Bedaquiline's exposure-response relationship revealed through modeling of mycobacterial load

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Tuberculosis (TB)

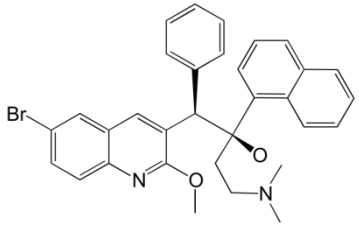
- Caused by *Mycobacterium tuberculosis*
- Effective 4-drug combination therapy
- 2014: 10 million cases and 1.5 million deaths

Drug-resistance development

0.5 million cases of multidrug-resistant (MDR) TB
Treatment success rate ~50%

WHO, Global Tuberculosis Report 2015

Bedaquiline



- Recently approved for MDR-TB
- *Pharmacokinetics*
  - Terminal half-life > 5 months
- *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 in patients with drug-resistant TB

Plan

- Utilize quantitative culture data and a previously developed population PK model in a nonlinear mixed-effects analysis
- Predict time to sputum culture conversion

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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

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

Mycobacterial growth incubator tube (MGIT)

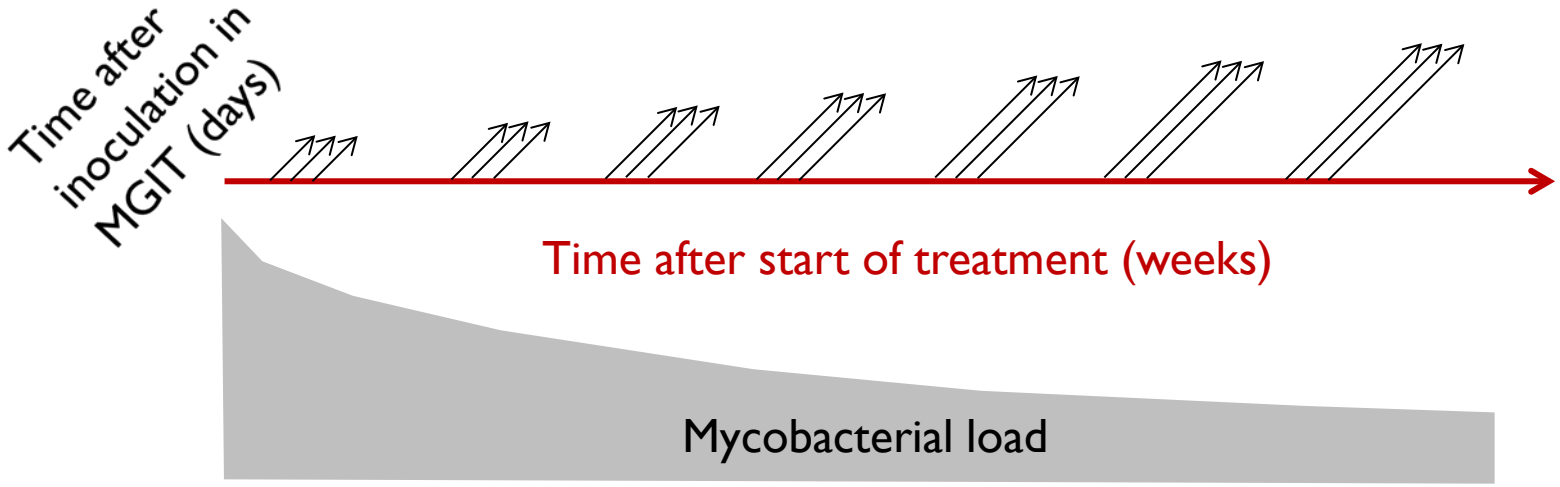
- Semi-automatic culture system
- Sample inoculated in growth tube
- Growing bacteria consume oxygen
- Signal at low oxygen level

Readout: time to positivity [days]

