Rifampicin and rifapentine significantly reduce concentrations of bedaquiline, a new anti-TB drug

Elin M. Svensson1*, Stephen Murray2, Mats O. Karlsson1 and Kelly E. Dooley3

1Department of Pharmaceutical Biosciences, Uppsala University, PO Box 591, 751 24 Uppsala, Sweden; 2Department of Clinical Research, Global Alliance for TB Drug Development, New York, NY, USA; 3Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

*Corresponding author. Tel: +46184714418 or +46708475571; Fax: +464714003; E-mail: elin.svensson@farmbio.uu.se

Received 9 September 2014; returned 27 October 2014; revised 12 November 2014; accepted 14 November 2014

Objectives: Bedaquiline is the first drug of a new class approved for the treatment of TB in decades. Bedaquiline is metabolized by cytochrome P450 (CYP) 3A4 to a less-active M2 metabolite. Its terminal half-life is extremely long (5–6 months), complicating evaluations of drug–drug interactions. Rifampicin and rifapentine, two anti-TB drugs now being optimized to shorten TB treatment duration, are potent inducers of CYP3A4. This analysis aimed to predict the effect of repeated doses of rifampicin or rifapentine on the steady-state pharmacokinetics of bedaquiline and its M2 metabolite from single-dose data using a model-based approach.

Methods: Pharmacokinetic data for bedaquiline and M2 were obtained from a Phase I study involving 32 individuals each receiving two doses of bedaquiline, alone or together with multiple-dose rifampicin or rifapentine. Sampling was performed over 14 days following each bedaquiline dose. Pharmacokinetic analyses were performed using non-linear mixed-effects modelling. Models were used to simulate potential dose adjustments.

Results: Rifamycin co-administration increased bedaquiline clearance substantially: 4.78-fold (relative standard error (RSE) 9.10%) with rifampicin and 3.96-fold (RSE 5.00%) with rifapentine. Induction of M2 clearance was equally strong. Average steady-state concentrations of bedaquiline and M2 are predicted to decrease by 79% and 75% when given with rifampicin or rifapentine, respectively. Simulations indicated that increasing the bedaquiline dosage to mitigate the interaction would yield elevated M2 concentrations during the first treatment weeks.

Conclusions: Rifamycin antibiotics reduce bedaquiline concentrations substantially. In line with current treatment guidelines for drug-susceptible TB, concomitant use is not recommended, even with dose adjustment.

Keywords: drug–drug interactions, population pharmacokinetics, tuberculosis

Introduction

In 2012 there were an estimated 8.6 million new cases of TB and 1.3 million TB-related deaths, demonstrating that TB remains a global health threat.1 The alarming increase of MDR-TB, i.e. TB resistant to isoniazid and rifampicin, has sparked renewed efforts within the area of anti-TB drug development. In 2013 two novel drugs (bedaquiline and delamanid) received conditional approval by the European Medicines Agency for the treatment of MDR-TB. For drug-susceptible TB, the current first-line treatment is highly effective,2 but requires four drugs and a treatment duration of at least 6 months, posing challenges for patients and TB control programmes.3,4 Early treatment discontinuation increases the risk of relapse, transmission in the community and perhaps resistance.5 The need for shorter, easier to follow treatment regimens for both drug-susceptible and drug-resistant TB is urgent.

Bedaquiline is one of the recently introduced drugs for treatment of MDR-TB; it is also under clinical evaluation for the treatment of drug-susceptible TB, but not within regimens containing rifamycins.6 Bedaquiline is a diarylquinoline with a novel mechanism of action: it disrupts the energy metabolism of mycobacteria by inhibiting mycobacterial ATP synthase.7,8 Phase II trials demonstrated that the addition of bedaquiline for 6 months to a multi-drug background regimen for MDR-TB significantly improved short-term outcomes (sputum culture conversion to negative after 2 months of treatment)9 and increased the proportion of negative culture results at both 24 weeks (the end of bedaquiline treatment)10 and after 96 weeks of follow-up.11 Cure rates at
week 120 were 58% in the bedaquiline group compared with 32% in the placebo group.11 Bedaquiline causes moderate QT prolongation; the clinical significance of this effect on QT interval is unclear.10 In the Phase II randomized controlled trial, there was an unexplained increase in late mortality (after completion of study drug) observed in the bedaquiline group compared with the placebo group.10,11 Bedaquiline is a cationic amphiphilic drug that is mainly metabolized by N-demethylation catalysed by the cytochrome P450 (CYP) 3A4 enzyme. The resulting metabolite, M2, is 3- to 6-fold less active in vitro in comparison with bedaquiline, and in vitro studies suggest that M2 may cause cytotoxicity and phospholipidosis at lower concentrations than the parent drug.10 In humans, however, M2 circulates at much lower concentrations than the parent drug, and the clinical exposure–response relationships for both efficacy and safety are poorly characterized for bedaquiline and M2. In the treatment of MDR-TB, bedaquiline is given at a dose of 400 mg once daily for 2 weeks followed by 200 mg three times weekly for 22 weeks; other dosing regimens are currently being investigated for drug-susceptible TB.

