Rifapentine Population Pharmacokinetics and Dosing Recommendations for Latent Tuberculosis Infection

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ONLINE DATA SUPPLEMENT

Supplemental Methods

Population pharmacokinetic modelling procedures

All model building was performed with NONMEM 7.41 (ICON Development Solutions, Elliott City, Maryland). Rifapentine plasma concentrations were transformed to natural log form. Pharmacokinetic parameter estimation was performed with the first-order conditional method. Inter-individual variability was modeled exponentially assuming a log-normal distribution. The residual error was described by an additive error on the individually predicted logarithmic concentrations (i.e., equivalent to an exponential error on non-logarithmic concentrations).

One and two compartment disposition models were evaluated with first-order absorption to describe rifapentine pharmacokinetics. Drug absorption delays were further evaluated with the addition of a lag time or a more flexible chain of transit compartments. Since only oral data were available, the relative bioavailability was fixed to 1. Inter-individual variability was tested on absorption parameters (i.e., bioavailability and mean transit time), drug clearance, and volume of distribution. Once a stable model was established, previously identified and well-established covariates (i.e., dose, meal-type, and HIV status) were incorporated into the base structural model followed by formal statistical assessment.

The full compartmental model for rifapentine pharmacokinetics with incorporated autoinduction can be represented with the Eq (1-3, where Eq (1) represents the amount of drug in the absorption compartment (A_a) with a series of *n* transit compartments (1), Eq (2) represents the

amount of drug in the central compartment (A_c), and Eq (3) is the amount of enzyme (ENZ), initially equal to 1 and increased as a result of the drug effect (EFF):

Eq (1) $$\frac{dA_a}{dt} = F \cdot \text{Dose} \cdot k_{tr} \cdot \frac{(k_{tr} \cdot t)^n \cdot e^{-k_{tr} \cdot t}}{\sqrt{2\pi} \cdot n^{n+0.5} \cdot e^{-n}} - k_a \cdot A_a$$

Eq (2) $$\frac{dA_c}{dt} = k_a \cdot A_a - {CL}/{V} \cdot A_c \cdot ENZ$$

Eq (3) $$\frac{dENZ}{dt} = k_{ENZ} \cdot (1 + EFF) - k_{ENZ} \cdot ENZ$$

In the above equations, k_{tr} is the transit rate constant, F is relative bioavailability, k_a is the absorption rate constant, CL is the clearance, V is the volume of distribution, and k_{ENZ} is the enzyme turnover rate. For autoinduction, linear and nonlinear drug effect (EFF) relationships were evaluated.

Model development was guided by graphical assessment of goodness-of-fit plots, condition number, and the likelihood ratio test. Simulation-based diagnostics, or visual predictive checks (VPCs), were used for model validation. Due to large variability in the dose for the combined dataset, the observed and simulated concentrations were normalized based on the typical population predictions (2). VPCs were based on 500 simulations using fixed and random effect parameter estimates, including dosing information and demographic information for each subject. The precision of all final parameters was evaluated using a nonparametric bootstrap approach with 1,000 resampled datasets. The predictive performance of the model was evaluated through an external model validation: 500 simulations of rifapentine concentration were performed with the validation cohort using the base structural model and parameter estimates

from the analysis cohort alone. Simulated concentrations were compared to observed concentrations through VPC.

Following model evaluation, pharmacokinetic parameters were re-estimated with all data (analysis and validation datasets), and covariate analysis was performed to further explore factors that explain inter-individual variability in clearance and/or bioavailability. Additional candidate covariates included weight, age, race, BMI and sex. Covariates were identified using stepwise covariate modeling (SCM) approach: covariates were added one at a time and then removed one at a time in a stepwise manner and evaluated using the likelihood ratio test. A significance level of $p<0.05$ was used for forward selection, and $p<0.01$ was used for backward elimination. Final inclusion of identified covariates was done taking into account statistical significance, clinical relevance, and scientific plausibility. The threshold for clinical relevance was a 20% change in the parameter estimate (3).

