



# Evaluation of the Exposure-QT Relationship During Bedaquiline Treatment Using a Time-Varying Tuberculosis–Specific Correction Factor (QTcTBT)

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## Introduction

- M2, the primary metabolite of bedaquiline (BDQ), causes QT prolongation.
- The Fredericia correction (QTcF) corrects poorly for HR in patients with active tuberculosis (TB), who typically experience tachycardia before treatment and achieve normalized HR during treatment [1,2].
- Model-based analyses can alleviate the bias associated with QTcF's HR correction but requires time and skilled personnel [3].
- A time-varying correction factor has been developed and validated to adjust for heart rate changes during TB treatment, allowing for a simple and straightforward correction. [4].

## Aims

- Evaluate the effect of time-on-treatment on QT prolongation when using QTcTBT.
- Characterize and assess the effect of M2 concentration on QT using QTcTBT.

## Methods

### Data

- 429 patients with multidrug-resistant (MDR) TB were collected from two Phase IIb trials.
  - In C208, a randomized, double-blind, placebo-controlled study, newly diagnosed patients received BDQ or a placebo for 8 weeks (Stage 1) and 24 weeks (Stage 2) [5,6].
  - In C209, a single-arm, open-label trial, both newly diagnosed, and treatment-experienced patients received BDQ for 24 weeks [7].
- Baseline and on-treatment ECG measurements.
- Derived M2 concentrations at time of ECG measurement, using a published PK model along with the observed PK data [8].

### QTc models (Adapted Tanneau's QTcF model [3])

#### Structural models

$$QT(t)_i = QT_{baseline,i} +$$

$$QT_{max} \times \left(1 - e^{-\frac{\ln(2) \times t}{t_{1/2}}}\right) + \left\{ \begin{array}{l} \text{Effect of time-on-treatment} \\ QT_{max} = \text{the maximal QT change,} \\ T_{1/2} = \text{the half-time needed to achieve the QTmax} \end{array} \right\}$$
$$A_{24} \times \cos\left(\frac{2 \times \pi \times (C_{time} - \varphi_{24})}{24}\right) + A_{12} \times \cos\left(\frac{2 \times \pi \times (C_{time} - \varphi_{12})}{12}\right) + \left\{ \begin{array}{l} \text{Circadian rhythm} \\ A = \text{the amplitude of the 24- or 12- hour oscillator} \\ \varphi = \text{the acrophase of the 24- or 12-hour oscillator} \end{array} \right\}$$
$$\frac{Emax \times M_2 \times \text{Concentration}_{M_2}}{EC50_{M_2} + \text{Concentration}_{M_2}} + \left\{ \begin{array}{l} \text{Drug effect (M2)} \\ Emax = \text{the maximal effect of M2 on QT} \\ EC50 = \text{the concentration achieving 50\% effect of Emax} \end{array} \right\}$$
$$Covariates + \left\{ \begin{array}{l} \text{Additive covariates relation} \\ \text{time-varying clofazimine and moxifloxacin usage,} \\ \text{baseline serum calcium and potassium levels, sex (female), race (Black), and patient age.} \end{array} \right\}$$

#### Statistical models

- Additive residual unexplained variability (RUV) was modeled at two levels: per sample and per triplicate on one occasion.
- Interindividual variability was modeled using an additive model for QTmax and an exponential model for QT baseline, EC50M2, and RUV.

### Evaluation of time-on-treatment effect

- Compared 3 models
  - No effect of time-on-treatment
  - Time-on treatment effect without systematic shift (fixed QTmax to 0)
  - Time-on treatment effect with systematic shift (estimated QTmax)

### Characterization and assessment of the effect of M2

- Linear, Emax, and power models for drug effects were examined.

### Model predictive performance evaluation

- Cross-validation was performed with 10 repetitions of 90%-10% train-validation splits.

