Supplementary Material 1. General modeling methods

Assessment of model adequacy and decisions about increasing (or decreasing) model complexity were driven by the data and guided by goodness-of-fit criteria, including (1) visual inspection of diagnostic scatter plots (including observed vs. predicted concentration, residual/weighted residuals vs. predicted concentration or time and histograms of individual random effects); (2) successful convergence of the minimization routine with at least 2 significant digits in parameter estimates; (3) plausibility of parameter estimates; (4) precision of parameter estimates; (5) correlation between model parameter estimation errors < 0.95; and (6) the Akaike information criterion (AIC), given the minimum objective function value and number of estimated parameters.

A full covariate modeling approach emphasizing parameter estimation rather than stepwise hypothesis testing was implemented for the population pharmacokinetic analysis. First, predefined covariate-parameter relationships were identified based on exploratory graphics, scientific interest, mechanistic plausibility or prior knowledge. Then a full covariate model was constructed with care to avoid correlation or collinearity in predictors; covariates with correlation coefficients greater than ~0.35 were not simultaneously included as potential predictors.

Inferences about clinical relevance of covariates were based on the resulting parameter estimates of the full model and measures of estimation precision (Bayesian 95% credible intervals). No hypothesis testing was conducted. This approach enables the direct assessment of clinical relevance of covariate effects and also provides some explanation for the apparent absence of a covariate effect (i.e., true lack of effect vs lack of information about the effect).

Covariate effects on linear clearance ($\text{CL}_L$) were further evaluated via simulation using the joint posterior probability distribution of parameter samples from the Bayesian Markov chain Monte Carlo (MCMC) chain. One set of sampled model parameter values was generated at each MCMC iteration. Each set of parameter values was then used to simulate $\text{CL}_L$ for the reference patient and over a grid of different covariate values. Each level was evaluated for categorical covariate values. Continuous covariates were fixed at their reference values except when they were the subject of perturbation (i.e., covariate effects were evaluated in a univariate fashion). Typical value simulations were used, so the resulting covariate effect distributions reflect parameter uncertainty for the reference patient and perturbed covariate settings, but do not reflect interindividual or residual variability.

REFERENCE