Rifapentine metabolite modelling procedures

To complete the model, 25-desacetyl-rifapentine concentration data were added and modeled. All of the included studies except Riomar and Rifaquin had metabolite data to contribute. All parameters from the parent drug model were fixed except residual variability. Then, the metabolite clearance (CL_m) and volume of distribution (V_d) were estimated. One and two compartment distribution models were tested, along with nonlinear elimination, and dose-dependent fraction metabolized (f_m) in accordance with previously published models (4-6). Stepwise covariate modeling was also performed; weight, HIV status, and sex were tested on metabolite parameters. Those with statistically significant effects and clinically relevant effect sizes were included in the model.

Supplemental Results

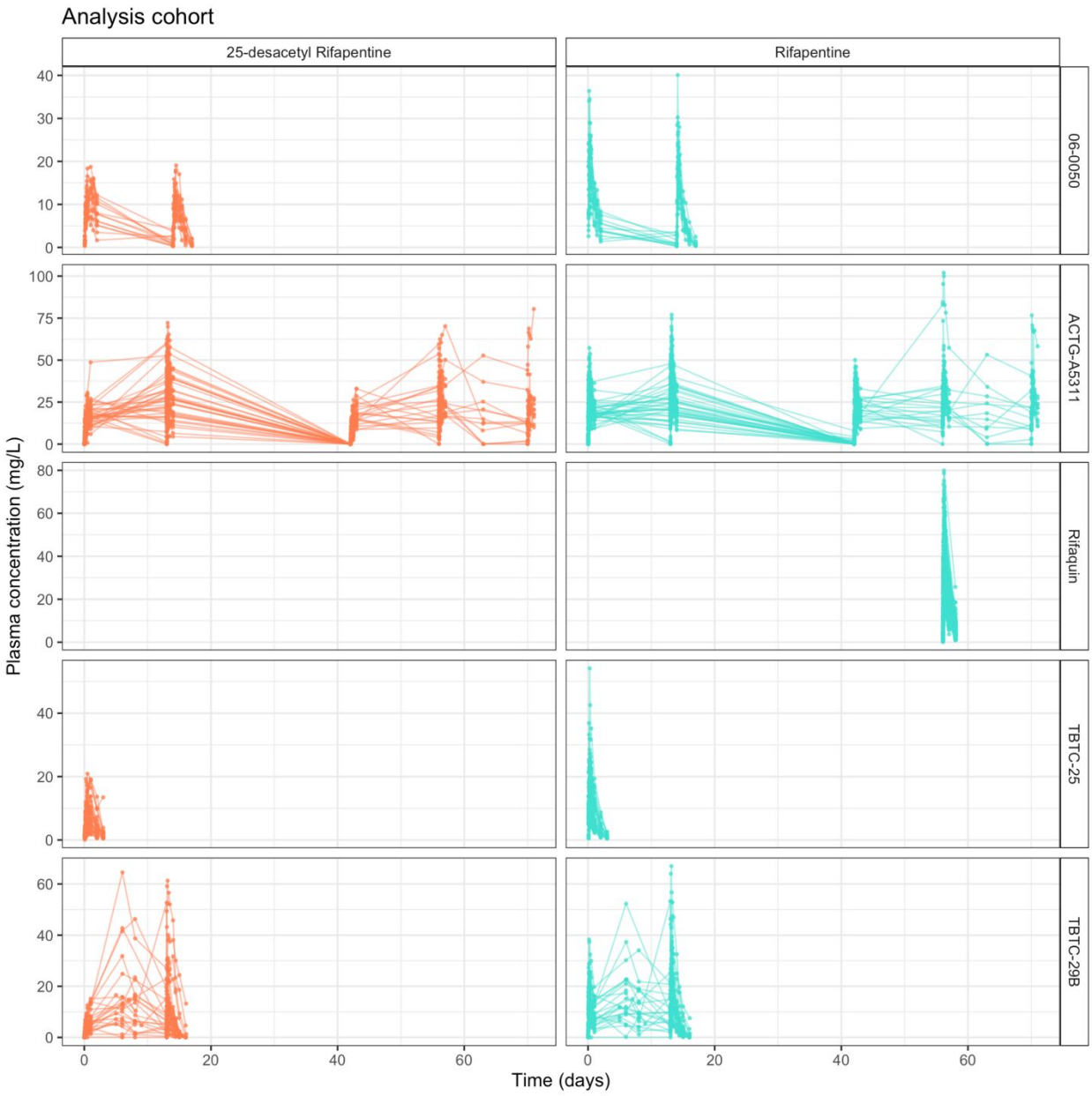

Figure E1-A. Summary of raw concentration data of rifapentine and metabolite in the analysis cohort. Dots represent unique plasma samples. Lines represent unique individuals.

