Supplemental Material

Detailed methods used to detect single nucleotide polymorphisms (SNPs):

Total Genomic DNA was isolated using the QIAamp DNA mini kit according to manufacturer's instructions. Purity was assessed following extraction by comparing the A260 and A280 ratio. DNA was normalised to 20ng/µl. Genotyping for *SLCO1B1* rs4149032, rs2306283, rs4149056 and rs11045819 was performed by real-time PCR allelic discrimination by standard methodology (95˚C for 15 min, then 40 cycles of 95˚C for 15 sec and 60˚C for 1 min). The Applied Biosystems assay IDs for the first three SNPs were C_1901709_10, C_1901697_20 and C_30633906_10, respectively. For rs11045819, the forward primer, reverse primer, VIC probe and FAM probe were 5′CAGTGATGTTCTTACAGTTACAGGTATTCTAA3′, 5′GAAGACTTTTTACTGTCAATATTAATTCTTACCTTTTCC3′, 5′-ACTATCTCAGGTGATGCT-VIC, and 5′-CACTATCTCAGTTGATGCT-FAM, respectively.

Detailed population modeling methods

Data was analysed using NONMEM (version 7.1.2)(18) and PSN v.3.4.2.(22). Population pharmacokinetic parameter estimates, between-subject variability modelled exponentially, and residual variability were obtained with the first-order estimation method with interaction (FOCE+I). The objective function value (OFV), 'goodness-of-fit' plots and visual predictive checks were used to evaluate and guide model building, a bootstrap (n=200) was performed for model validation. Proportional, additive and combined residual error models were tested separately for

rifabutin and 25-desacetyl rifabutin. Nested models were hypothesis-tested using the likelihood ratio test in which the change in OFV approximates the X^2 distribution ($X^2_{1,0.05} > 3.84$). Non-nested models were compared using the Akaike information criterion (AIC).

Table S1: Expected mean±SD area under the concentration–time curve over 24 h ($AUC_{0–24}$) for rifabutin and des-rifabutin ($AUCM_{0–24}$) for specific subpopulations based on 500 simulations from the final model.

	Female	*Male*	*Carrier*	*Non-Carrier*	*Female Carrier*	*Male Carrier*	*Female non-Carrier*	*Male non-Carrier*
$AUC_{0–24}$ (ng.h/L)	2830.4±160.2	2607.2±145.2	3050.4±187.3	2646.9±147.2	3142.9±176.8	2989.3±152.4	2788.1±153.6	2559.3±141.3
p-value	< 0.001		< 0.001		0.015		< 0.001	
					< 0.001[#]		< 0.001†	
$AUCM_{0–24}$ (ng.h/L)	277.1±18.9	272.3±19.3	327.8±26.6	267.1±19.2	328.5±25.4	327.2±29.2	270.3±17.5	265.3±19.2
p-value	0.032		< 0.001		0.70		0.035	
					< 0.001[#]		< 0.001†	

[#] comparing female heterozygous carriers of *SLCO1B1* rs1104581 versus female non-carriers, † comparing male heterozygous carriers of *SLCO1B1* rs1104581 versus male non-carriers

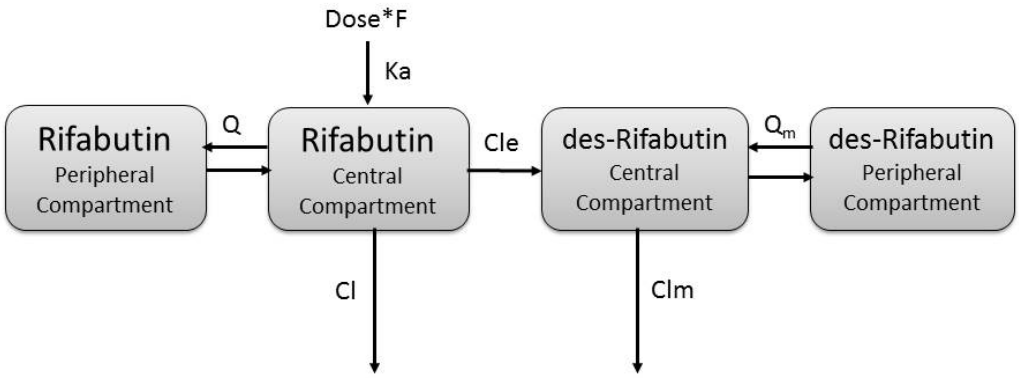

FIG S1. Structural model for rifabutin and 25-desacetyl rifabutin (des-Rifabutin).