Rifampicin has been called the backbone of TB therapy and is the most important contributor to the high cure rates of current first-line treatment. Rifampicin administered at the recommended dose of 600 mg daily is a strong inducer of CYP3A4 and other metabolizing enzymes, this induction causes a wide range of clinically significant drug–drug interactions.12 Rifapentine belongs to the same class of rifamycin compounds, but it has a lower MIC against Mycobacterium tuberculosis and a longer half-life.13 Rifapentine administered once weekly is used for the treatment of TB, is currently being investigated for drug-susceptible TB.

A study was conducted to assess the effects of rifamycin administration on bedaquiline and M2 pharmacokinetics (PK), safety and tolerability, comparing rifapentine with rifampicin. A descriptive non-compartmental analysis evaluating secondary PK parameters of single-dose bedaquiline with and without the perpetrator drug has been performed.17,18 However, assessing drug–drug interactions for drugs with extremely long half-lives is challenging, and previous modelling work with bedaquiline showed that ratios of 14 day AUC (AUC0–14d) following single doses of bedaquiline with and without the perpetrator drug may substantially underestimate the predicted impact of the interaction during long-term co-administration.19–21 The objective of this analysis was to quantify the effect of repeated doses of rifampicin or rifapentine on the single-dose PK of bedaquiline and M2 using a model-based approach and to predict the impact of these rifamycins on bedaquiline and M2 during long-term co-administration.

**Patients and methods**

**Study design**

A Phase I, two-arm open-label trial (study number TMC207-CL002) with a two-period, single-sequence design was performed to assess the PK interaction between bedaquiline and rifampicin (Arm 1) or rifapentine (Arm 2) (Figure 1). Healthy volunteers received a single 400 mg dose of bedaquiline on Day 1 followed by PK sampling (Days 1–14). On Day 20, Arm 1 participants started 600 mg rifampicin daily and Arm 2 participants started rifapentine 600 mg daily. On Day 29, a second 400 mg dose of bedaquiline was given to all study participants, again followed by 14 days of PK sampling (Days 29–43). Rifampicin dosing continued throughout the PK sampling period. Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 6, 8, 12 and 24 h and thereafter every 24th hour until 336 h after each bedaquiline dose and additionally just before the start of the rifampicin administration on Day 20. All clinical research was conducted in accordance with good clinical practice and with local ethics legislation; written informed consent was given by all participants.

**Quantification of BDQ and M2**

Blood samples were collected in tubes containing sodium heparin. The plasma was separated by centrifugation at 1500 g for 7 min within 30 min of collection and stored at −20°C until analysis. The concentrations of bedaquiline and M2 were determined in the plasma samples after protein precipitation with a validated HPLC methodology with tandem MS detection. Internal standards were used, linearity was demonstrated between 1 and 2000 ng/mL for both compounds and 10-fold dilution for analysis of samples up to 16000 ng/mL was possible. The lower limit of quantification was 1 ng/mL for both compounds. The bias and precision were well within the acceptable limits of ±15% and coefficient of variation 15%.

