9th International Workshop on Clinical Pharmacology of TB Drugs
24 October 2016, Liverpool, UK

A model-based analysis to describe bedaquiline's **exposure-response** relationship and predict the impact of **drug-drug interactions**

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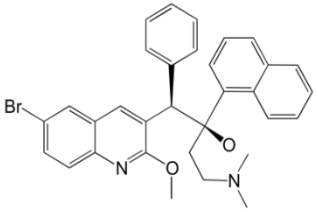
Bedaquiline



- Recently approved for MDR-TB
- *Pharmacokinetics*
  - Terminal half-life > 5 months
  - Metabolized by CYP3A4
- *Pharmacodynamics*
  - Targets mycobacterial energy metabolism
  - Shortens time to sputum culture conversion
  - Increases the rate of relapse free cure

No exposure-response relationship described!

Van Heeswijk *et al.* Journal of Antimicrobial Chemotherapy, 2014
Diacon *et al.* New England Journal of Medicine, 2014

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Objective

Characterize the PK-PD relationship between bedaquiline **exposure** and **mycobacterial response** and evaluate the potential **impact** of known pharmacokinetic **drug-drug interactions**

Plan

- Utilize **quantitative culture data** and a previously developed population PK model in a **nonlinear mixed-effects** analysis
- Predict **time to sputum culture conversion** under different **drug-drug interaction scenarios**

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Study design and data

- Phase IIb registration study
- Double-blind, placebo controlled
- Optimized background regimen (OBR)
- Bedaquiline dosed at 400 mg QD until week 2, thereafter at 200 mg thrice weekly
- Evaluation of response:
  - Triplicate spot sputum samples
  - Mycobacterial load quantified by time to positivity in mycobacterial growth incubator tubes (MGIT)

Diacon *et al.* New England Journal of Medicine, 2014

Mycobacterial growth incubator tube (MGIT)

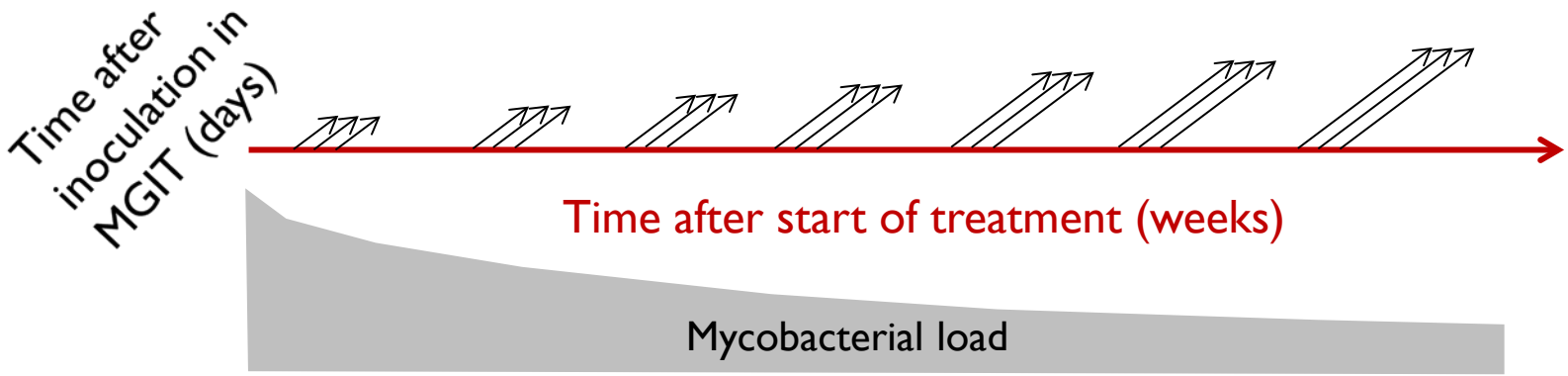
- Semi-automatic culture system
- Sample inoculated in growth tube
- Growing bacteria consume oxygen
- Signal at low oxygen level

Readout: time to positivity [days]

