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Application of the Multistate Tuberculosis Disease Model in Rifampicin Treated Pulmonary Tuberculosis Patients

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Objectives

To apply the Multistate Tuberculosis Disease Model [1], linked to rifampicin pharmacokinetics (PK), to clinical Phase IIa colony forming unit (CFU) data in drug-susceptible pulmonary tuberculosis (TB) patients. In addition, to perform clinical trial simulations using the developed final model in order to predict retrospective clinical data as an external validation of the disease template approach.

Methods

CFU data from 24 patients [2] receiving 0 (n=4, negative control group), 5 (n=3), 10 (n=8) or 20 (n=8) mg/kg rifampicin were analyzed using non-linear mixed effects modeling implemented in NONMEM 7.3 [3]. A previously developed rifampicin population PK model [4] was linked to the Multistate Tuberculosis Disease Model, including fast-, slow- and non-multiplying as well as dead bacterial states, earlier developed using *in vitro* data [1]. Drug effect was implemented as exposure-response relationships tested at several effect sites in the Multistate Tuberculosis Disease Model, including inhibition of growth of the fast-multiplying state and as stimulation of the death rate of all states, both alone and in all possible combinations. External validation was performed by clinical trial simulation from the final model comparing the model predicted 95% prediction interval based on parameter uncertainty of the typical decline in CFU versus time to the mean±standard error of four datasets not used for model building.

Results and Discussion

All system specific Multistate Tuberculosis Disease Model parameters were fixed to *in vitro* estimates except $B_{\max}$ (Table 1). The parameter $B_{\max}$ described number of bacteria at stationary phase and was estimated throughout model building. All patients were assumed to have a stationary phase infection. The final model predicted the patient data well (Figure 1). Drug effect was best described by an on/off effect inhibiting growth of fast-multiplying bacteria in addition to slope models stimulating the death rate of slow- and non-multiplying bacteria (Figure 2). Stimulation of the death rate of the fast-multiplying state was not statistically significant. Clinical trial simulations predicted well four retrospective clinical trials using the final Multistate Tuberculosis Disease Model (Figure 3).

