



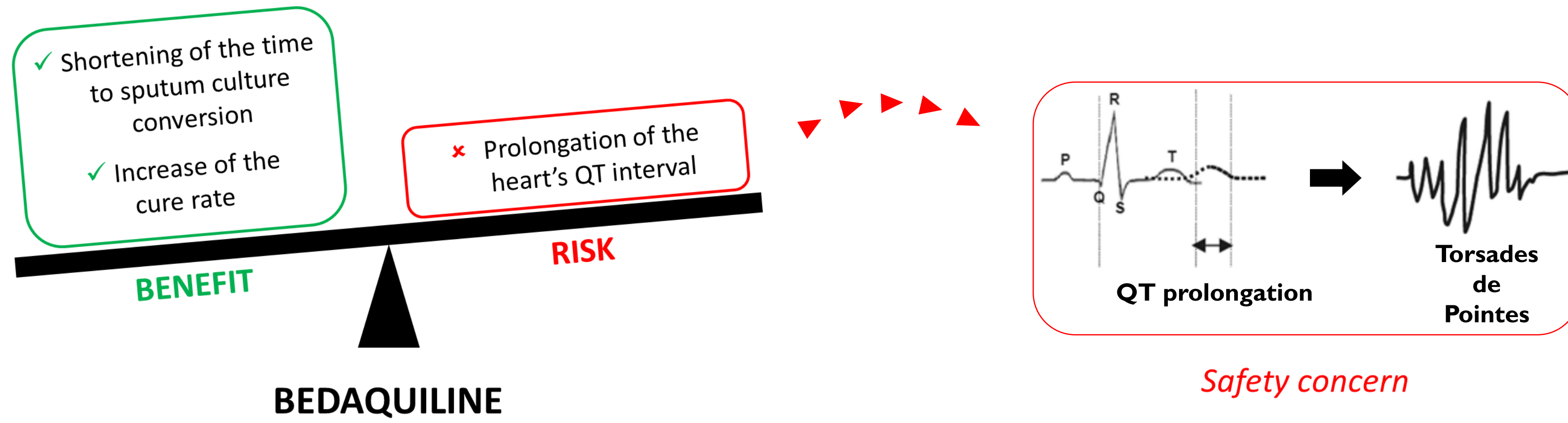
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# Bedaquiline appears to antagonize its main metabolite's QTcF interval prolonging effect

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## Introduction and purpose



Our **objective** was to investigate potential relationships between:

bedaquiline (BDQ) /  
main metabolite (M2)  
concentrations

&

QTcF interval prolongation  
(QT interval corrected with  
Fridericia's coefficient)

in multi-drug resistant (MDR) tuberculosis (TB) patients

## Data and method

**2 phase IIb studies:**  
C208 [1] & C209 [2]

- Enrolling *newly diagnosed* or *treatment-experienced* MDR-TB subjects
- 24 weeks** of BDQ on top of a **background regimen** of **5-7 anti-TB drugs**

**QT measurements:**

- Single **ECGs** performed **weekly**
- Triplicate ECGs** at pre-dose & 5h post-dose at week 2, 8, 12 (only C209) and 24

A **sequential approach** was used,  
building on a previously established PK-model (with low shrinkage)  
for BDQ and M2 for these trials [3]

- The *individual model-predicted BDQ and M2 concentrations* at the time of QT observations were evaluated as **predictors** (covariates) of the model for QTcF interval

## Results

The relationship between BDQ/M2 concentrations and QTcF data was best described by a **competitive antagonist model**

$$QTcF = QTcF_{w/o \text{ TB treatment}} + \underbrace{Study_{shift}}_{\text{Background TB treatment effect}} + \underbrace{\frac{E_{max,M2} * Conc_{M2}}{1 + \frac{Conc_{BDQ}}{EC_{50,BDQ}} + \frac{Conc_{M2}}{EC_{50,M2}}}}_{\text{Exposure effect}}$$

| Parameter [unit]      | QTcF <sub>w/o TB treatment</sub> [ms] | C208 <sub>shift</sub> [ms] | C209 <sub>shift</sub> [ms] | E <sub>max,M2</sub> [ms] | EC <sub>50,M2</sub> [ng/mL] | EC <sub>50,BDQ</sub> [ng/mL] | prop RUV [%] |
|-----------------------|---------------------------------------|----------------------------|----------------------------|--------------------------|-----------------------------|------------------------------|--------------|
| Typical value (RSE %) | 399 (0.3)                             | 0.84 (85.1)                | 4.19 (36.8)                | 12.9 (5.4)               | 14 (5.5)                    | 229 (7.9)                    | 2.8 (1.4)    |
| IIV CV % (RSE%)       | 4.1 (3.5)                             | -                          | -                          | 86 (6.3)                 | -                           | -                            | 28 (5.1)     |

Table 1. Parameter estimates and uncertainties.