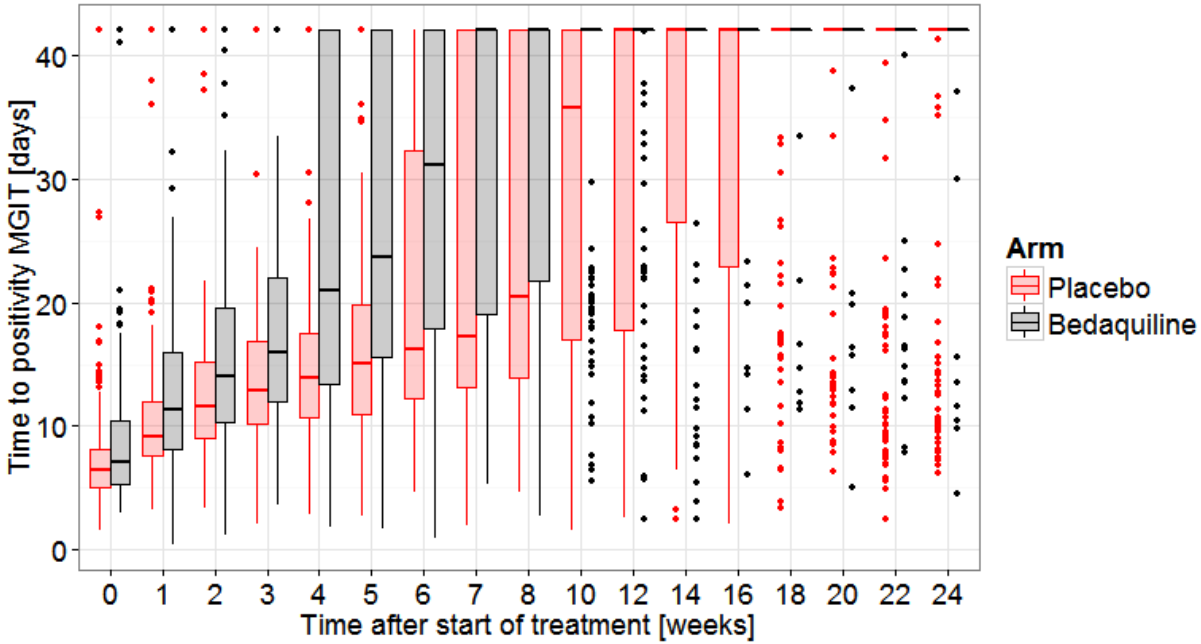
Siddiqi and Rüsch-Gerdes, MGIT™ Procedure Manual for BACTEC™ MGIT960™ TB System, 2006

Time considerations

- Two scales
  - **Patient:** Time after start of treatment, **weeks**
  - **Sample:** Time after inoculation in MGIT, **days** < 42



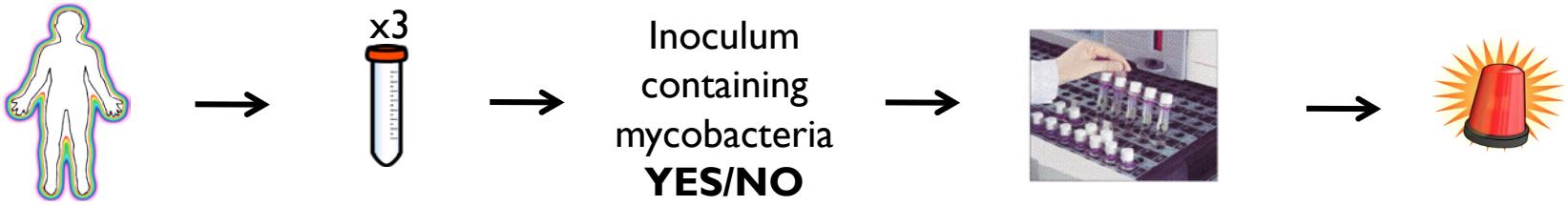
Time to positivity data



102 (bedaquiline) + 104 (placebo) drug-resistant TB patients: ~7400 samples

Model structure

(i) Mycobacterial load model	(ii) Probability of bacterial presence	(iii) Bacterial growth linked to hazard in time-to-event model



Covariates: Resistance type, gender, ethnicity, baseline bacterial load, etc.

