

New dosing regimen for bedaquiline

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Bedaquiline dosing

- BDQ has terminal elimination half-life of ~6months
- Loading doses used to achieve therapeutic range quickly
- Registered dosing: 14 days 400 mg daily (loading), then 200 mg 3 times a week
- In the ZeNix trial of different doses & durations of linezolid for RR-TB BDQ dosed 200 mg daily for 8 weeks (loading), then 100 mg daily
- Both dosing strategies are recommended by WHO

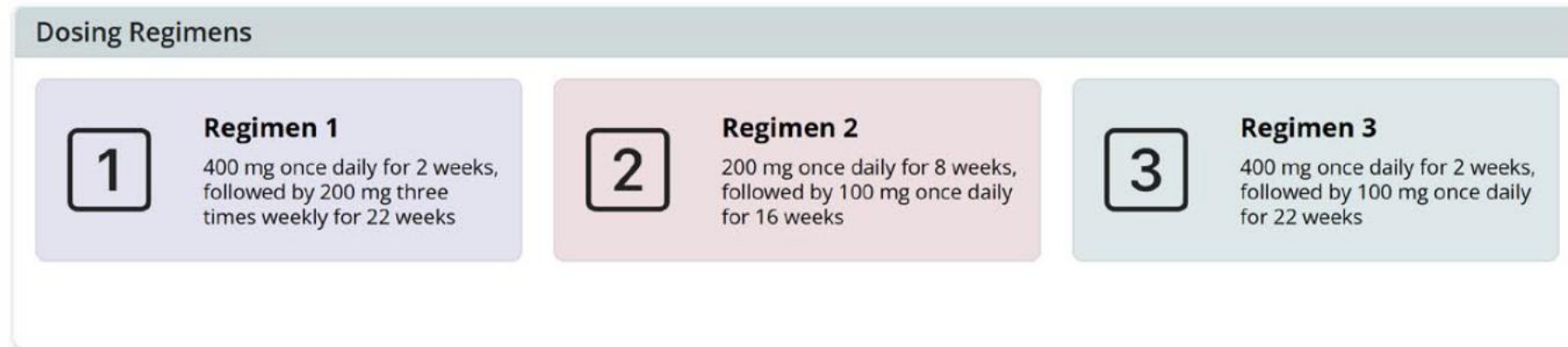
Participants with concentrations below 5th percentile