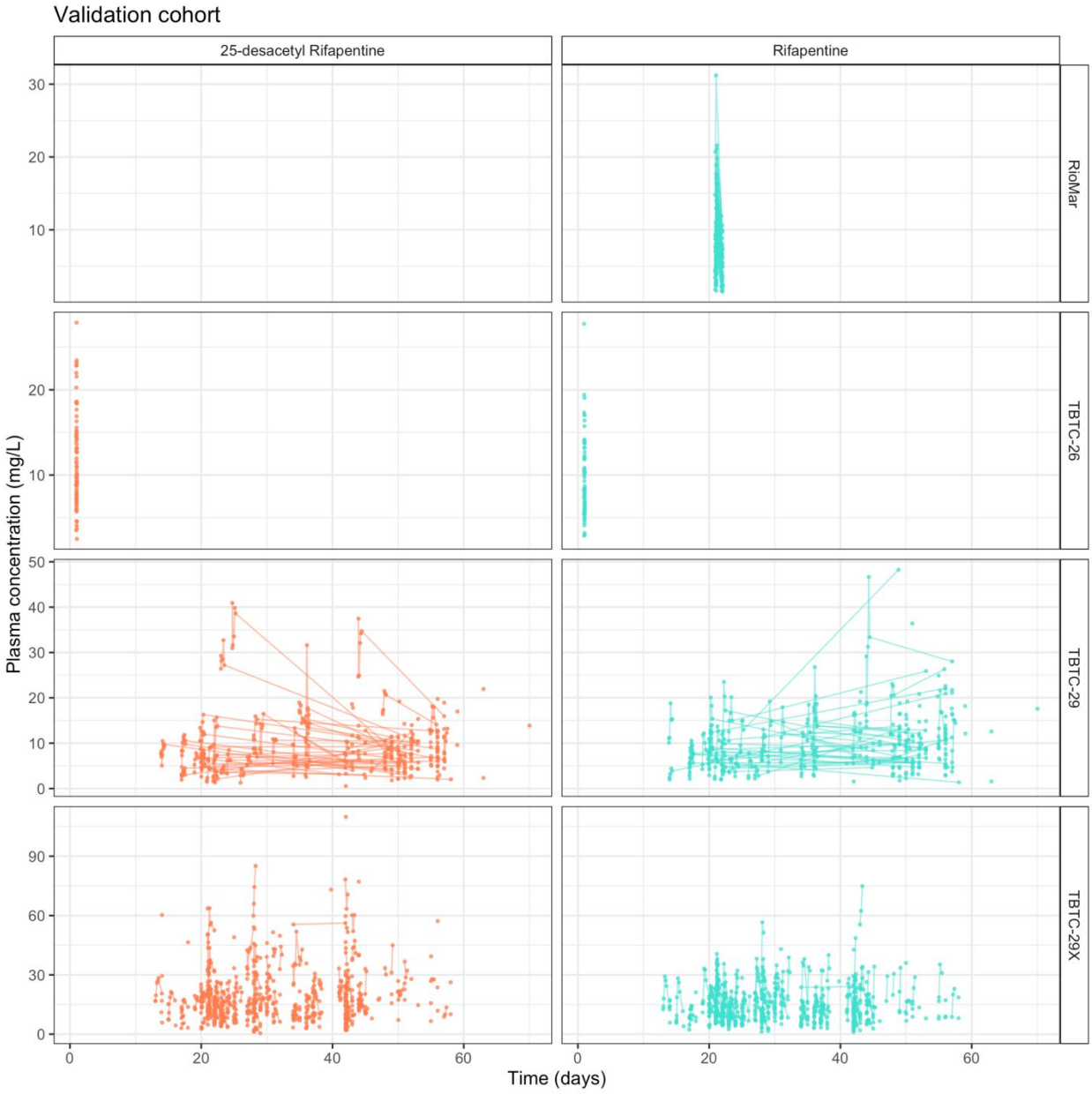

Figure E1-B. Summary of raw concentration data of rifapentine and metabolite in the validation cohort. Dots represent unique plasma samples. Lines represent unique individuals.