The coefficient of variation (CV) is reported as the square root of (exp(variance) - 1). The relative standard error (RSE) for inter-individual variability (IIV) is reported on the approximate standard deviation scale (standard error/variance estimate)/2. prop RUV: proportional residual unexplained variability.

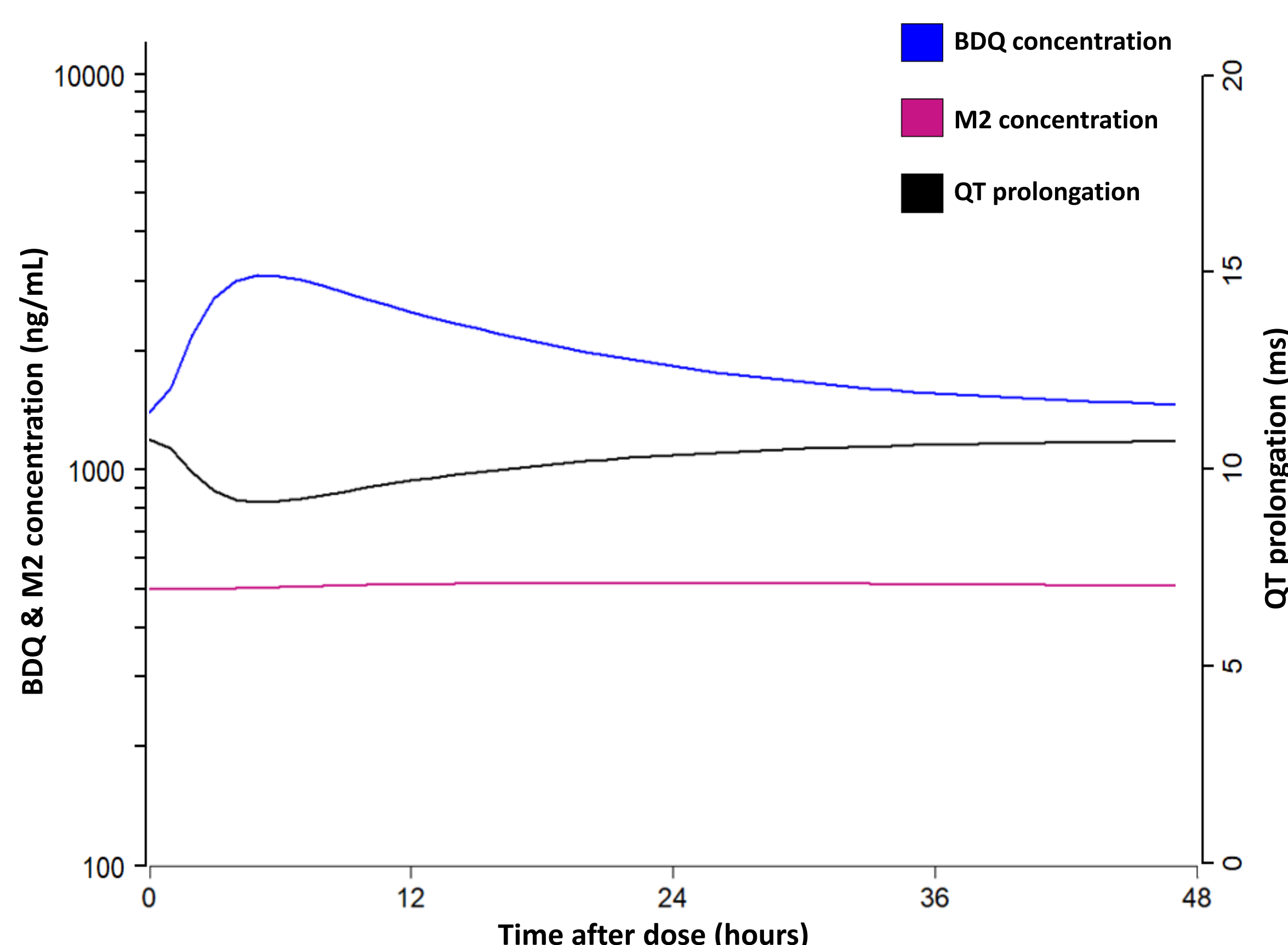


Figure 1. Typical QT and BDQ/M2 concentration profile in C208 study at predicted steady state during a standard dosing regimen.