Drug	Month 1	Month 2	Month 4	Month 6
BDQ	11%	21%	26%	35%
CFZ	10%	9%	7.5%	14%

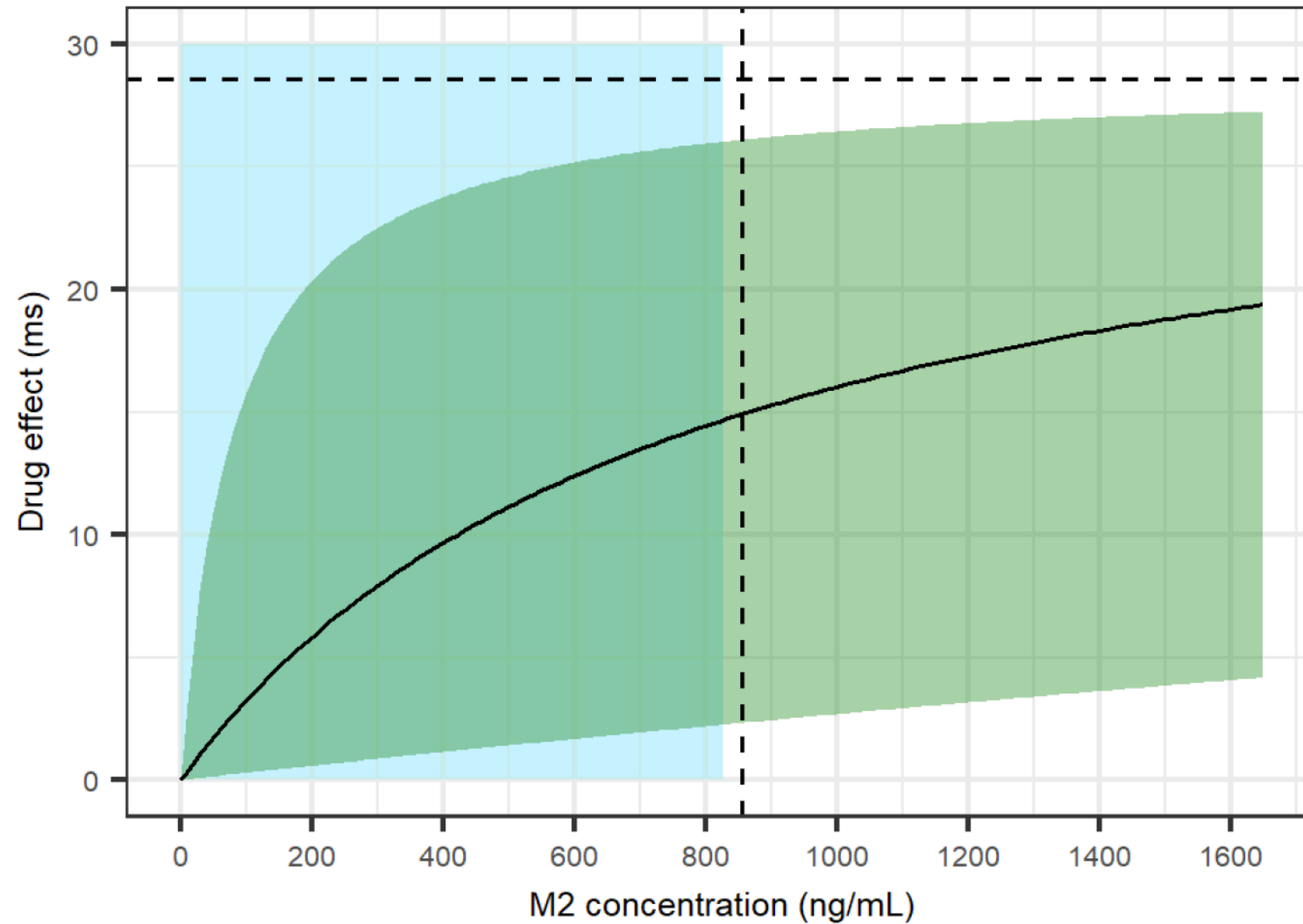
Likely that 3 times a week dosing of BDQ more difficult to adhere to than CFZ daily dosing

Population pharmacokinetic model of BDQ dosing strategies

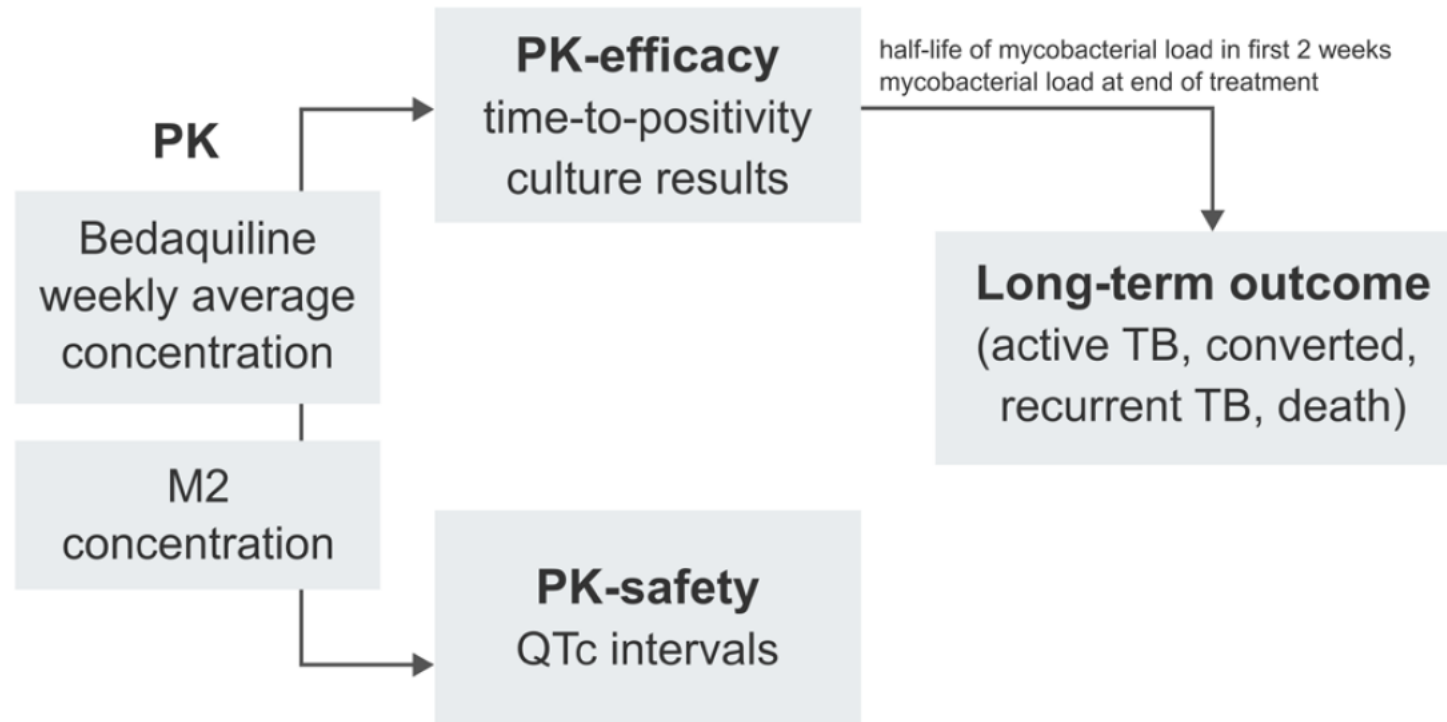
Simulations for efficacy & safety (QTc) for 3 strategies:



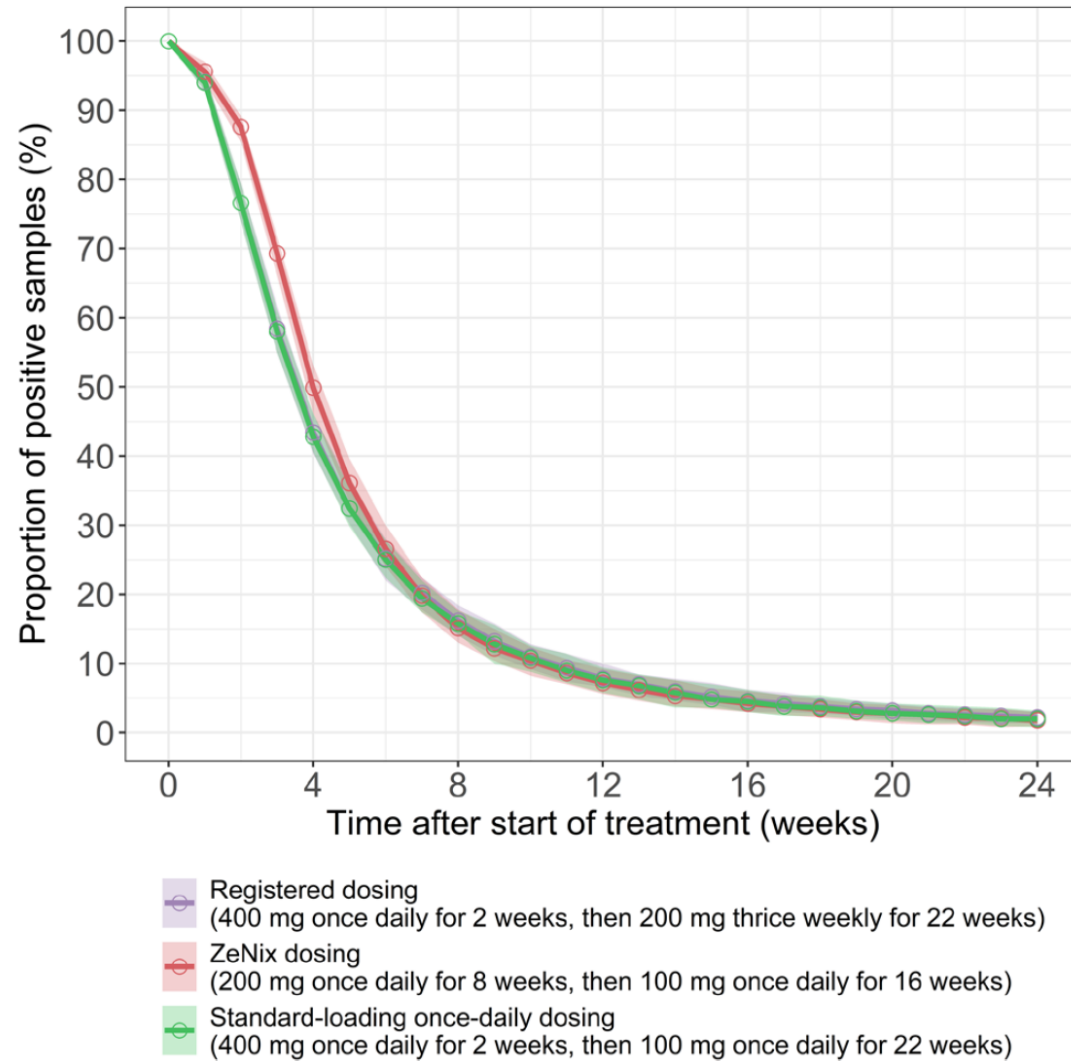
Bedaquiline M2 metabolite causes QT prolongation



