SUPPLEMENTARY MATERIAL

Pharmacodynamics and the Bactericidal Activity of Bedaquiline in Pulmonary Tuberculosis

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- Structural and statistical model diagrams
- Bedaquiline PK model parameters: prior point value estimates
- PK-PD model parameters: prior distributions
- PK-PD model: goodness-of-fit plots and statistics

Structural and statistical model diagrams

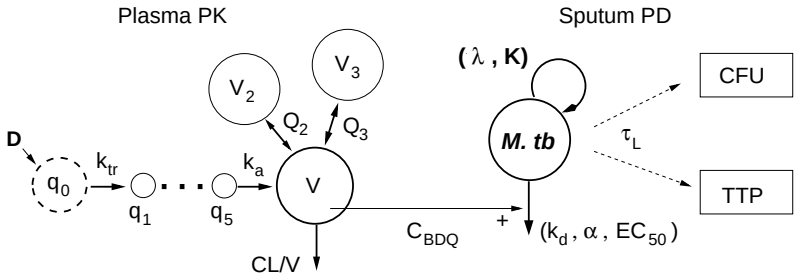

Figure S1: Bedaquiline pharmacokinetic-pharmacodynamic (PK-PD) structural model. D, dose; q_0, drug mass depot, $q_1, \ldots, q_5$, drug mass transit compartments; V, central volume of distribution, V_2, V_3, peripheral volumes of distribution; CL, systemic clearance; Q_2, Q_3, intercompartmental clearances; λ, sputum *M. tuberculosis* accumulation rate constant; K, sputum *M. tuberculosis* carrying capacity; k_d, drug kill rate constant; α, drug kill delay constant; EC_{50}, half-maximum effect drug concentration; τ_L, liquid culture time constant; CFU, sputum solid culture CFU; TTP and liquid culture time to positivity. The PK and PD models are linked by the BDQ plasma concentration, $\mathrm{C}_{\mathrm{BDQ}}$.

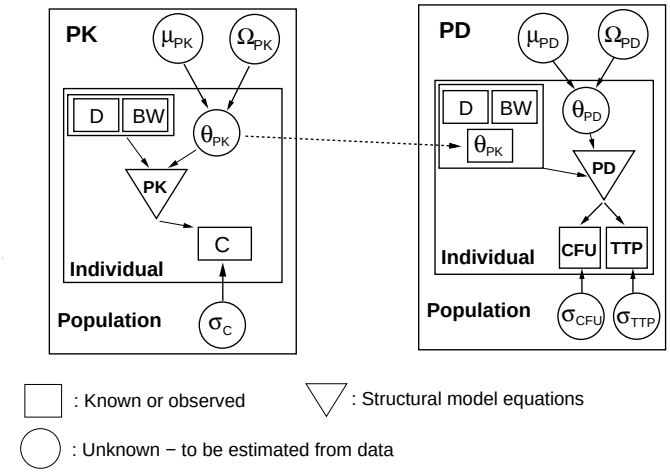

Figure S2: Graphical representation of the hierarchical statistical model. Population and individual levels for the pharmacokinetic (PK) and pharmacodynamic (PD) model components. μ: population mean; Ω: population variance; σ residual error; D: dose; BW: body weight; θ: unmeasured model parameters; C: observed drug concentrations; CFU and TTP: observed CFU and TTP. Arrows denote dependencies.

Bedaquiline PK model parameters: prior point value estimates

Bedaquiline concentration-time profile after a single 400 mg dose from:

Dooley, K. E., J. G. Park, S. Swindells, R. Allen, D. W. Haas, Y. Cramer, F. Aweeka, 399 I. Wiggins, A. Gupta, P. Lizak, S. Qasba, R. van Heeswijk, C. Flexner, D. Sutherland, M. Free, M. Chicurel, C. W. Tedder, S. L. Koletar, H. Harber, A. Luetkemeyer, J. Dwyer, J. Hackman, and A. Weiss. 2012. Safety, tolerability, and pharmacokinetic interactions of the antituberculous agent TMC207 (bedaquiline) with efavirenz in healthy volunteers: AIDS Clinical Trials Group Study A5267. J Acquir Immune Defic Syndr 59:455462.