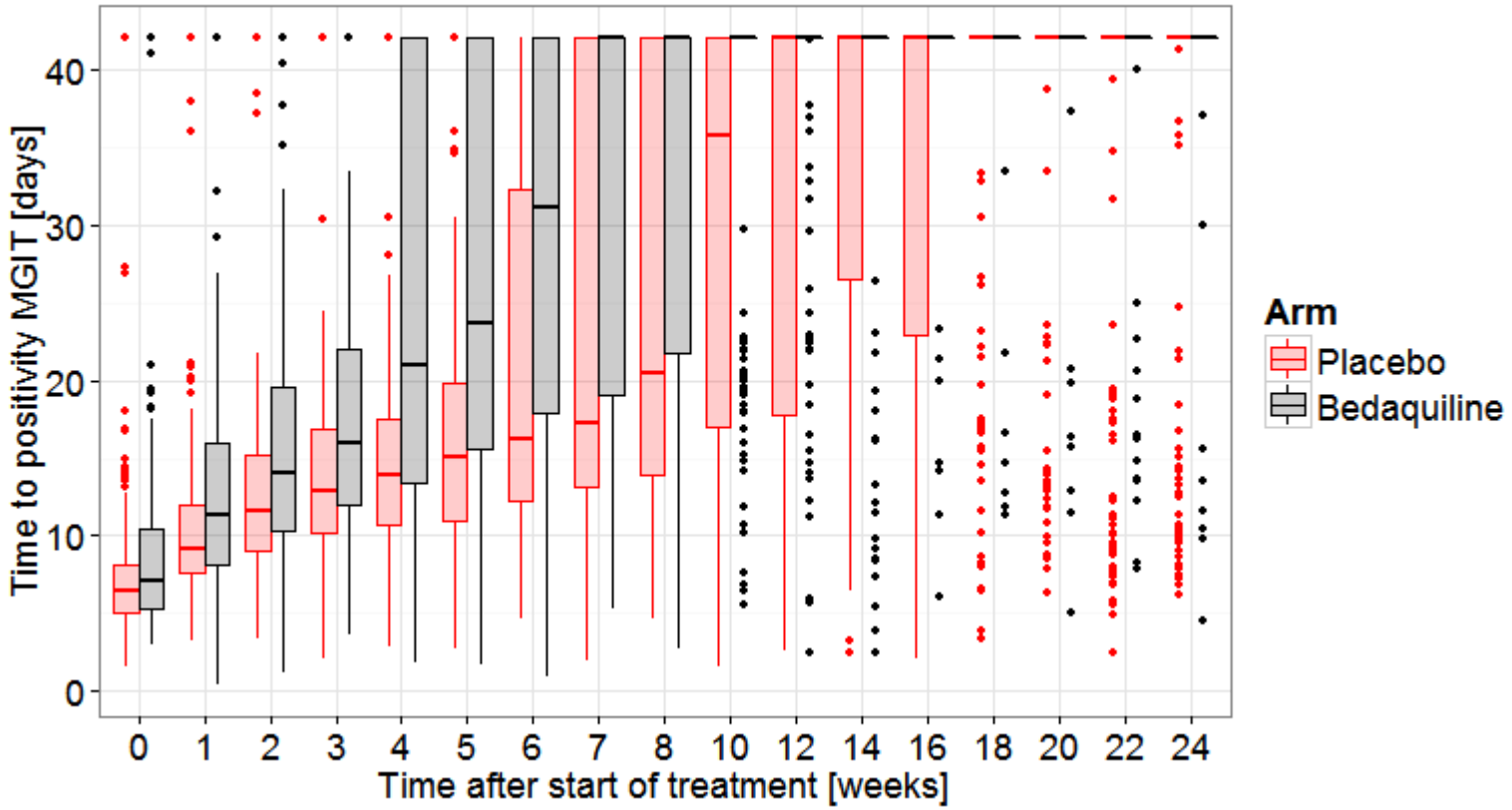
Siddiqi and Rüsch-Gerdes, MGIT™ Procedure Manual for BACTEC™ MGIT960™ TB System, 2006

Time considerations

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



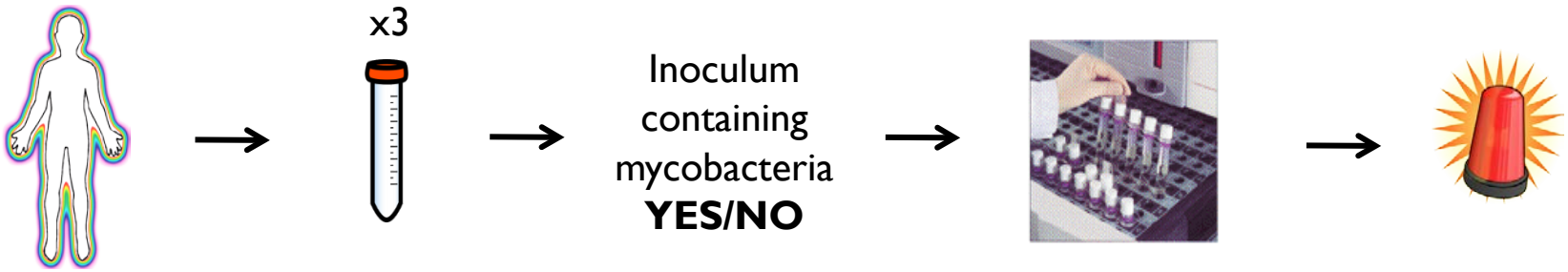
Mycobacterial load data
Box-plots of **time to positivity**