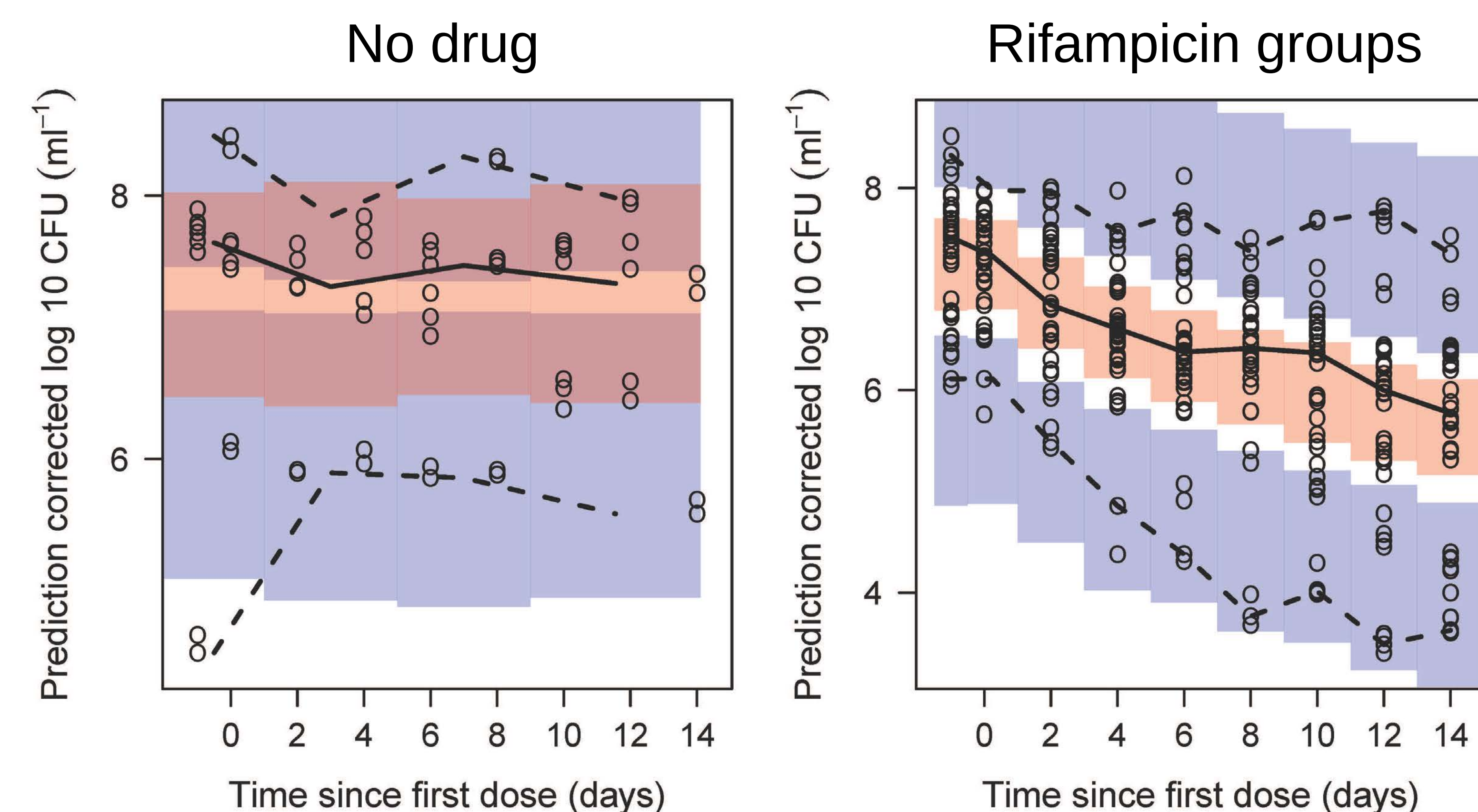


Figure 1 Prediction corrected visual predictive check (pcVPC) of the final model for the group that received no drug (left) and all groups that received drug (right). Solid and dashed lines are the median, 2.5th and 97.5th percentiles of the observed data. Shaded areas are the 95% confidence intervals of the 97.5th (blue), median (red) and 2.5th (blue) percentiles of the simulated data. Open circles are observations.