**Model development**

The population PK of bedaquiline and M2 was described with non-linear mixed-effects modelling estimating both the structural components (absorption, distribution, elimination and the effects of covariates on these parameters) and the stochastic components that capture random variability. Between-subject variability (BSV) and between-occasion variability (BOV) were assumed to be log-normally distributed, and the two bedaquiline doses were regarded as separate occasions. The disposition parameters were estimated relative to the bioavailability since only data collected after oral administration of bedaquiline were available. The fraction of bedaquiline metabolized to M2 was assumed to be constant between the two doses, and parameters for M2 were estimated as relative to this fraction. Allometric scaling was applied to CL and V using body weight and fixed coefficients of 0.75 and 1, respectively.20 Bedaquiline and M2 data in molar units (transformed with molecular weights of 555.50 g/mol for bedaquiline and 541.47 g/mol for M2) were fitted simultaneously. The effects of concomitant rifamycin administration were parameterized as instantaneous changes in CL of bedaquiline and M2. Different timepoints for the onset of the effect 1–8 days after the start of rifamycin administration were evaluated. A previously developed model for bedaquiline and M2 was used as the starting point, and historical data from a similarly designed drug–drug interaction study with bedaquiline and efavirenz...
Table 1. Summary of demographic data for all included individuals and per arm

|                  | All, N=32   | Rifampicin, N=13 | Rifapentine, N=16 |
|------------------|-------------|-----------------|-------------------|
| Age (years), median (range) | 35.5 (19–55) | 38 (21–53) | 34 (19–55) |
| Weight (kg), median (range)   | 81.8 (57.3–122) | 80.5 (59.8–109) | 83.3 (57.3–122) |
| Female, n (%)                | 4 (12.5) | 2 (15.4) | 2 (12.5) |
| Race, n (%)                  | white 28 (87.5) | 12 (92.3) | 15 (93.8) |
|                             | black or African American 2 (6.2) | 0 (0) | 1 (6.2) |
|                             | American Indian or Alaska native 1 (3.1) | 0 (0) | 0 (0) |
|                             | Asian 1 (3.1) | 1 (7.7) | 0 (0) |

in a comparable population were fitted simultaneously with the new data to increase the precision of parameter estimates. The error model used was additive on a logarithmic scale (rendering it proportional on a normal scale) with separate estimation of the magnitude of the error for the two studies.

The analysis was conducted with the first-order conditional estimation method including eta–epsilon interaction in the software NONMEM 7.2. Perl-speaks-NONMEM (version 3.7.5) functionalities and Xpose (version 4) aided the development work and the graphical evaluation. Pirana linked between the above-mentioned software and the computational cluster and was used for documentation of the analysis process. Model selection was based on goodness-of-fit statistics such as the objective function value (minus twice the log-likelihood) plus graphical evaluation using visual predictive checks (VPCs, based on 1000 simulations) and was guided by scientific plausibility. Parameter precisions of the final model were determined with a non-parametric bootstrap (n=1000).

Impact of interaction effect

The impact of rifamycins on bedaquiline PK during continuous co-administration was quantified by comparing predicted average steady-state concentrations ($C_{\text{ss,avg}}$, Equation 1) calculated from apparent clearance ($CL/F$, where $F$ is bioavailability), the dose and the dosing interval ($t$). With the same bedaquiline dosing strategy in both cases, relative $C_{\text{ss,avg}}$ ($\text{Rel}_{\text{C}_{\text{ss,avg}}}$), comparing bedaquiline with rifamycin co-administration to bedaquiline administered alone, is described by Equation 2. As long as the fraction of bedaquiline metabolized to M2 is assumed to be constant, analogous equations can be used in calculations for M2.

$$C_{\text{ss,avg}} = \frac{F \cdot \text{dose}}{CL \cdot t}$$

(1)

$$\text{Rel}_{\text{C}_{\text{ss,avg}}} = \frac{C_{\text{ss,avg}}^{\text{RIForRPT}}}{C_{\text{ss,avg}}^{\text{RIForRPT}}} = \frac{CL/F}{CL/F_{\text{RIForRPT}}}$$

(2)