F- bioavailability, ka- first order absorption rate constant, Q- intercompartmental clearance for rifabutin, Q_m- intercompartmental clearance for des-rifabutin, Cl-clearance of rifabutin, Cl_e- clearance of rifabutin to des-rifabutin, Cl_m- clearance of des-rifabutin

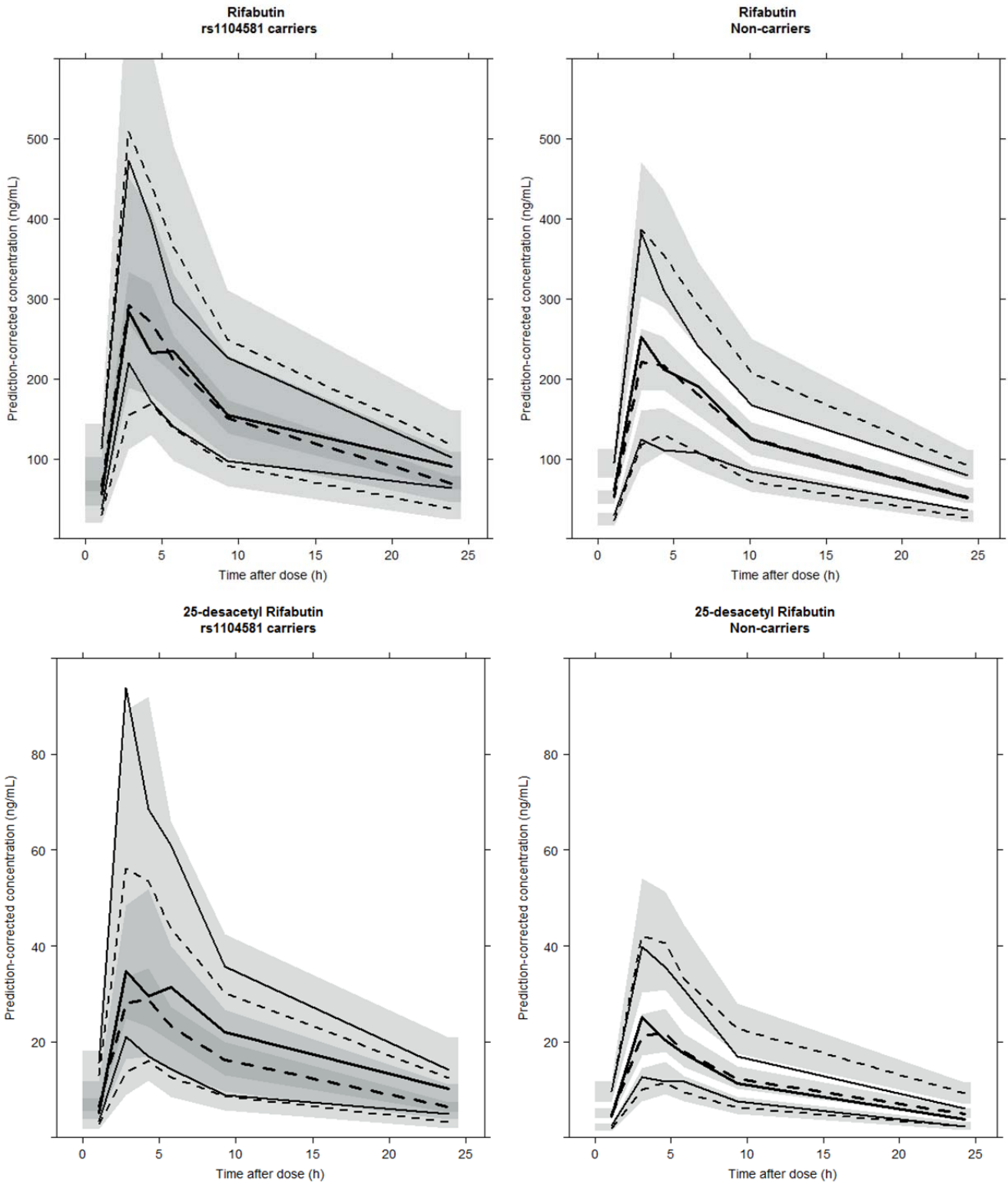

FIG S2. Prediction-corrected visual predictive check of the final model for rifabutin (top) and des-rifabutin (bottom) separated for rs1104581 carriers (left) and non-carriers (right). The solid upper, middle and lower lines represent the 90th, 50th and 10th percentile of the patients' observations. The dashed upper, middle and lower lines represents 90th , 50th and 10th percentile of simulated data. The grey shaded areas are the simulated confidence intervals for the corresponding percentiles.