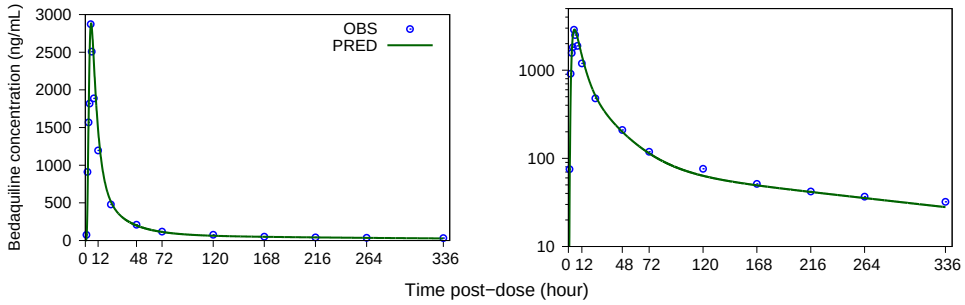

Figure S3: Mean concentrations of bedaquiline in plasma versus time after a single 400 mg oral dose. OBS, observed data; PRED, model-predicted curve generated from the structural model using the point values shown in Table S1.

Table S1: PK model parameters. Point value estimates obtained from a sum of exponentials curve fit to the bedaquiline mean concentration-time profile.

Parameter	Value (units)	Description
D	400 mg	Dose
F_{max}	1	Maximum bioavailability
BW	70 kg	Body weight (standard value)
k_{tr}	2.4 h^{-1}	Transit compartment mass transfer rate constant
k_a	0.9 h^{-1}	Oral absorption rate constant
V	90 L	Central compartment volume of distribution
V_2	60 L	Peripheral compartment volume of distribution
V_3	650 L	Peripheral compartment volume of distribution
Q_2	4 L/h	Intercompartmental clearance
Q_3	3.4 L/h	Intercompartmental clearance
CL	6.2 L/h	Systemic clearance

The observed data points were extracted from the published plot using g3data (version 1.5.2 [`http://github.com/pn2200/g3data`]). The curve fit was obtained using the R statistical software (version 3.3.3; R Development Team, [`https://www.R-project.org`]), and the PK (version 1.3.5 [`https://CRAN.R-project.org/package=PK`]) and PKconverter (version 1.5 [`https://CRAN.R-project.org/package=PKconverter`]) packages.

PK-PD model parameters: prior distributions.

Table S2: Prior population mean and interindividual variability distributions.

Parameter (units)	$\exp(\mu)$		ω^2
PK parameters[a]			
k_{tr} (1/h)	LN(0.88, 0.04)	[0.2, 20]	HN(0.11)
k_a (1/h)	LN(0, 0.04)	[0.1, 10]	HN(0.11)
V_c (L)	LN(4.50, 0.04)	[10, 1000]	HN(0.11)
V_{2c} (L)	LN(4.09, 0.04)	[10, 600]	HN(0.11)
V_{3c} (L)	LN(6.48, 0.04)	[60, 6000]	HN(0.11)
Q_{2c} (L/h)	LN(1.39, 0.04)	[1, 40]	HN(0.11)
Q_{3c} (L/h)	LN(1.10, 0.04)	[1, 30]	HN(0.11)
CL_c (L/h)	LN(1.79, 0.01)	[2, 30]	HN(0.11)
PD parameters			
N_0 (CFU/mL)	LN(13.98, 0.35)	$[1 \times 10^3, 1 \times 10^9]$	HN(6.0)
T_0 (h)	LN(4.60, 0.01)	[24, 400]	HN(0.1)
τ_L (h)	LN(3.0, 0.01)	[10, 40]	HN(0.1)
λ (1/h)	LN(-6.91, 0.15)	[0.0003, 0.003]	- [a]
K (CFU/mL)	LN(18.4, 0.6)	$[1 \times 10^7, 1 \times 10^9]$	- [a]
k_d (1/h)	LN(-4.02, 0.01)	[0.004, 0.09]	HN(0.2)
α (1/h)	LN(-3.91, 0.01)	[0.004, 0.1]	HN(0.2)
EC_{50} (mg/L)	LN(0.34, 0.01)	[0.3, 8]	HN(0.2)
H	LN(0, 0.01)	[0.1, 10]	HN(0.1)

LN: lognormal distribution, LN(M_μ, S_μ^2)[truncation bounds], with geometric mean = $\exp(M_\mu)$, and geometric standard deviation = $\exp(S_\mu)$.
HN: Half-normal distribution, HN(SD), with SD = $\omega^2 \cdot \sqrt{\pi/2}$, where $\omega^2 = \log(\text{CV}^2 + 1)$, and CV the coefficient of variation.
[a] Parameter uncertainty and interindividual variability were combined.