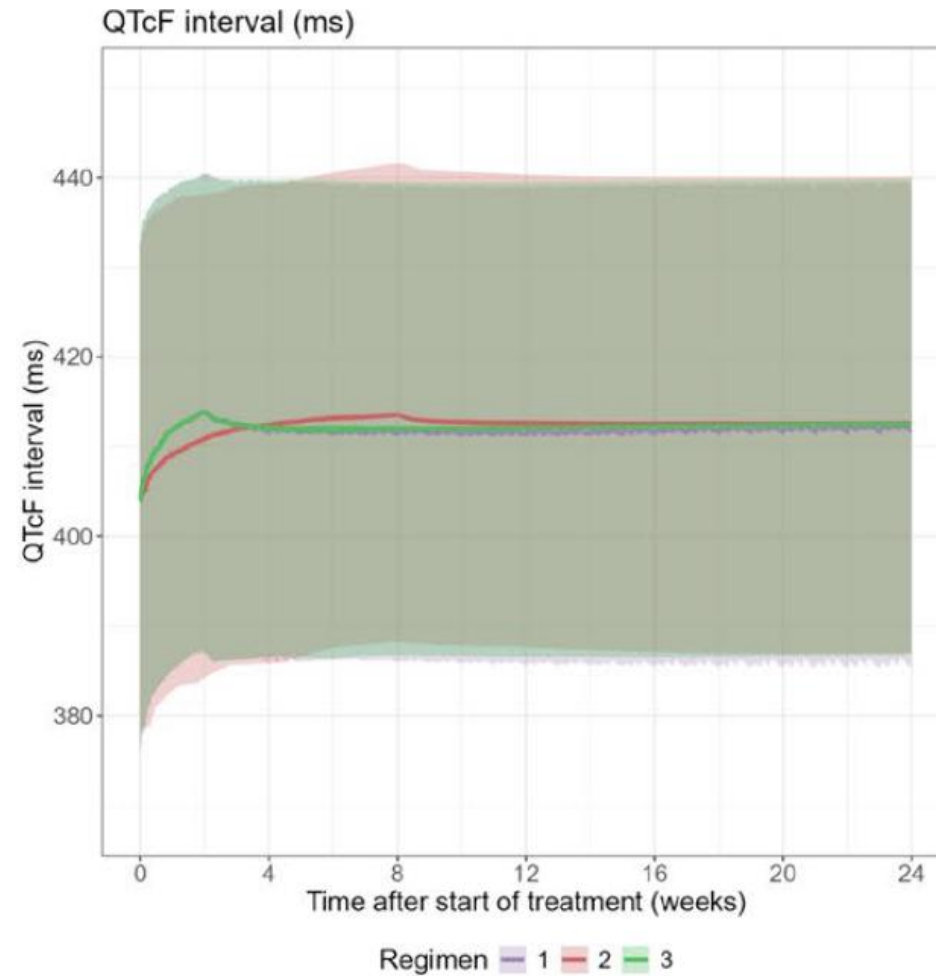
Modelling dosing strategies for efficacy & toxicity



Simulated sputum culture conversion of the 3 regimens



QT effects of the 3 regimens



1

Regimen 1

400 mg once daily for 2 weeks, followed by 200 mg three times weekly for 22 weeks