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

Modeling approach

(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, Pharmacometric models to improve treatment of tuberculosis, 2016

Model structure

(i) Mycobacterial load model

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

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

Significant covariates

- Baseline bacterial load (mTTP)
- Drug-resistance type (DR)
- Bedaquiline exposure ($AUC_{0\text{-}24h,day14}$), 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

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

(ii) Probability of bacterial presence

$$P_{pos} = \frac{P_{max} * \boldsymbol{MBL(TAST)_i}}{\boldsymbol{MBL(TAST)_i} + \boldsymbol{MBL_{50}}}$$

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

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

$$B(t = 0) = \boldsymbol{MBL(TAST)_i}$$

$$h(t) = B(t)$$

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

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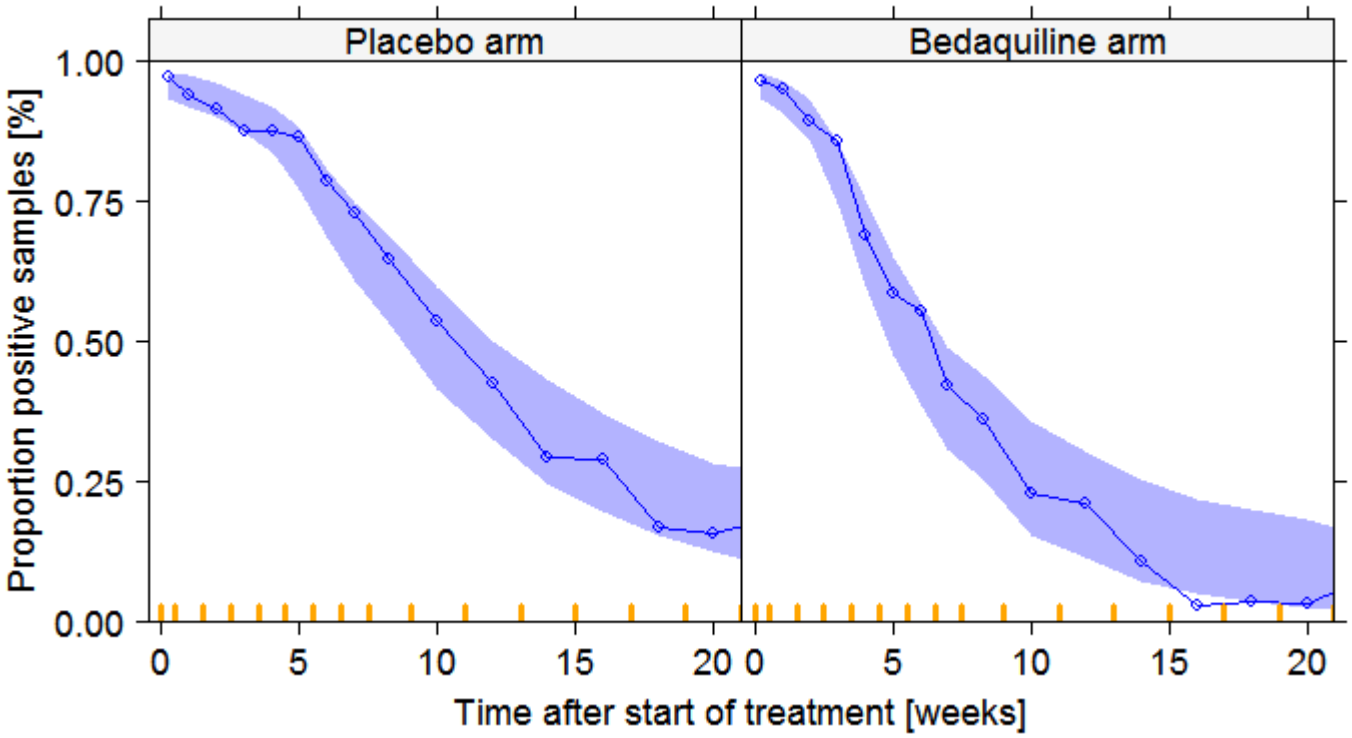
Model evaluation