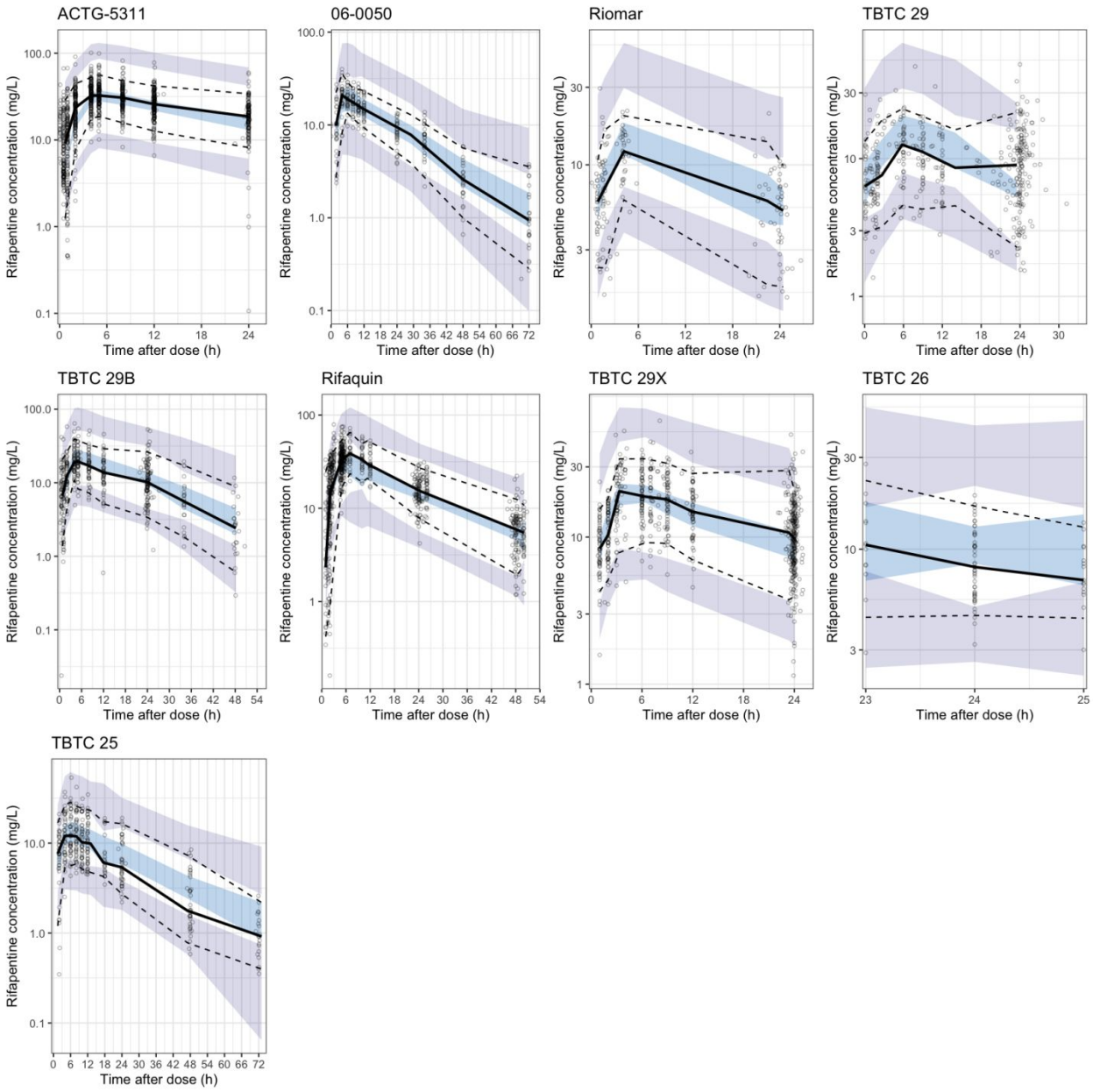

Figure E2. Final visual predictive check (VPC) of full rifapentine population pharmacokinetic model, stratified by study. Dots represent observed rifapentine concentrations. Lines correspond to 5th (dashed), 50th (solid), 95th (dashed) percentiles of observed data. Shaded areas are the model-predicted 95% confidence intervals for the median (light blue), and 5th and 95th (dark blue) percentiles obtained from 500 simulated datasets.

Rifapentine metabolite model results

The pharmacokinetics of 25-desacetyl-rifapentine were best described with a one compartment distribution model with first order elimination and dose-dependent fraction metabolized. The typical CL_m was 3.11 L/h and V_m was 2.15 L. HIV infection was found to be a strong predictor ($p<0.001$) of CL_m, such that HIV-positive individuals had 35% higher CL_m. Model evaluation through VPC (Figure E3) demonstrated that the model predicted the metabolite concentrations well.