PK: individual model-derived exposures[1]

[1] Svensson *et al.* CPT:PSP, accepted 2016

Model structure

Significant covariates

- Baseline bacterial load
- Drug-resistance type (MDR vs [pre-]XDR)
- Bedaquiline exposure
  - Weekly average concentration ($C_{avg,w}$)
  - EC_{50} > median observed $C_{avg,w}$

→ Bedaquiline concentrations matter

→ PK DDIs matter

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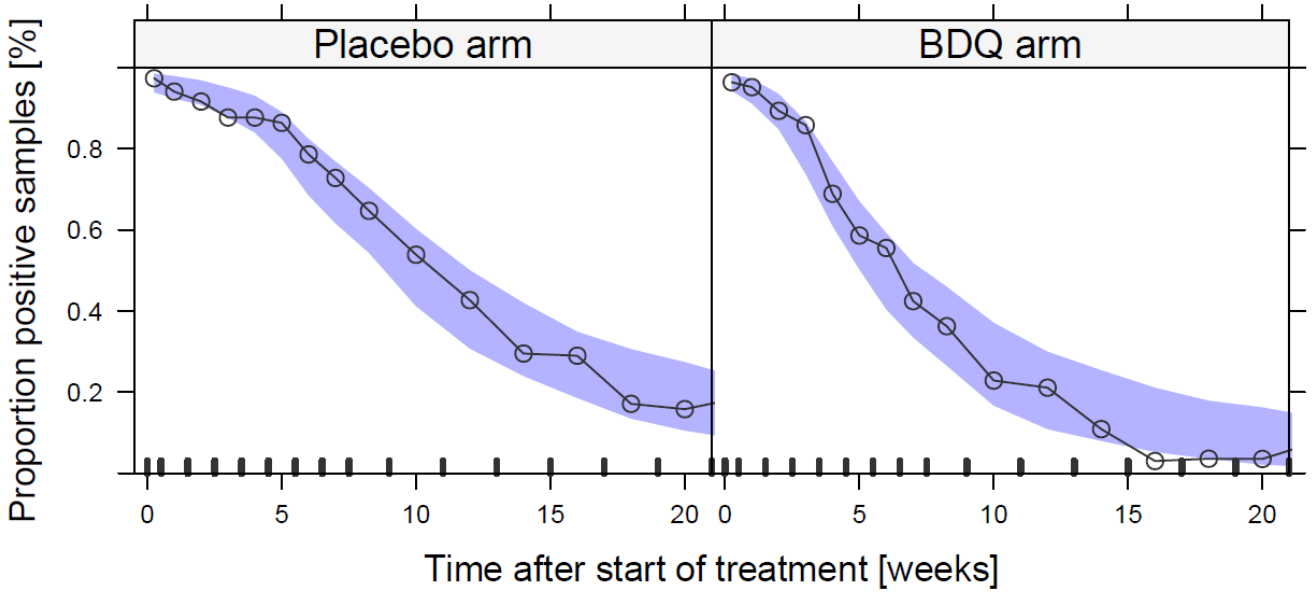
Model evaluation