PK-PD model: goodness-of-fit plots and statistics

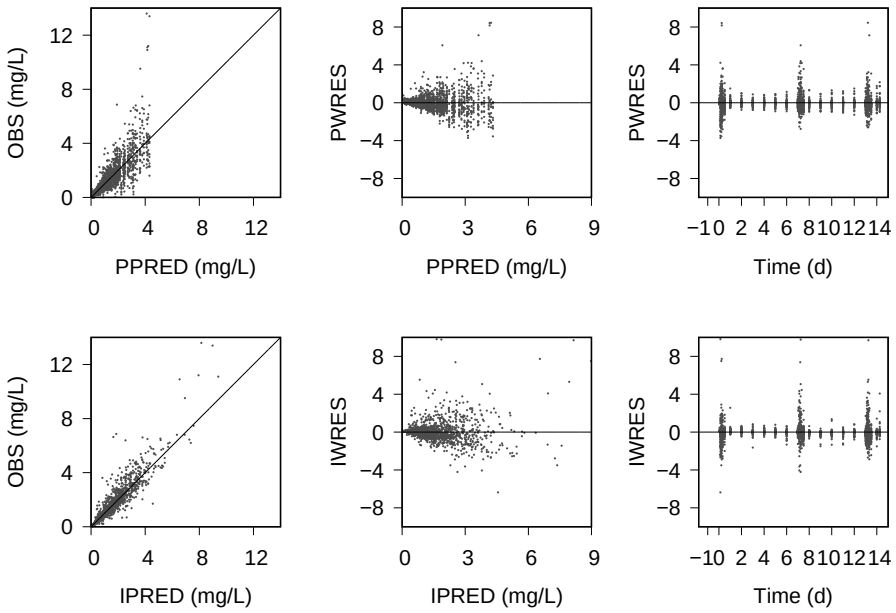

Figure S4: Goodness-of-fit plots for model-predicted and observed bedaquiline concentrations. The plots are: observed individual data (OBS) versus population predicted mean (PPRED) and individual predicted (IPRED) values, with the diagonal lines representing perfect fit; and the weighted residuals of the population mean (PWRES) and individual (IWRES) versus the corresponding predictions and time. The horizontal lines represent zero residual error.

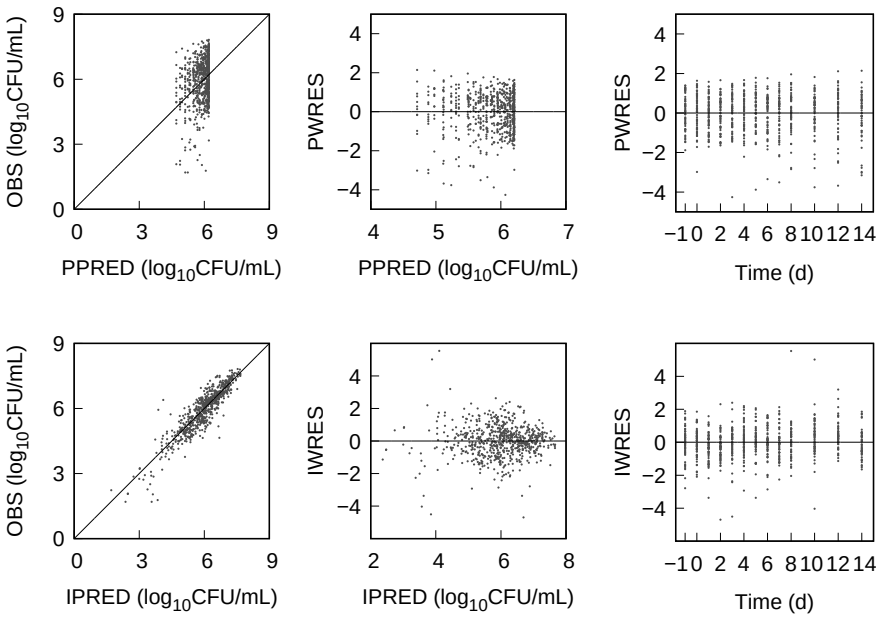

Figure S5: Goodness-of-fit plots for model-predicted and observed CFU data. The plots are: observed individual data (OBS) versus population predicted mean (PPRED) and individual predicted (IPRED) values, with the diagonal lines representing perfect fit; and the weighted residuals of the population mean (PWRES) and individual (IWRES) versus the corresponding predictions and time. The horizontal lines represent zero residual error.