Non-compartmental analysis and posterior predictive check

PK drug–drug interactions are commonly quantified by the geometric mean of ratios (GMRs) of observed exposure (AUC) and $C_{\text{max}}$ of the victim drug with and without the perpetrator drug. Means of ratios have previously been reported for this study, for other similar studies with bedaquiline and antiretroviral drugs and in the product label. For comparison, the PK data were also evaluated with a non-compartmental analysis (NCA) approach and GMRs of AUC$_{0-14\text{d}}$ were calculated. An R package implementing traditional NCA procedures computing AUC and $C_{\text{max}}$ and allowing simultaneous analysis of observed data and datasets with the same design, but observations generated by stochastic simulations from the final model (n=1000), was utilized. Additionally, a posterior predictive check comparing the NCA results of the observed and simulated data served as a model diagnostic. The posterior predictive check can give confidence intervals of a given statistic (here AUC$_{0-14\text{d}}$) calculated on model-generated data to be compared with the same statistic calculated on the original data. Agreement between the two indicates that the model is valid for analysis of the given statistic.

Results

Study population and PK observations

The trial included 32 healthy volunteers, with 16 individuals in each rifamycin arm. The median age was 31 years, the median weight was 82 kg, 12.5% were female and 87.5% were of white race (Table 1). Bedaquiline alone and in combination with the rifamycins was generally well tolerated. There were three premature discontinuations, all in the rifampicin arm: two due to failure to comply with study procedures and one due to an adverse event with unlikely relationship to study treatment. In total, 1419 observations each of bedaquiline and M2 plasma concentrations were available. Other than the 32 pre-dose samples from the first occasion, no concentrations were below the lower limit of quantification for bedaquiline, but 19 M2 observations from the sampling 1 h post-dose during the first occasion were. The observations below the lower limit of quantification were excluded from the analysis. Trial data were fitted together with a historical bedaquiline PK dataset including 1083 bedaquiline and 1055 M2 plasma concentration observations between 0 and 336 h after a 400 mg bedaquiline dose administered alone or together with efavirenz.

Model development

The structure of the previously developed population PK model, including absorption through a dynamic transit compartment model, three disposition compartments for bedaquiline and two for M2, fitted the current study data well. Rifampicin and rifapentine increased bedaquiline CL to 478% [relative standard error (RSE) 9.1%] and 389% (RSE 5.0%) of the CL of bedaquiline when administered alone, respectively. For both rifamycins, the induction effect on M2 CL was similar to that on bedaquiline CL, and estimation of a separate fixed effect parameter for the change...
in M2 CL did not improve the fit of the model significantly, while a separate random effect did. The coefficient of variation (CV) for the induction effects’ BSVs were between 18% and 33% (Table 2). The correlation between individual effects on bedaquiline and M2 were positive, i.e. a strong effect on bedaquiline was associated with a strong effect on M2, and the correlation between individual induction effects and individual CL values was negative (i.e. for individuals with already high CL the induction effect was less pronounced). Parameterizing the CLs to change after 3 days of rifamycin administration provided the best fit based on objective function value, and the magnitude of the estimated interaction effect remained similar over the evaluated range of timepoints for onset. The residual errors for bedaquiline and M2 observations from the same timepoint were correlated by 55%. A weighting factor was applied to allow larger residual errors during the absorption period (all observations between 0 and 6 h post-dose) and was estimated at 2.2 (RSE 6.9%). The model parameters were estimated with good precision and are listed in Table 2. The model described the data well, as shown by the VPC in Figure 2, although the variability in bedaquiline and M2 concentrations during rifamycin induction was somewhat overpredicted.

Impact of interaction effect
The interaction with rifampicin during continuous co-administration is predicted to decrease the CL_{ss,avg} of bedaquiline and M2 to 21% (RSE 9.10%) of the levels expected when bedaquiline is administered alone. The interaction with rifapentine is only slightly less strong and would decrease the CL_{ss,avg} of bedaquiline and M2 to 25% (RSE 5.0%). Typical bedaquiline and M2 concentration–time profiles (for a 70 kg healthy volunteer) during the first 4 weeks of bedaquiline administration alone or with rifamycin co-administration were simulated (Figure 3). Results of simulations of a dose adjustment to mitigate the interaction effect are shown in Figure 4 and are further explained in the Discussion section.