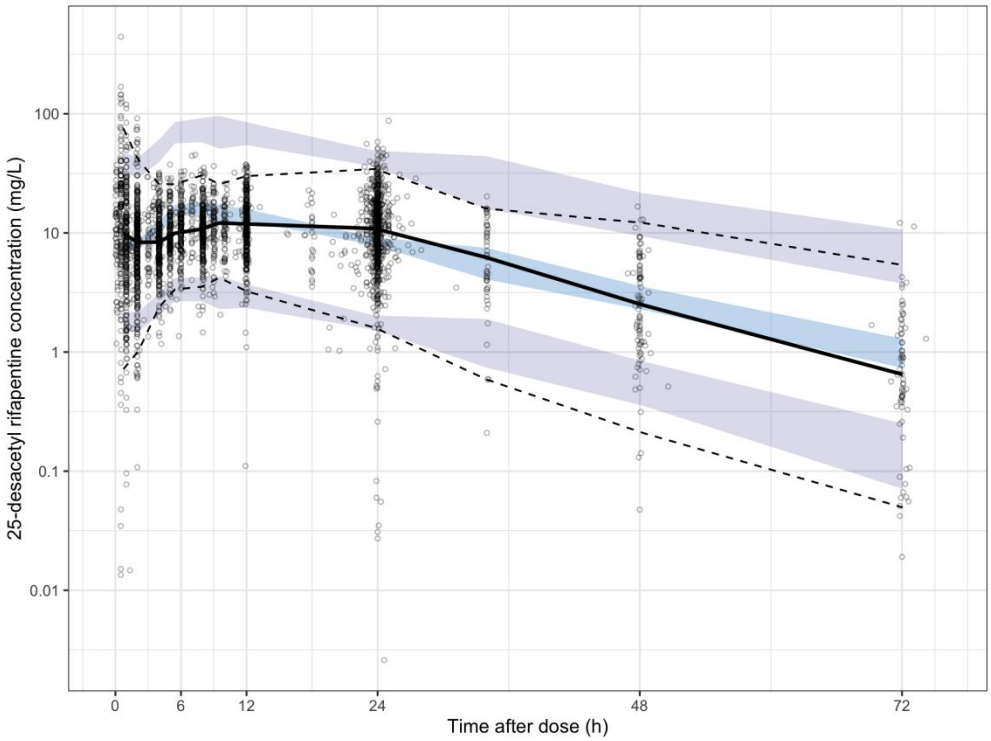

Figure E3. Visual predictive check (VPC) of 25-desacetyl-rifapentine (i.e., metabolite) pharmacokinetic model. Dots represent observed 25-desacetyl-rifapentine concentrations. Lines correspond to 5th (dashed), 50th (solid), 95th (dashed) percentiles of observed data. Shaded areas are the model-predicted 95% confidence intervals for the median (light blue), and 5th and 95th

(dark blue) percentiles obtained from 500 simulated datasets. The dependent variable was prediction corrected (2).

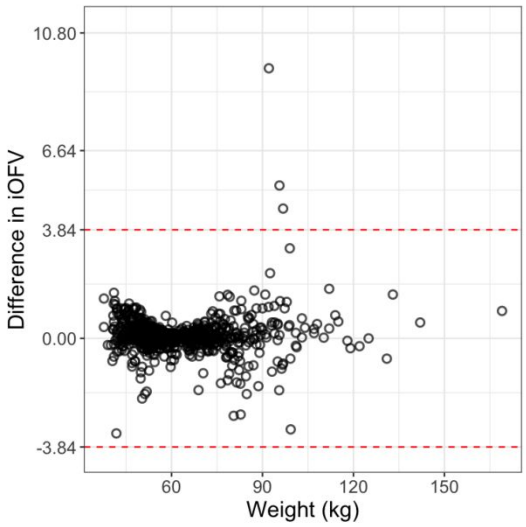

Figure E4. Individuals influencing the relationship between weight and clearance. Each circle represents one individual. Influential individuals are those with change in iOFV > |3.84|. Red dashed lines represent the statistical significance threshold (p=0.05) per likelihood ratio test. iOFV = individual objective function.

	Increase in clearance			
	Once Weekly	**Twice Weekly**	**Thrice Weekly**	**Daily**
600 mg	16%	29%	44%	72%
900 mg	20%	35%	52%	72%
1200 mg	26%	39%	56%	72%