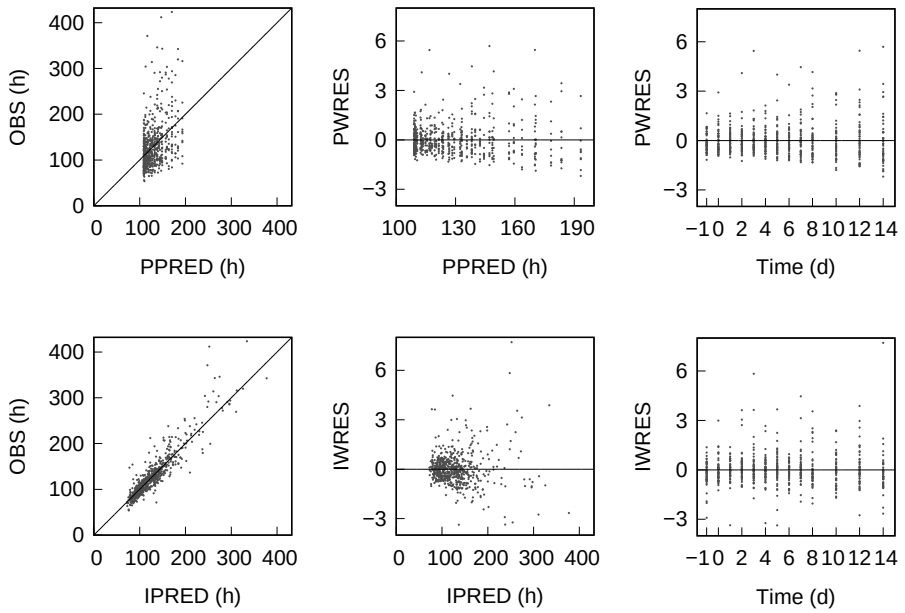

Figure S6: Goodness-of-fit plots for model-predicted and observed TTP data. The plots are: observed individual data (OBS) versus population predicted mean (PPRED) and individual predicted (IPRED) values, with the diagonal lines representing perfect fit; and the weighted residuals of the population mean (PWRES) and individual (IWRES) versus the corresponding predictions and time. The horizontal lines represent zero residual error.

Table S3: Goodness-of-fit summary statistics for Figures S4-S6.

Parameter (units)	Mean (SD)	Median [2.5th, 97.5th][a]
BDQ (n=1767)		
OBS (mg/L)	1500 (1320)	1110 [134, 4720]
IPRED (mg/L)	1430 (1130)	1120 [151, 4220]
PPRED (mg/L)	1480 (996)	1230 [202, 4110]
IWRES	0.0 (1.0)	-0.0285 [-1.74, 2.25]
PWRES	0.0 (1.0)	-0.0374 [-1.91, 2.02]
CFU (n=681)		
OBS ($\log_{10}$CFU/mL)	5.92 (1.05)	6.1 [3.22, 7.51]
IPRED ($\log_{10}$CFU/mL)	5.96 (0.915)	6.05 [3.74 , 7.32]
PPRED ($\log_{10}$CFU/mL)	5.85 (0.38)	5.95 [4.88, 6.21]
IWRES	0.0 (1.0)	0.0099 [-1.98, 1.86]
PWRES	0.0 (1.0)	0.181 [-2.33, 1.49]
TTP (n=619)		
OBS (h)	130 (51.1)	119 [72.5, 286]
IPRED (h)	129 (44.4)	120 [79, 58]
PPRED (h)	129 (21.5)	123 [109, 184]
IWRES	0.0 (1.0)	-0.0786 [-1.66, 2.46]
PWRES	0.0 (1.0)	-0.205 [-1.32, 2.77]

n, sample size; OBS, observed; PPRED, population predicted; IPRED, individual predicted; PWRES population predicted weighted residual; IWRES, individual predicted weighted residual.

[a] Values in brackets are the 2.5th and 97.5th percentiles.