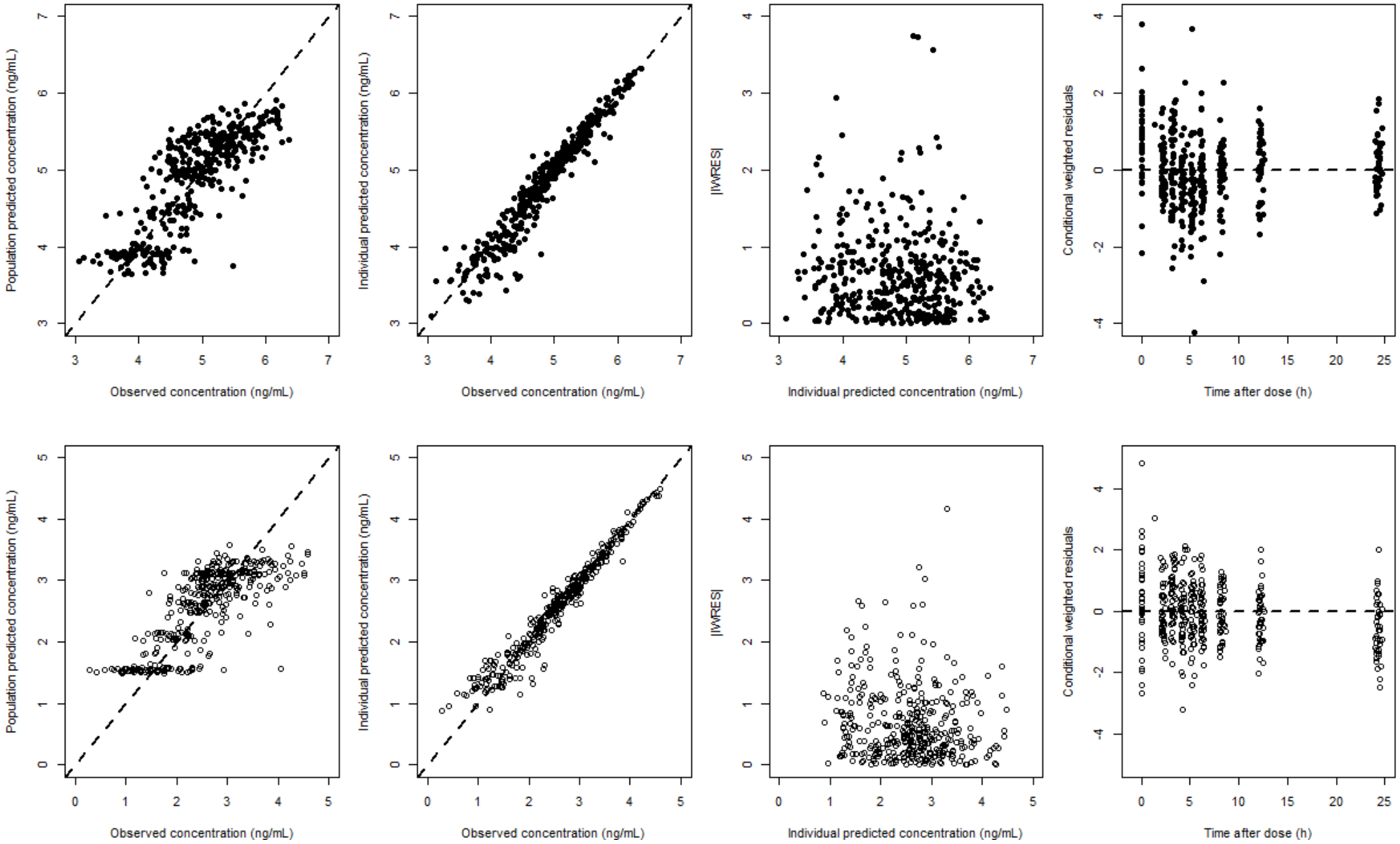

FIG S3. Goodness-of-fit plots for rifabutin (closed circles, top row) and des-rifabutin (open circles, bottom row) for the final model.