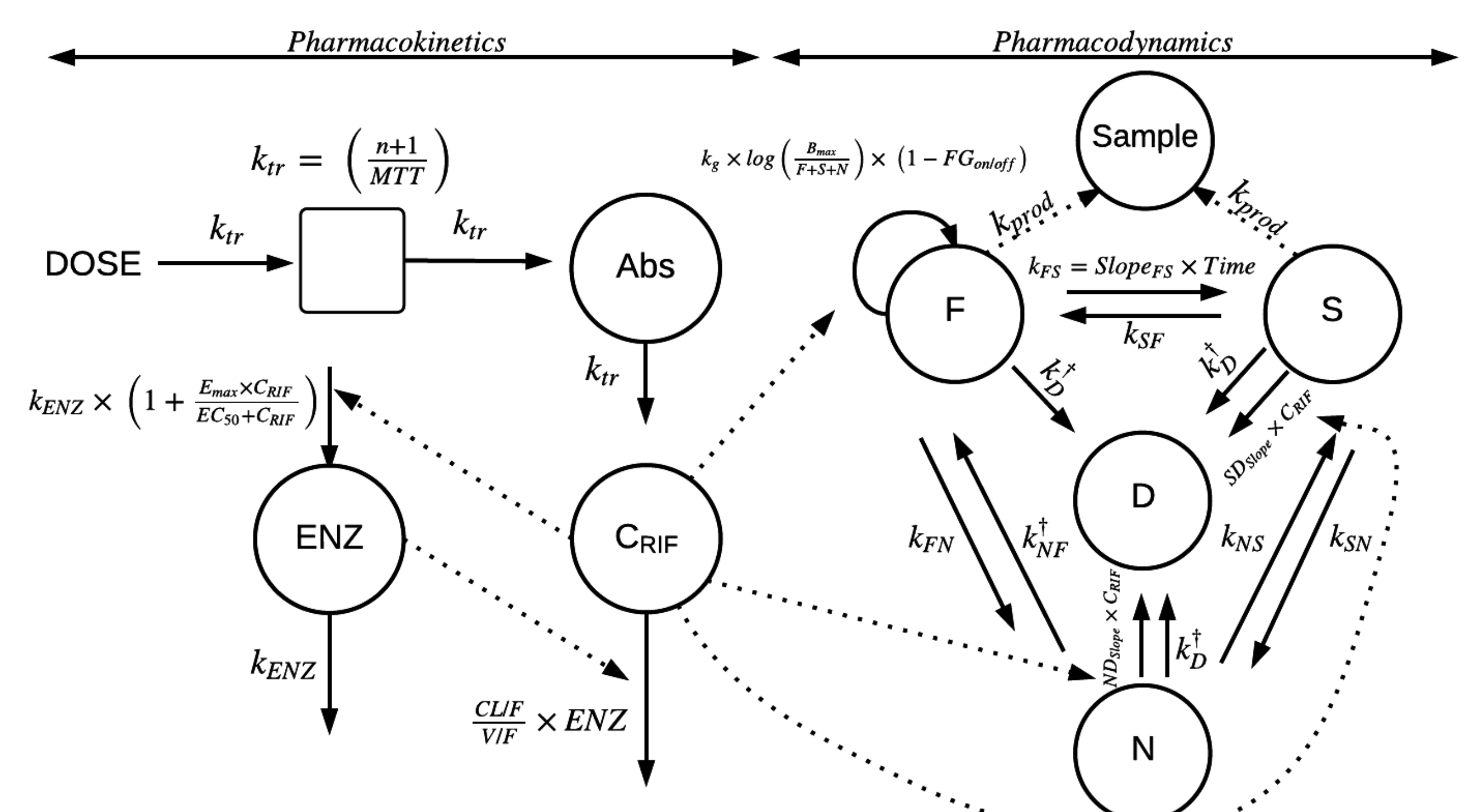
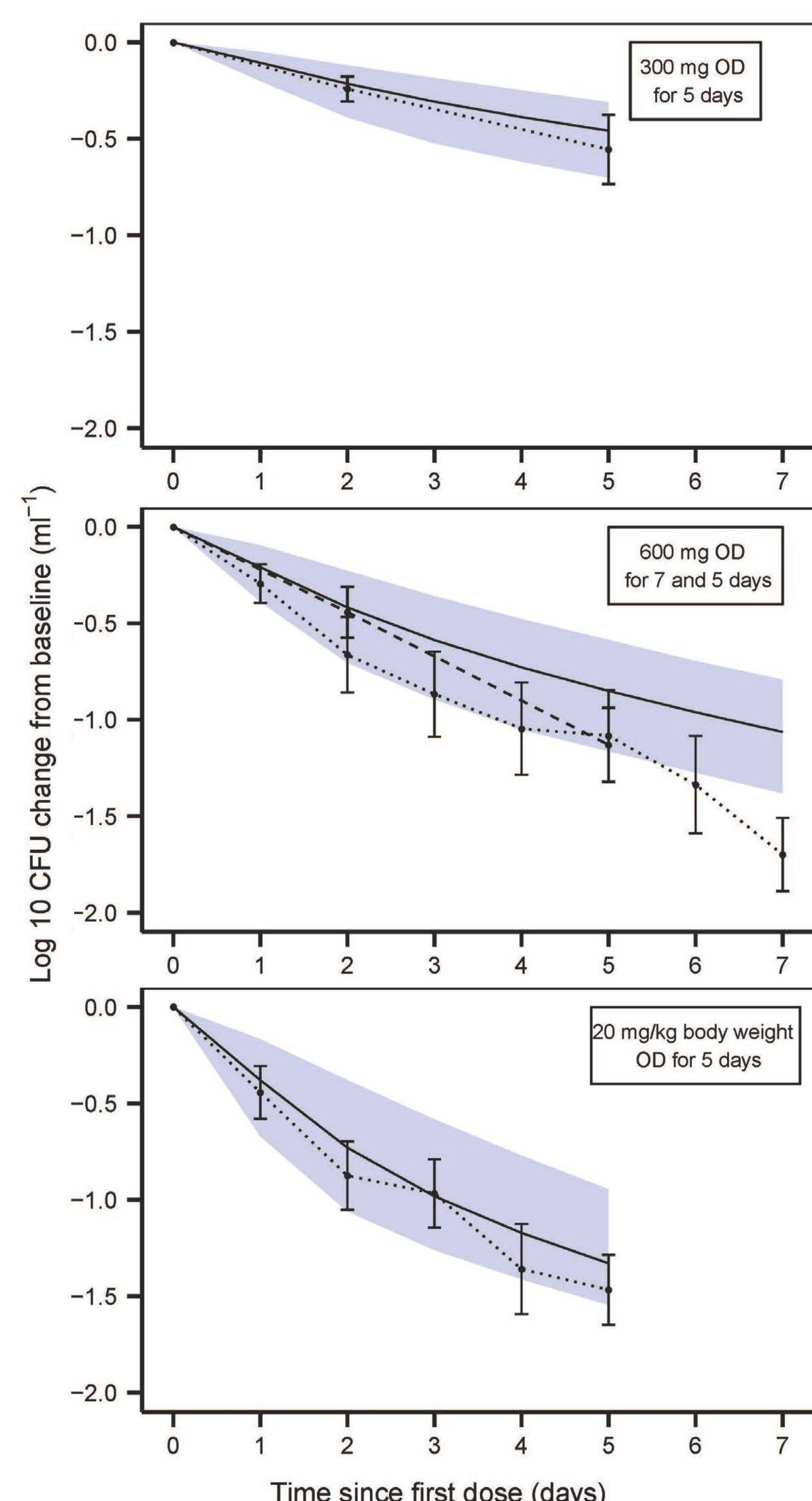


