



# Confirming model-predicted pharmacokinetic interactions between bedaquiline and lopinavir/ritonavir or nevirapine in patients with HIV and drug resistant tuberculosis

Margreke JE Brill<sup>1</sup>, Elin M Svensson<sup>1</sup>, Mishal Pandie<sup>2</sup>, Gary Maartens<sup>2</sup>, Mats O Karlsson<sup>1</sup>

<sup>1</sup>Pharmaceutical Biosciences, Uppsala University, Sweden; <sup>2</sup>Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, South Africa

## Objective

- Lopinavir/ritonavir is a cytochrome P450 3A4 (CYP3A4) inhibitors, whereas nevirapine induces CYP3A4.
- Aim:** to quantify lopinavir/ritonavir and nevirapine drug-drug interaction effects on anti-tuberculosis drug bedaquiline and its metabolite M2 in patients co-infected with HIV and multidrug resistant tuberculosis (MDR-TB) using population pharmacokinetic (PK) analysis.
- The results were compared to model-based predictions from single-dose studies in subjects without tuberculosis [1].

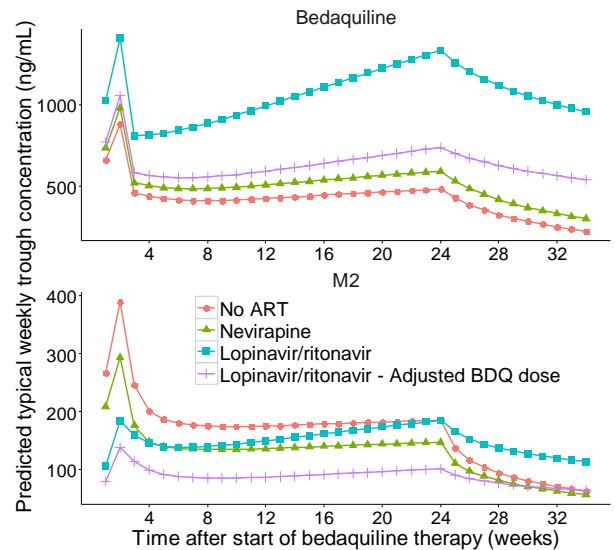
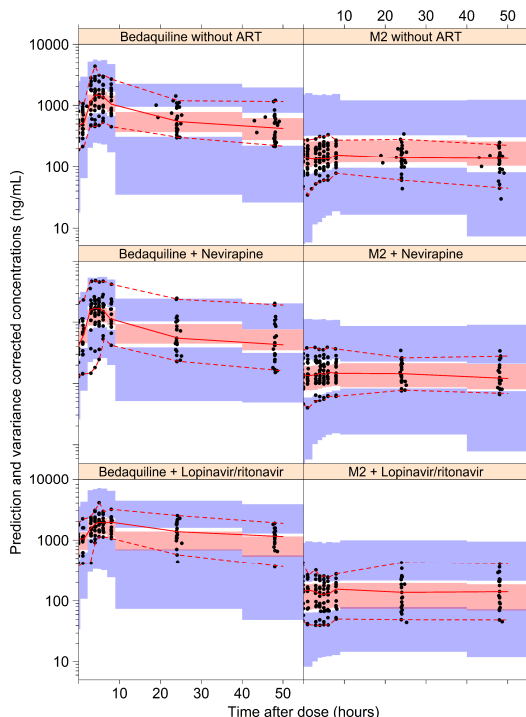
## Methods

- An observational PK study was performed in 3 groups of MDR-TB patients during the bedaquiline maintenance dosing period: HIV-seronegative patients without antiretroviral treatment (ART) and HIV-infected patients using ART regimens containing either lopinavir/ritonavir or nevirapine [2].
- Bedaquiline and M2 samples were collected over 48 hours after a 200 mg dose [2] somewhere between week 3 and 24 of bedaquiline treatment.
- A previously developed population PK model for patients was used as prior information to inform parameter estimation using the NWPRI functionality in NONMEM 7.3 [1,3].
- Three models were tested: i) A model with fixed priors and no estimation ii) a 'Full-Prior' model with priors and parameter estimation, iii) a 'Reduced-Prior' model in which the drug-drug interaction priors were removed.
- The uncertainty of the parameters estimates were calculated using SIR [4].

## Results

- Both the Full-Prior and Reduced-Prior model were able to describe bedaquiline and M2 concentrations well for all three patient groups, Figure 1 (On this poster, graphical results are shown for the Reduced-Prior).
- Drug interaction estimates were close to their prior values, Table 1.
- Lopinavir/ritonavir co-administration substantially reduced bedaquiline clearance. Simulation of an adjusted bedaquiline dosing regimen showed a normalization of bedaquiline exposure in case of lopinavir/ritonavir co-administration, Figure 2.