Visual predictive checks

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



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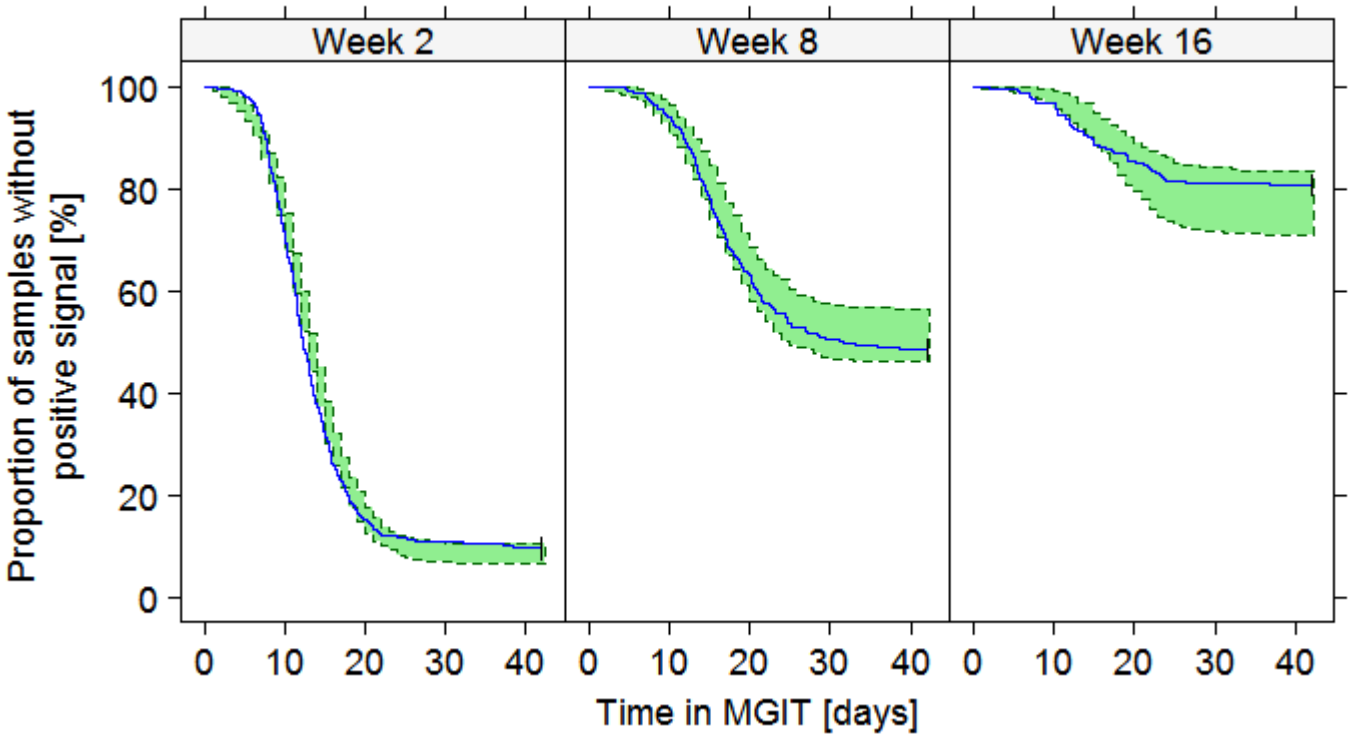
Model evaluation