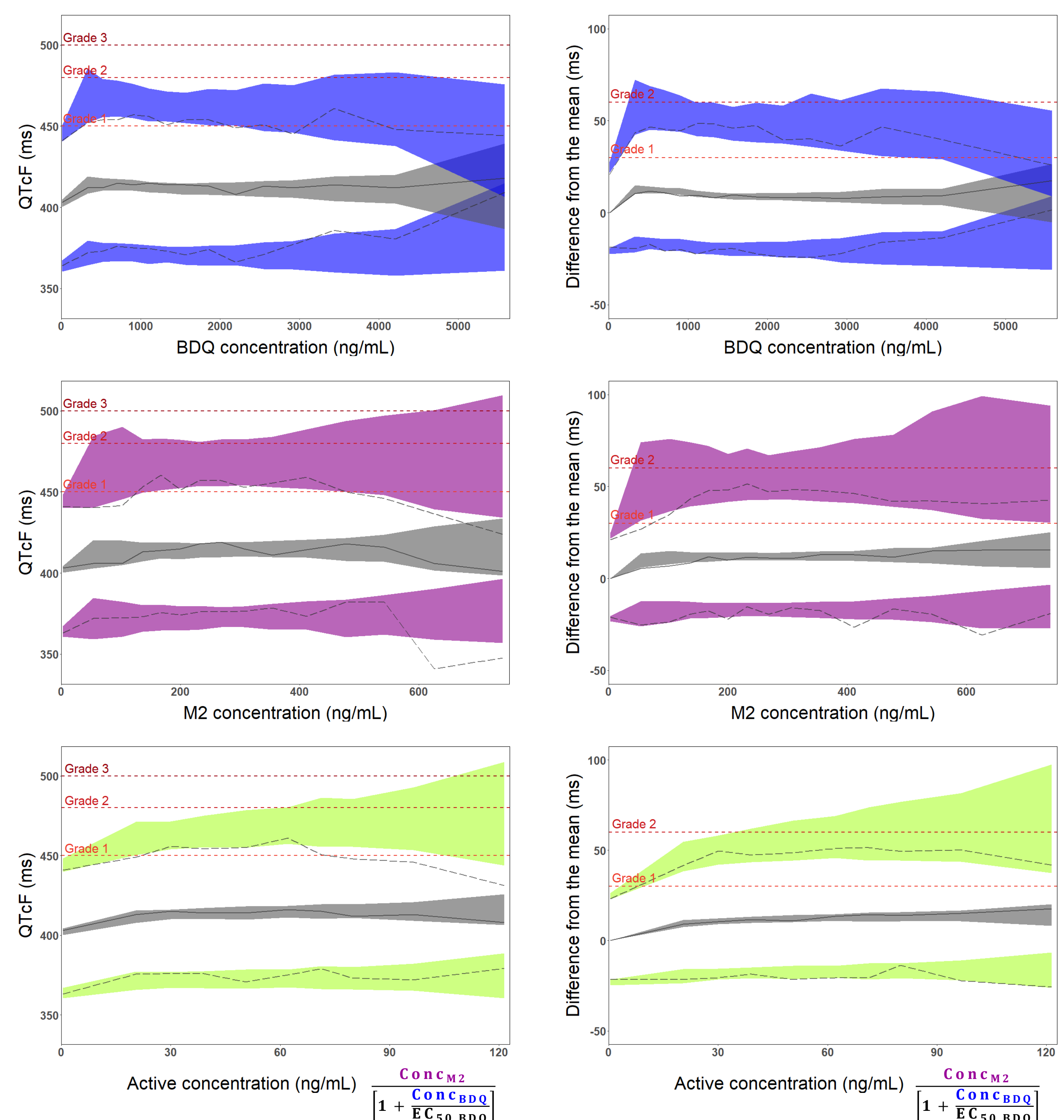


Figure 2. Visual predictive checks of the model

Median (solid line), 2.5th, and 97.5th percentiles (dashed lines) of the observed data are compared to the 95% CI (shaded areas) for the median, 2.5th, and 97.5th percentiles of the simulated data (1000 simulations). Dashed vertical lines represent the different safety grades of abnormal QTcorrected interval and change from baseline, based on the ICH E14 Guidance (CHMP/ICH/2/04; May 2005).

Analysis of *BDQ and M2 effect alone* (with an Emax model) displayed a 1255 and 160 points increase in the objective function value, respectively

Analysis of data from *each study separately* (C208 and C209) showed robustness of the results (pharmacologic mechanism and parameters estimates)

## Conclusion

The QTcF interval prolongation was explained by an **effect of the background regimen** and **M2 exposure**, with **bedaquiline** antagonizing the effect of M2

## References

- [1] Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasileva I, et al., 'Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline'. NEJM. 2014
- [2] Pym AS, Diacon AH, Tang S-J, Conradie F, Danilovits M, Chuchottaworn C, et al., 'Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis'. ERJ. 2016
- [3] Svensson EM, Dosne A-G, Karlsson MO, 'Population Pharmacokinetics of Bedaquiline and Metabolite M2 in Patients With Drug-Resistant Tuberculosis: The Effect of Time-Varying Weight and Albumin.' CPT PSP. 2016

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