Table E1. Change in rifapentine clearance by dose and dosing frequency. Values reflect the percent change from first dose to last dose of a one-month treatment course.

	AUC/MIC	Free AUC/MIC	Cmax/MIC	Free Cmax/MIC
600 mg once weekly	3936.7	78.7	226.4	4.5
600 mg twice weekly	4011.7	80.2	236.8	4.7
600 mg thrice weekly	3846.7	76.9	232.1	4.6
600 mg daily	4928.3	98.6	308.6	6.2
900 mg once weekly	5481.7	109.6	317	6.3
900 mg twice weekly	5500	110	328.5	6.6
900 mg thrice weekly	5248.3	105	321.2	6.4
900 mg daily	6921.7	138.4	433.2	8.7
1200 mg once weekly	6773.3	135.5	393.1	7.9
1200 mg twice weekly	6733.3	134.7	405.1	8.1
1200 mg thrice weekly	6415	128.3	395.8	7.9
1200 mg daily	8600	172	538.1	10.8

Table E2. Pharmacokinetic-pharmacodynamic indices by rifapentine dose and dosing frequency. Values reflect a typical HIV-negative individual. AUC was integrated over 24 hours on day 21 of therapy, and thus, reflects steady state AUC for daily dosing. Free AUC and Cmax assume a fraction unbound of 0.02. MIC (minimum inhibitory concentration) was set to 0.06 mg/L. AUC = area under the concentration time curve. Cmax = maximum concentration.

Supplemental References

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