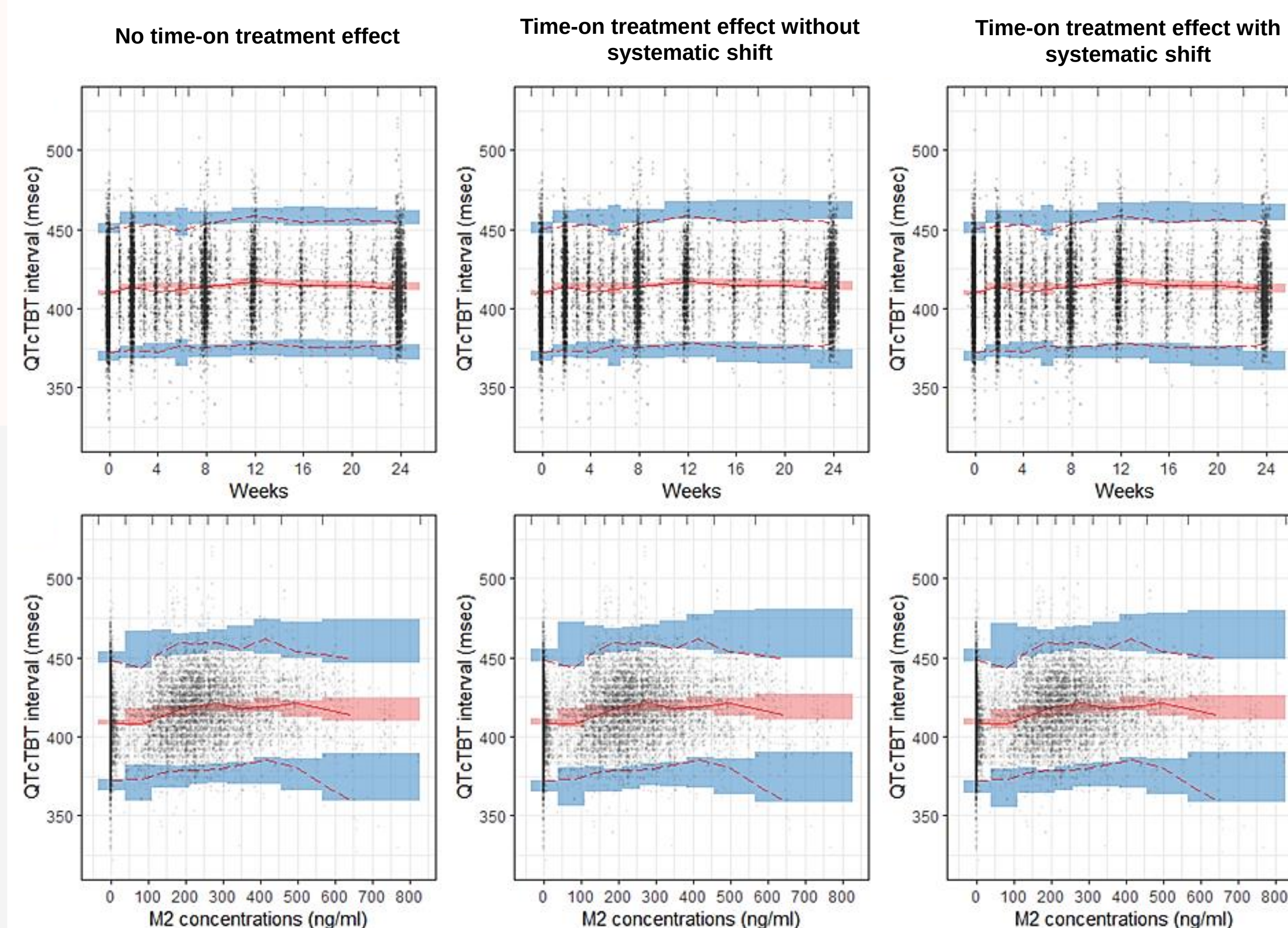
| 1            | 2            | 3            | 4        | 5        | 6        | 7        | 8        | 9        | 10       |
|--------------|--------------|--------------|----------|----------|----------|----------|----------|----------|----------|
| Prediction 1 | Training     | Training     | Training | Training | Training | Training | Training | Training | Training |
|              | Prediction 2 |              |          |          |          |          |          |          |          |
|              |              | Prediction 3 |          |          |          |          |          |          |          |
| ⋮            | ⋮            | ⋮            | ⋮        | ⋮        | ⋮        | ⋮        | ⋮        | ⋮        | ⋮        |

Sum OFV<sub>prediction</sub> = OFV<sub>pred,1</sub> + OFV<sub>pred,2</sub> + ...  
↓  
10 repetitions  
Compared the mean and its 95% CIs (mean ± 1.96  $\frac{\sigma}{\sqrt{10}}$ ) of the sum OFV<sub>prediction</sub> between models.