Non-compartmental analysis and posterior predictive check
The GMRs calculated from NCA of observed data that compared the AUC_{0–14d} of bedaquiline and M2 with and without rifamycins were 4.1% for bedaquiline with rifampicin, 42.8% for bedaquiline with rifapentine, 78.9% for M2 with rifampicin and 85.5% for M2 with rifapentine. Using NCA to analyse datasets with the same design as the original study, but simulated by the final model, the median (2.5 and 97.5 percentiles) GMRs of AUC_{0–14d} in the 100 datasets were, for bedaquiline, 40.6% (34.5%–47.7%) with rifampicin and 47.8% (41.9%–54.3%) for rifapentine, and those for M2 were 76.7% (64.7%–90.7%) and 89.0% (76.4%–104.6%), respectively. These GMRs agreed well with the GMRs from the observed data; the 95% prediction intervals included the observed value in all cases, confirming the model’s good performance.

Discussion
Using a model-based approach, we estimate that both rifampicin and rifapentine at standard doses substantially increase bedaquiline and M2 CL 5-fold and 4-fold, respectively. The most likely mechanism is via up-regulation of CYP3A4, the enzyme responsible for metabolism of bedaquiline and M2. The increased CL with rifamycins reduces bedaquiline CL_{ss,avg} levels to 21%–25% of the average concentrations expected when bedaquiline is administered alone. While the exposure–response relationship of bedaquiline is not yet well defined, it is still likely that such a marked decrease in drug exposure is clinically important and could result in lower efficacy.

The M2 metabolite is not thought to contribute significantly to the activity of bedaquiline treatment, but it may contribute to drug-related toxicities. Concentrations of the M2 metabolite are predicted to be decreased in similar fashion to the parent drug with prolonged dosing in the presence of rifamycins; however, the increased bedaquiline CL will result in higher peak concentrations of M2 during the first week of treatment (Figure 3). Dose adjustments when bedaquiline is co-administered with rifampicin or rifapentine to achieve average bedaquiline exposures similar to average exposures when bedaquiline is administered alone are theoretically possible, but peak and trough concentrations would inevitably be more extreme unless the dosing interval is shortened. An example of such a regimen for bedaquiline co-administered with rifampicin is 1000 mg of bedaquiline daily during the first 2 weeks and thereafter 1000 mg three times weekly; typical profiles for this alternative dosing schema compared with the standard regimen (400 mg daily during the first 2 weeks and thereafter 200 mg three times weekly) with and without rifampicin are illustrated in Figure 4. Higher bedaquiline doses would necessarily mean increased M2 peak concentrations early in the treatment period, and the safety implications of this increase are unclear. Both bedaquiline and M2 inhibit the cardiac hERG/IKr potassium channels in vitro, and modest QT prolongation has been observed during clinical trials. Exposure–response data indicate that there may be an association between M2 exposures and observed QT prolongation, though exposures explain very little of the variability in QT prolongation; no concentration–QT relationship was evident for bedaquiline. Moreover, M2 is a cationic amphiphilic compound that induces phospholipidosis (intracellular accumulation of phospholipids and formation of lysosomal lamellar bodies) in vitro to a greater extent than bedaquiline. For the above-mentioned example of 1000 mg of bedaquiline with rifampicin, the typical C_{max} for M2 after the first and last doses during the 2 weeks of daily bedaquiline administration at the start of therapy would be increased by co-administration of rifampicin to 45.7% and 179% compared with 400 mg daily without rifampicin, respectively. However, the M2 concentrations remain well below the bedaquiline concentrations and the model seems to modestly overpredict M2 C_{max}, as shown by the VPC (Figure 2), which should be kept in mind when drawing inferences from the simulation results. The BSV in CL of bedaquiline and M2 with rifamycin induction and, consequently, in average steady-state concentrations are decreased because of the correlation between CL and the induction effect, which may be beneficial. However, the safety implications of increased M2 peak concentrations or more frequent bedaquiline administration are unknown. An adjusted bedaquiline dosage during rifamycin co-administration would also be more costly and cannot be recommended at this time. Assessment of the PK interaction between bedaquiline and rifabutin, another rifamycin generally claimed to be a less strong inducer, is currently ongoing and will indicate whether rifabutin is a viable alternative rifamycin that can be used in combination therapies for drug-susceptible TB that include bedaquiline.
Table 2. Final model parameter estimates with precision obtained from non-parametric bootstrap (n = 1000)