Figure 2 Final PKPD model



Parameter	Typical Estimate	RSE(%)	95% CI
CL/F (L · h ⁻¹)	10.0 FIX	-	-
V/F (L)	86.7 FIX	-	-
MTT (h)	0.713 FIX	-	-
NN	1.00 FIX	-	-
E _{max}	1.04 FIX	-	-
EC ₅₀ (mg · L ⁻¹)	0.0705 FIX	-	-
k _{ENZ} (h ⁻¹)	0.00369 FIX	-	-
F	1.00 FIX	-	-
(F _{fat}) _{CL/F}	0.311 FIX	-	-
(F _{fat}) _{V/F}	0.188 FIX	-	-
k _G (days ⁻¹) ‡	0.206 FIX	-	-
k _{FN} (days ⁻¹)	8.98 · 10 ⁻⁷ FIX	-	-
k _{SN} (days ⁻¹)	0.186 FIX	-	-
k _{SF} (days ⁻¹)	0.0145 FIX	-	-
k _{NF} (days ⁻¹)	0.00 FIX	-	-
k _{NS} (days ⁻¹)	0.00123 FIX	-	-
k _D (days ⁻¹)	0.00 FIX	-	-
Slope _{FS} (days ⁻²)	0.00166 FIX	-	-
F ₀ (ml ⁻¹)	4.11 FIX	-	-
S ₀ (ml ⁻¹)	9770 FIX	-	-
B _{max} (ml ⁻¹)	2.61 · 10 ⁹	30.6	1.48 · 10 ⁹ – 4.41 · 10 ⁹
IIV B _{max} (CV%)	152	15.9	97.8 – 194
FG _{on/off}	1.00 FIX	-	-
SD _{slope} (L · mg ⁻¹ · days ⁻¹)	0.200	41.6	0.0783 – 0.396
ND _{slope} (L · mg ⁻¹ · days ⁻¹)	0.106	19.0	0.0663 – 0.208
ε (CV%)	110	12.0	80.7 – 134
ε _{repl} (CV%)	23.1	10.2	18.9 – 27.1

Table 1 Final model parameters

Figure 3 Shaded areas are the 95% confidence interval for the typical final model prediction of log 10 CFU change from baseline versus time. Solid lines are the typical predictions from the final model for the study design indicated in each graph. Dots are the observed external mean values at each designated time point with standard errors shown as error bars. The dots are connected with dotted and/or dashed lines

Conclusions

The Multistate Tuberculosis Disease Model was successfully applied to clinical data with rifampicin treated patients. Retrospective data was successfully predicted using clinical trial simulation with the final model which confirmed the utility of the approach in anti-tubercular drug development.

References

- [1] Clewe, O., Hu, Y., Coates, A. R. and Simonsson, U. S. H. A Semi-Mechanistic Pharmacokinetic-Pharmacodynamic Template Model for Studying Anti-tubercular Drug Effects *In Vitro*. Washington, DC, 5-9 September 2014, Abstr A-026. <<http://www.icaonline.com/php/icaac2014abstracts/data/papers/2014/A-026.htm>>.
- [2] Jindani, A., Aber, V. R., Edwards, E. A. and Mitchison, D. A. The early bactericidal activity of drugs in patients with pulmonary tuberculosis. *Am. Rev. Respir. Dis.* **121**, 939–949 (1980).
- [3] Beal, S., Sheiner, L. B., Boeckmann, A. and Bauer, R. J. NONMEM User's Guides. (1989–2013), Icon Development Solutions, Ellicott City, MD, USA, 2013.
- [4] Smythe, W., Khandelwal, A., Merle, C., Rustomjee, R., Gninafon, M., Bocar Lo, M., Sow, O. B., Olhiano, P. L., Lienhardt, C., Horton, J., Smith, P., McIlleron, H. and Simonsson, U. S. H. A semimechanistic pharmacokinetic-enzyme turnover model for rifampin autoinduction in adult tuberculosis patients. *Antimicrob. Agents Chemother.* **56**, 2091–2098 (2012).

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