**Figure 1** Prediction and variability corrected visual predictive checks of the Reduced-Prior model for bedaquiline (left panels) and M2 concentrations (right panels) for the control group receiving no anti-retroviral treatment (n=17), the nevirapine group (n=17) and the lopinavir/ritonavir group (n=14). The lines represents the median and the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles of the observed data. The shaded areas indicate the CI<sub>95%</sub> of the median and 2.5<sup>th</sup> and 97.5<sup>th</sup> percentile of the simulations.



**Figure 2** Predicted typical bedaquiline and M2 trough concentrations simulated using the Reduced-Prior model for a typical MDR-TB patient on standard bedaquiline dosing (two weeks 400 mg daily, thereafter 200 mg three times weekly until week 24) without interacting co-administration, with concomitant nevirapine, with concomitant lopinavir/ritonavir and for an adjusted bedaquiline dosing (two weeks 300 mg daily, thereafter 100 mg three times weekly until week 24) with lopinavir/ritonavir co-administration.

**Table 1** Parameter values for drug-drug interaction effects in the evaluated models including 95% confidence intervals

	Prior values [1]	Full-Prior model	Reduced-Prior model
	Value (CI <sub>95%</sub> )	Estimates (CI <sub>95%</sub> )	Estimates (CI <sub>95%</sub> )
Nevirapine drug interaction effect parameters			
<i>Fixed effects</i>			
Factor change BDQ CL	0.915 (0.81-1.02)	0.904 (0.80-1.00)	0.816 (0.67-0.99)**
Factor change M2 CL	1.05 (0.84-1.26)	1.08 (0.92-1.26)	1.19 (0.92-1.56)**
Ritonavir-boosted lopinavir drug interaction effect parameters			
<i>Fixed effects</i>			
Factor change BDQ CL	0.347 (0.28-0.41)	0.332 (0.27-0.40)	0.250 (0.17-0.35)**
Factor change M2 CL	0.578 (0.48-0.68)	0.563 (0.48-0.65)	0.585 (0.44-0.69)**
<i>Random effects</i>			
BSV effect BDQ CL (CV %)	34.6 (19.7-44.7)	174.7 (130-199)	95.9 (84.5-125)**
Scaling BSV for M2 effect*	0.335 (-0.22-0.89)	0.491 (0.23-0.72)	0.484 (0.16-0.80)**

BDQ, bedaquiline; CL, clearance; CV, coefficient of variation; BSV, between-subject variability.  
\* The correlation between BSV in LPV/r interactions effects on BDQ and M2 CLs was 100%, BSV in the effect on M2 was scaled from BSV in the effect on BDQ with an estimated factor.  
\*\* These parameters were not supported by prior information.

## Conclusions

- Earlier model-based prediction of lopinavir/ritonavir and nevirapine interaction effects on bedaquiline and M2 clearances from single-dose studies (prior values) are confirmed for MDR-TB and HIV co-infected patients receiving long-term treatments (Table 1) [1].
- To normalize bedaquiline exposure in patients with concomitant lopinavir/ritonavir therapy, an adjusted bedaquiline dosing regimen is proposed (Figure 2).

## References

- Svensson *et al.* Impact of Lopinavir-Ritonavir or Nevirapine on Bedaquiline Exposures and Potential Implications for Patients with Tuberculosis-HIV Coinfection. *Antimicrob. Agents Chemother.* **58**, 6406–12 (2014).
- Pandie, M. *et al.* Drug–drug interactions between bedaquiline and the antiretrovirals lopinavir/ritonavir and nevirapine in HIV-infected patients with drug-resistant TB. *J. Antimicrob. Chemother.* **dkv447** (2016).
- Svensson, *et al.* Population pharmacokinetics of bedaquiline and metabolite M2 in drug-resistant tuberculosis patients – the effect of time-varying weight and albumin. (Submitted).
- Dosne, A.-G. *et al.* Application of Sampling Importance Resampling to estimate parameter uncertainty distributions. *PAGE* (2013).

## Acknowledgements

MP acknowledges funding in the form of a FIDSSA-GSK Research Fellowship and a Discovery Foundation Academic Fellowship Award. GM was supported in part by the National Research Foundation of South Africa (grant specific unique reference numbers 85810 and 90729, respectively). ES and MK were supported by the Innovative Medicines Initiative Joint Undertaking (www.imi.europa.eu) (grant agreement 115337 to ES and MK) for the PreDiCT-TB consortium.