2

Regimen 2

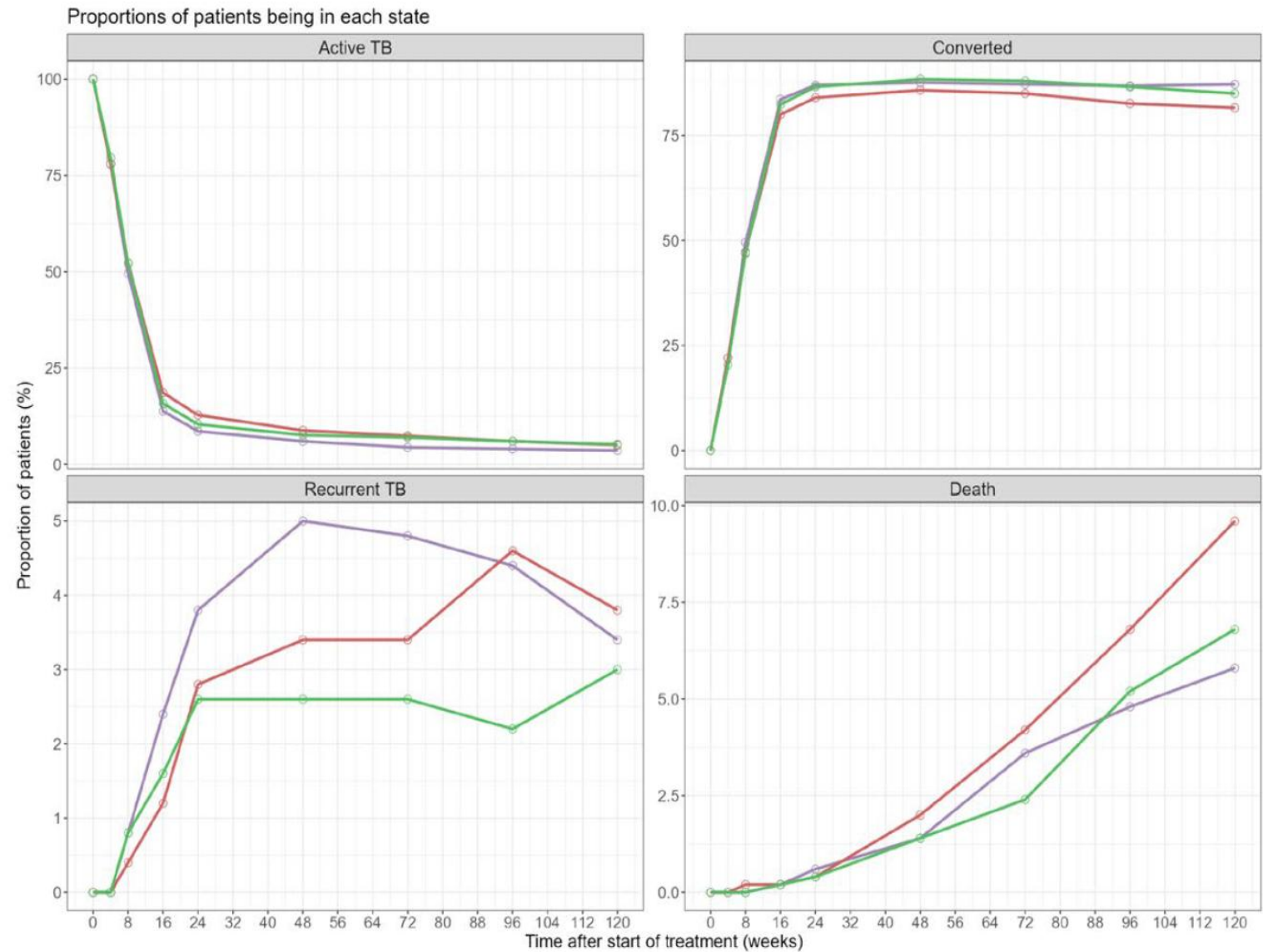
200 mg once daily for 8 weeks, followed by 100 mg once daily for 16 weeks

3

Regimen 3

400 mg once daily for 2 weeks, followed by 100 mg once daily for 22 weeks

Long-term outcomes



1

Regimen 1

400 mg once daily for 2 weeks, followed by 200 mg three times weekly for 22 weeks

2

Regimen 2

200 mg once daily for 8 weeks, followed by 100 mg once daily for 16 weeks

3

Regimen 3

400 mg once daily for 2 weeks, followed by 100 mg once daily for 22 weeks

Conclusions

- Daily BDQ dosing desirable with other RR-TB drugs dosed daily
- 14 day loading dose followed by daily dosing predicted to have more rapid sputum culture conversion & slightly better efficacy than the slow 2 month loading
- QT effects similar with the 3 dosing regimens