Visual predictive checks

Positive **samples** over **time after start of treatment**



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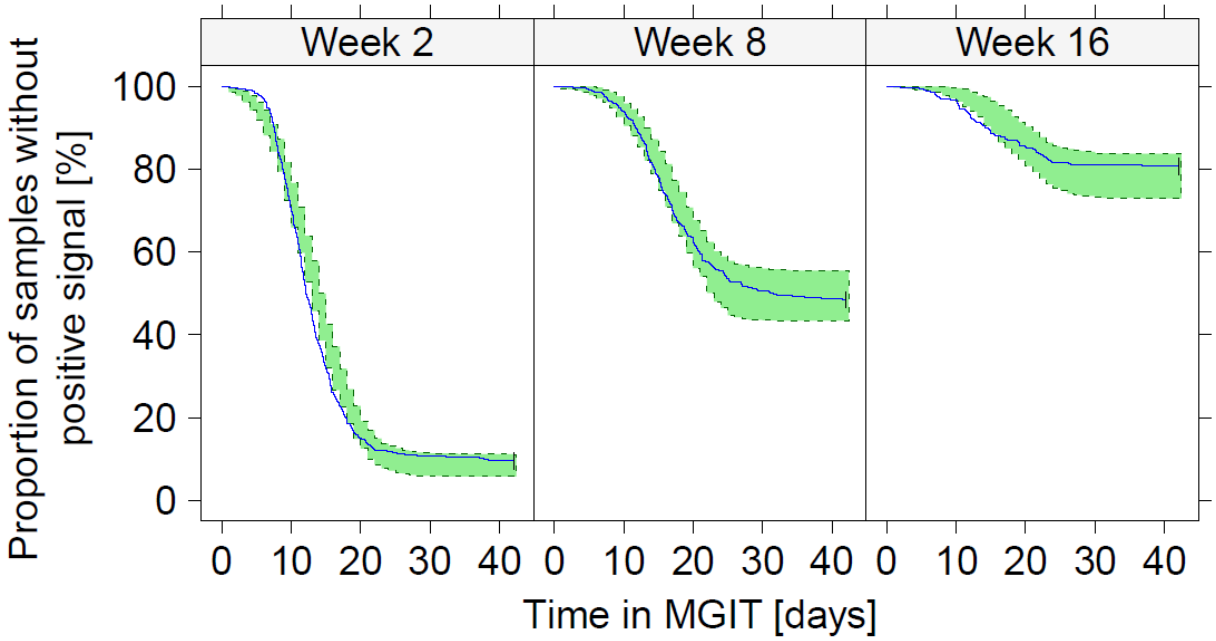
Model evaluation

Visual predictive checks

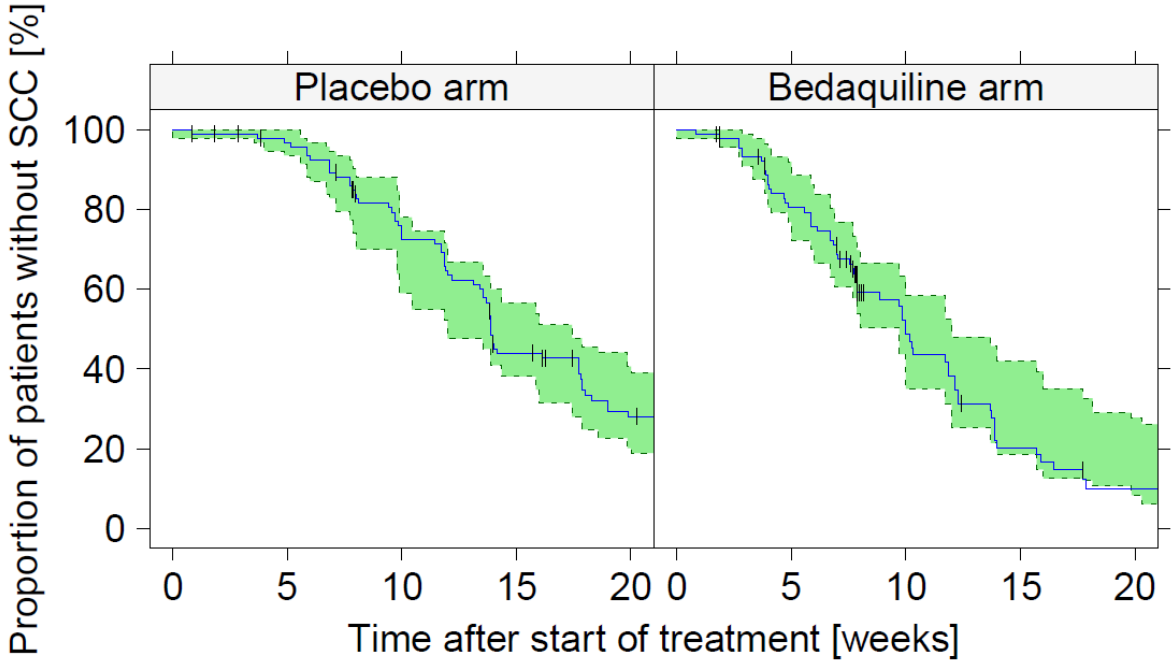
Positive **samples** over **time in MGIT**