## Results

- The Emax model was the best to describe the M2 effect.

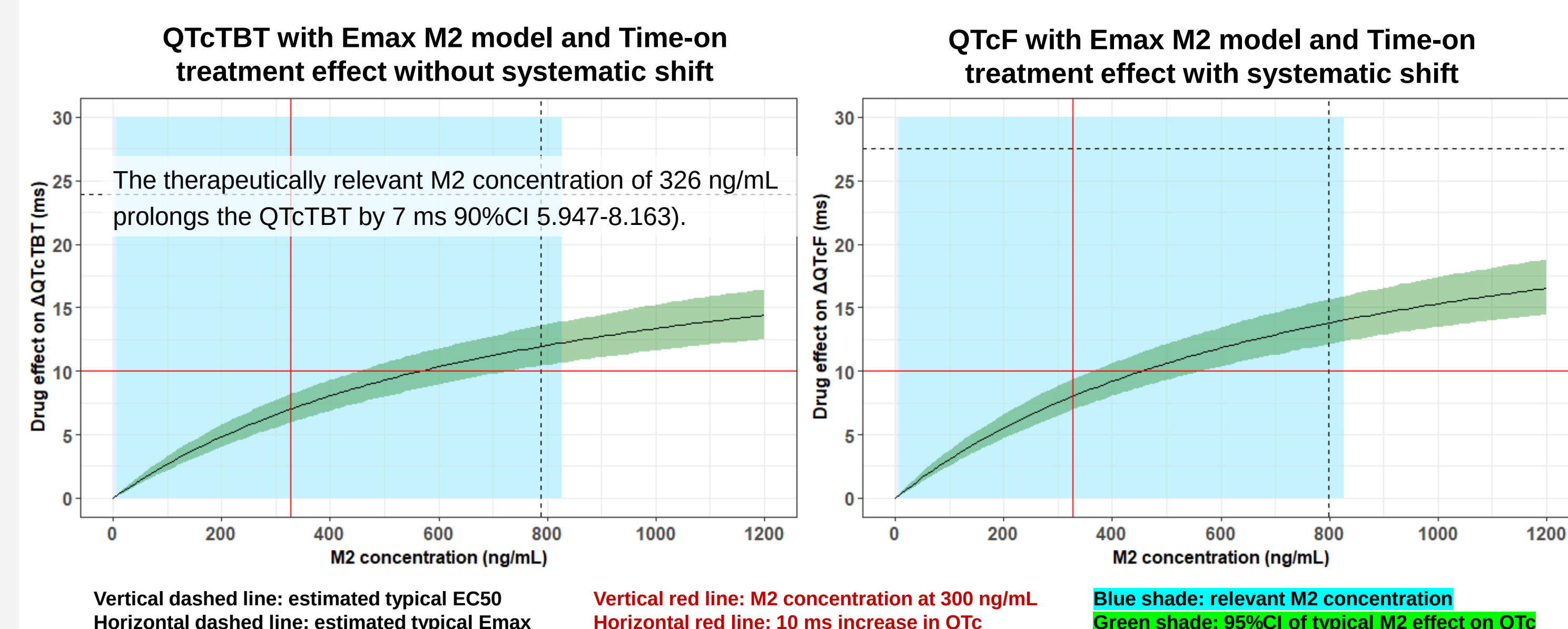
### Visual predictive checks of the QTcTBT with Emax M2 effect



### Model performance of the QTcTBT from 10 repetitions of 10-fold cross-validation

- The models incorporating time effects, assuming either no change in typical QT over time (normalized OFV 0, 95% CI -6 to 6), or estimating QT changes (OFV -7, 95% CI -12 to 1), performed comparably
- The model without time effects (OFV +283, 95%CI 280 to 286) performed worst.
- QT change was considered clinically minor at 24 weeks (-1.83 ms) by the QTcTBT model with systematic shift.

### Simulation of the M2 effect (Emax model) on ΔQTc from sampling importance resampling (SIRs)



## Conclusion

- QTcTBT was used instead of QTcF to address the non-drug related secular trend in QT, driven by TB disease improvement, and simplify quantification of BDQ's QT prolonging effect.
- The estimated QT prolongation of BDQ due to an M2 effect at therapeutically relevant concentrations was similar across the investigated QTc models, with the upper bound of the 90% CI being less than 10 ms.