AUC_{24\,h}$	$fAUC_{24\,h}$/MIC
1	0.067	10.84	21.11	0.064	97.6	377	141
2	0.056	7.07	34.97	0.064	96.7	616	318
3	0.059	5.17	12.34	NA	97.0	216	26
4	0.033	6.23	24.73	NA	97.2	1138	127
5	0.046	5.25	16.48	0.094	98.1	547	110
6	0.052	8.68	13.65	NA	97.1	429	49
7	0.07	6.93	19.04	0.047	97.1	267	165
8	0.056	8.3	11.7	0.047	96.2	313	253
9	0.032	4.44	15.01	0.064	96.2	980	582
10	0.047	6.58	9.45	0.125	97.8	341	60
11	0.05	6.34	18.24	0.064	96.2	524	311
12	0.05	5.52	11.53	0.047	98.5	326	104
13	0.057	5.77	9.04	0.064	96.8	168	84

$AUC_{24\,h}$**:** Area under the concentration curve last 24 h before redosing **CL:** Total body clearance for dalbavancin | $fAUC_{24\,h}$**:** Free area under the concentration curve last 24 h before redosing | **MIC:** Minimum inhibitory concentration | **NA:** MIC not available, target calculated with *S. aureus* breakpoint 0.25 mg/L | **Q:** Inter-compartmental clearance | **V1:** Central volume of distribution | **V2**: peripheral volume of distribution |

Model based dose identification of dalbavancin for long-term suppressive outpatient treatment of ventricular assist device-infections
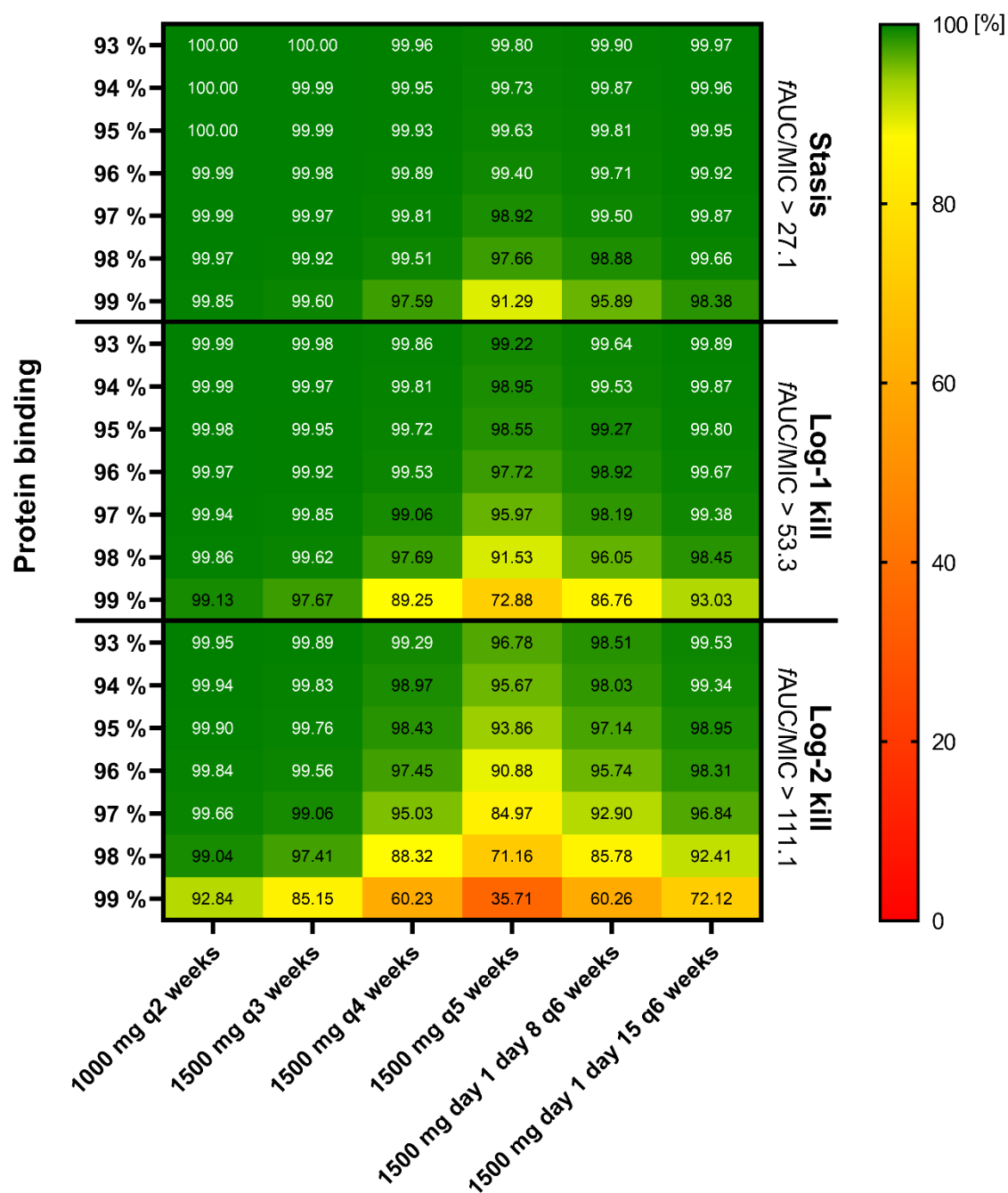
Figure S3: Cumulative fraction of response of various dalbavancin regimens (against MIC distribution of *Staphylococcus aureus* according to EUCAST) at three PK/PD targets. [2]| *f*AUC: Free area under the concentration curve | **MIC:** Minimum inhibitory concentration