Model evaluation

Posterior predictive checks

Time to sputum culture conversion (SCC) in **patients**



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Bedaquiline PK DDIs

Perpetrator drug	Mechanism	Effect on bedaquiline clearance
Efavirenz[1]	Inducing CYP3A4	+ 107%
Lopinavir/ritonavir[2]	Inhibiting CYP3A4	- 65%
Rifampicin[3]	Inducing CYP3A4	+ 378%

[1] Svensson *et al.* AAC, 57(6), 2013
[2] Svensson *et al.* AAC, 58(11), 2014
[3] Svensson *et al.* JAC, 70, 2015

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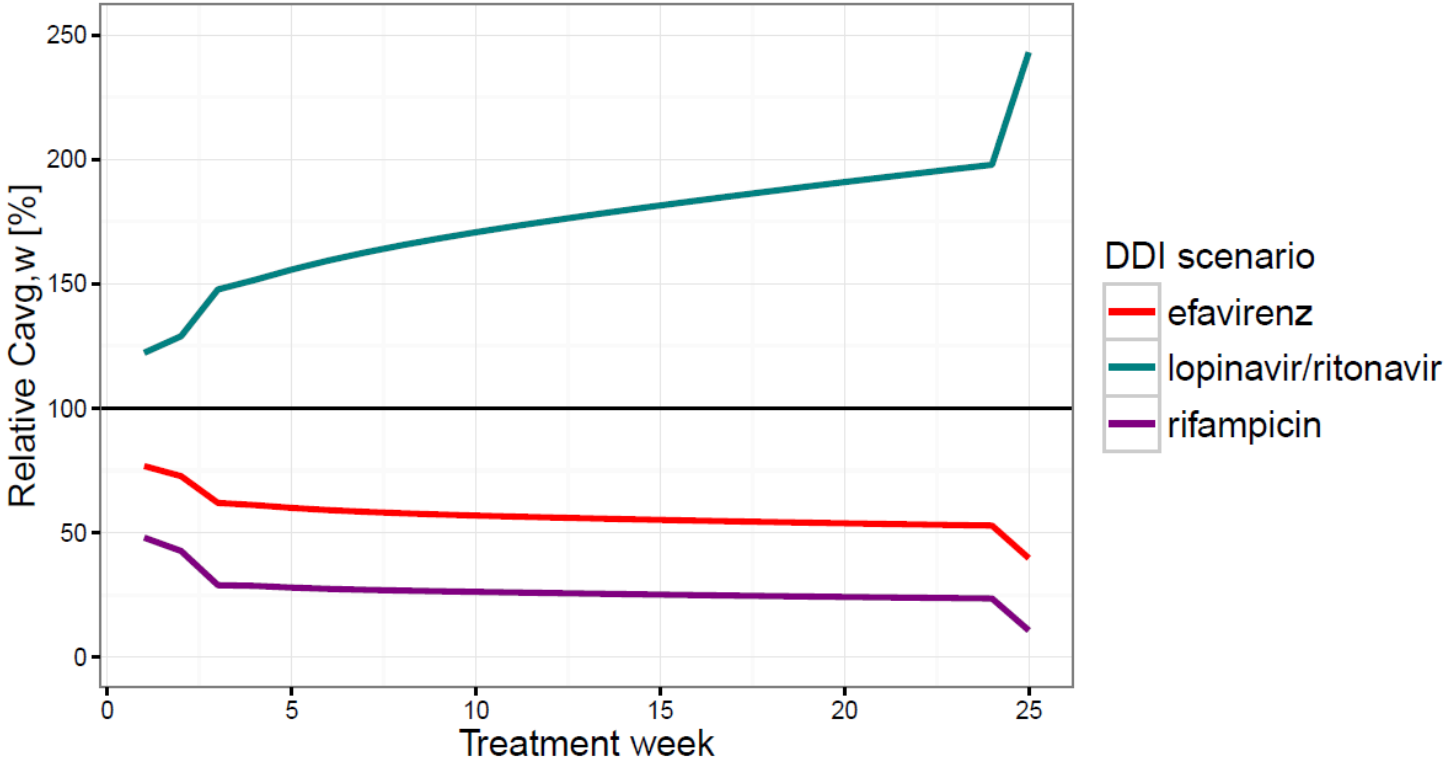
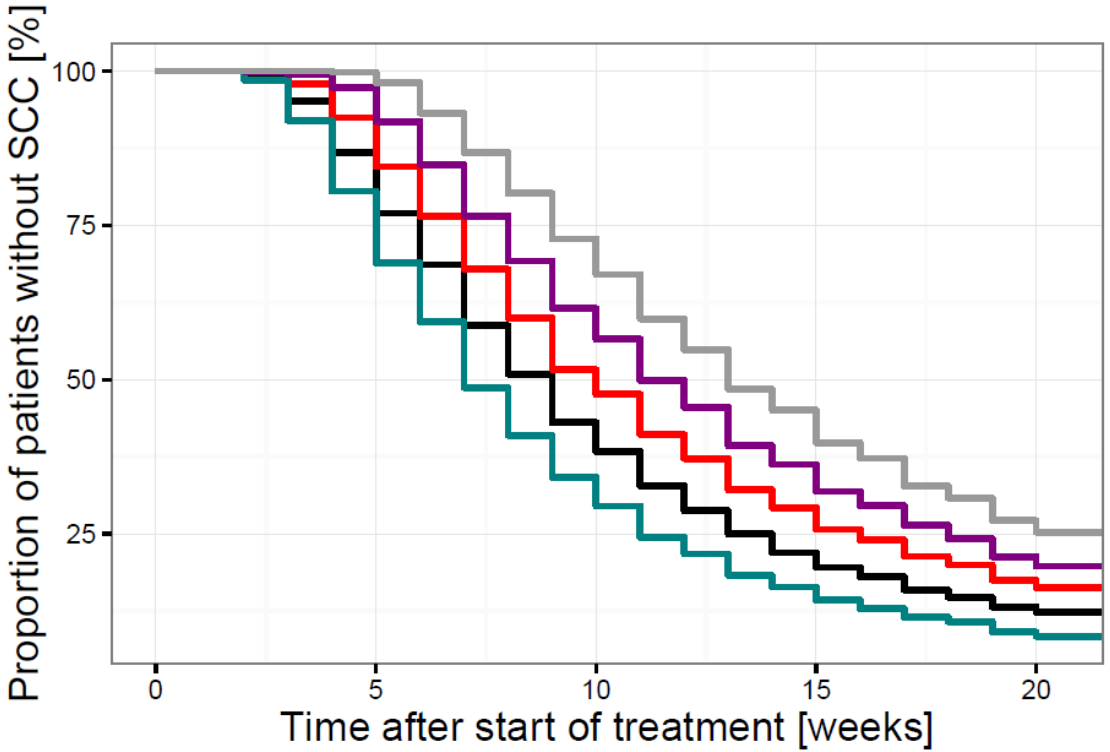
Typical bedaquiline PK DDIs



Impact of bedaquiline exposure

MDR-TB, median baseline bacterial load



DDI scenario	Proportion patients without SCC at w. 20
no DDI	**12.3%**
efavirenz	**16.3% (+29%)**
lopinavir/ritonavir	**8.4% (-32%)**
rifampicin	**19.8% (+64%)**
no bedaquiline	**25.3% (+105%)**

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Summary

- ✓ Novel model with **three linked components**:
  (i) longitudinal representation of mycobacterial load in patients
  (ii) probability of bacterial presence in sputum
  (iii) time-to-event model for time to positivity in MGIT
- ✓ **Predicts time to sputum culture conversion well**
- ✓ Bedaquiline **exposure-response relationship** characterized
- ✓ Enables **interpretation** of **drug-drug interactions** and **optimization** of **novel anti-tuberculosis regimens**

Acknowledgments

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Thank you!