Visual predictive checks

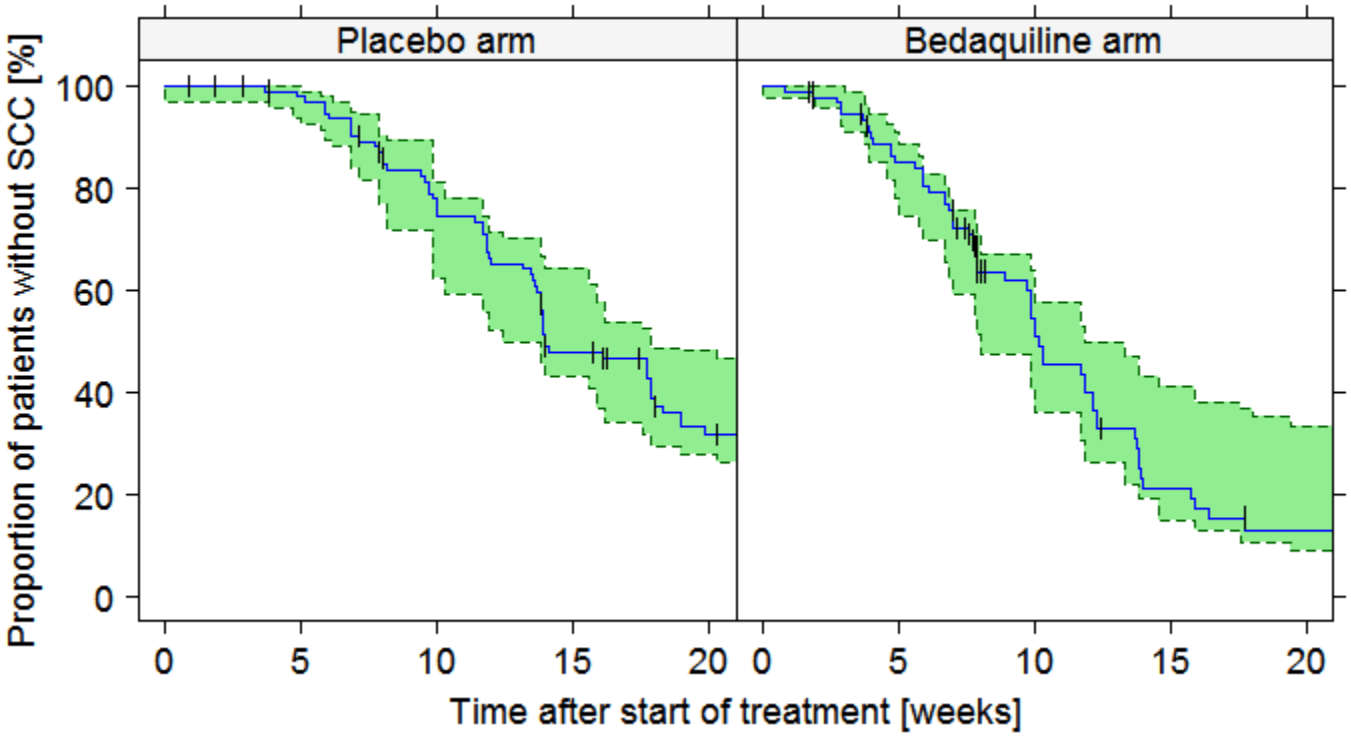
Positive **samples** over **time in MGIT**