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Back-up slides

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Model structure

(i) Mycobacterial load model

$$MBL(TAST)_i = MBL_0 * \left(\frac{mTTP_{0,i}}{mTTP_{0,p}}\right)^{COV_{TTP}} * e^{-\frac{\ln(2)}{HL_i} * TAST}$$

$$HL_i = HL * (1 + DR_i * COV_{DR}) * \left(1 - \frac{C_{avg,w}}{(EC_{50} + C_{avg,w})}\right) * e^{ETA_{HL,i}}$$

Significant covariates

- Baseline bacterial load (mTTP)
- Drug-resistance type (DR)
- Bedaquiline exposure ($C_{avg,w}$), EC_{50} > median AUC_i

MBL = mycobacterial load
HL = half-life of bacterial load
TAST = time after start of treatment

Model structure

(i) Mycobacterial load model

(ii) Probability of bacterial presence

(iii) Bacterial growth linked to hazard in time-to-event model

$$\boldsymbol{MBL(TAST)_i}$$

$$P_{pos} = \frac{P_{max} * \boldsymbol{MBL(TAST)_i} * e^{\boldsymbol{ETA_{occ,i,j}}}}{\boldsymbol{MBL(TAST)_i} * e^{\boldsymbol{ETA_{occ,i,j}}} + 0.5}$$

$$\frac{dB(t)}{dt} = B(t) * \boldsymbol{k_{growth}} * (\boldsymbol{B_{max}} - B(t))$$

$$B(t=0) = \boldsymbol{MBL(TAST)_i} * e^{\boldsymbol{ETA_{occ,i,j}}}$$

$$h(t) = B(t) * \boldsymbol{h_{scale}}$$

TAST = time after start of treatment
t = time after inoculation in MGIT

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Abbreviations:
RSE, relative standard error; MLB, mycobacterial load; IIV, inter-individual variability; IOV, inter-occasion variability; P_{max}, maximal risk of positive sample; MBL_{50}, MBL value corresponding to 50% of P_{max}; k_g, growth rate in MGIT; B_{max}, maximal bacteria carrying capacity in MGIT

Sub-model	Parameter [unit]	Value	$C_{95\%}$
MBL in patients	MBL_0 [n bacteria/inoculum]	$2.14*10^3$	$1.39*10^3$,$3.46*10^3$
	Half-life MBL [weeks]	0.81	0.71,0.93
	IIV half-life MBL [variance]	0.33	0.25,0.45
	Box-Cox transformation IIV half-life MBL	0.66	0.34,1.05
	Bedaquiline maximal effect on half-life MBL	-1 FIX	-
	EC_{50} bedaquiline effect on half-life MLB [µg/ml]	1.42	1.00,2.05
	(pre-) XDR effect on half-life MBL [%]	28.1	9.1,51.5
	Baseline TTP effect on MBL_0	-3.69	-4.15,-3.30
	IOV sputum sampling MBL [variance]	3.71	3.29,4.38
Probability of bacterial presence	P_{MAX} positive	0.969 FIX	-
	MBL_{50} [n bacteria/inoculum]	0.5 FIX	-
Growth in MGIT (hazard)	k_g [1/(day*bacteria)]	$1.38*10^{-6}$	$7.77*10^{-5}$,$2.24*10^{-6}$
	B_{max} [n bacteria]	$4.76*10^5$	$2.79*10^5$,$8.88*10^5$
	Scaling of hazard	$9.52*10^{-5}$	$5.08*10^{-5}$,$1.64*10^{-6}$