Model evaluation
Posterior predictive checks

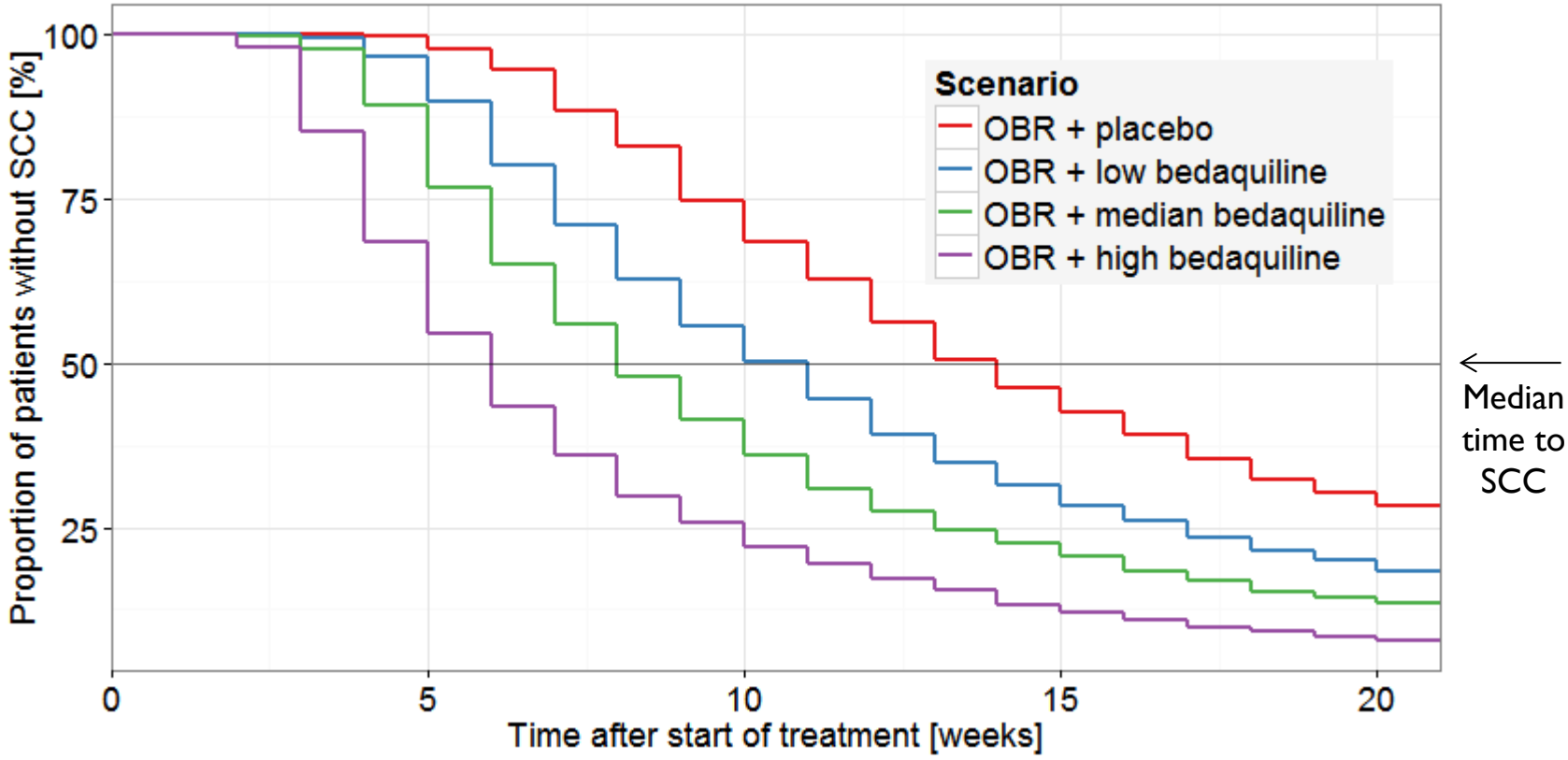
Time to sputum culture conversion (SCC) in **patients**

Time between start of treatment and the first of two consecutive sampling occasions with only negative cultures obtained at least 4 weeks apart



Impact of bedaquiline exposure

MDR-TB, median baseline bacterial load



median = median $AUC_{0\text{-}24h,day14}$, **low** = half median, **high** = double median
High/low are well within range of observed exposures.

Impact of bedaquiline exposure

Simulations including parameter uncertainty

Scenario MDR-TB, median baseline bacterial load	**Median time to SCC** [weeks] (90% CI)	**Proportion without SCC at week 20** [%] (90% CI)
OBR + Placebo	14 (12 – 15)	28.2 (22.8 – 34.2)
OBR + Bedaquiline, low exposure	11 (10 – 11)	18.5 (15.2 – 21.9)
OBR + Bedaquiline, median exposure	8 (8 – 9)	13.5 (10.3 – 16.9)
OBR + Bedaquiline, high exposure	6 (5 – 7)	7.8 (5.3 – 11.2)

median = median $AUC_{0\text{-}24h,day14}$, **low** = half median, **high** = double median
High/low are well within range of observed exposures.

Discussion and further work

- ✓ Impact of drug-drug interactions

Perpetrator drug	Effect on bedaquiline clearance	Effect on bedaquiline $C_{avg,ss}$
Efavirenz[1]	+ 107%	- 52%
Rifampicin[2]	+ 378%	- 79%
Lopinavir/ritonavir[3]	- 65%	+ 188%

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

- ✓ Recent model improvements
  - Dynamic PK (weekly AUC)
  - Inter-occasion variability in sputum
- ✓ Validation of model and detected exposure-response relationship on other datasets planned

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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 (SCC) well
- ✓ Bedaquiline exposure-response relationship characterized
  - Median time to SCC shortened from **11 to 6 weeks** in typical MDR-TB patients with high bedaquiline exposure compared to patients with low exposure
- ✓ Enables interpretation of drug-drug interactions and optimization of novel anti-tuberculosis regimens

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Thank you!

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Lewis Sheiner Student Session, PAGE 2016