| Fixed effects | Value (RSE %) | Random effects | Value, % CV (RSE %) |
|---------------|--------------|----------------|---------------------|
| MTT (h)       | 0.97 (11.5)  | BOV F          | 18.5 (16.8)         |
| KA (h⁻¹)      | 0.12 (3.9)   | BSV F          | 12.1 (29.5)         |
| NN            | 8.41 (36.2)  | BOV MTT        | 64.7 (12)           |
| CL/F (L/h)    | 3.20 (6.5)   | BSV CL         | 28.2 (11.7)         |
| V/F (L)       | 16.2 (12.9)  | BSV CLM2       | 53.8° (20.9)        |
| Q1/F (L/h)    | 4.71 (5.6)   | BSV Rif BDQ    | -78.2° (17.2)       |
| VP1/F (L)     | 2801 (10.1)  | BSV Rif M2     | -66.4° (32.3)       |
| Q2/F (L/h)    | 3.10 (6.0)   | BSV Rif BDQ    | -69.2° (32.3)       |
| VP2/F (L)     | 137 (10.4)   | BSV Rif M2     | -34.6° (57.5)       |
| CLM2/Ffm (L/h)| 13.1 (6.6)   | BSV V          | 42.8 (14.6)         |
| VM2/Ffm (L)   | 882 (4.9)    | BSV Q1         | 21.1 (13.2)         |
| Q1M2/Ffm (L/h)| 105 (8.6)    | BSV VM2        | 36.4 (12.3)         |
| VP1M2/Ffm (L) | 3349 (3.8)   | BSV VP1M2      | 21.0 (22.4)         |
| Weighting of samples 0–6 h | 2.19 (6.9) | Prop err BDQ | 15.7 (4.4) |
| Factor change BDQ/M2 CL with RIF | 4.78 (9.1) | Prop err M2 | 55.4° (8.6) |
| Factor change BDQ/M2 CL with RPT | 3.96 (5.0) | Prop err BDQ | 15.7 (4.4) |

MTT, mean transit time; KA, absorption rate constant; NN, number of transit compartments; Q, intercompartmental clearance; VP, volume of distribution of peripheral compartments; fm, fraction metabolized from bedaquiline to M2; Prop err, proportional error; BDQ, bedaquiline; RIF, rifampicin; RPT, rifapentine.

Correlations presented in the block structure used in the NONMEM code, originally estimated as covariances.

Performing a posterior predictive check comparing NCA results from the traditional approach with NCA results obtained from simulated data, the model predicted 95% confidence intervals for the ratio of observed to predicted values of AUC0–14d. The model predicted 95% confidence intervals for the ratio of observed to predicted values of AUC0–14d were 8% (RSD 3.0%) and 78% (RSD 3.9%). The difference in the percentage of the total AUC that is observed when comparing bedaquiline and M2, which confirms the model's validity for evaluating the model developed on data from healthy volunteers and patients with TB is described as differences in bioavailability, clinical studies and PK properties in healthy volunteers and patients with TB, respectively. The model predictions indicate that the long-term half-life of bedaquiline and M2 is generally decreased, which would result in a larger fraction of unbound drug and hence higher CL and lower exposure to the terminal elimination phase. NCA GMRs based on partial AUCs will, thus, unavoidably contribute to the bias in the NCA GMRs. More importantly, the interaction effect of the rifamycins on bedaquiline involves induction of metabolic enzymes that primarily affect the elimination of bedaquiline and similar for M2. When rifampicine is given together with bedaquiline and M2, which confirms the model's validity for evaluating the model developed on data from healthy volunteers and patients with TB.
Rifampicin and rifapentine significantly reduce concentrations of bedaquiline

not necessarily fully representative of patients with TB. The relative
effect of co-administration of the rifamycins on bedaquiline and M2
metabolism are, nevertheless, expected to be similar between
healthy volunteers and patients. Conducting crossover studies
(the gold standard for evaluating drug–drug interactions) in
patients with TB would require giving bedaquiline alone and then
together with a rifamycin-containing regimen, thereby delaying
full multidrug treatment, which is not ethically acceptable.
Studies in healthy volunteers allow us to assess the direction and
magnitude of the interaction effect and are, thus, valuable for

Figure 2. VPC showing the 5th, 50th and 95th percentiles (lines) of the logarithm of observed bedaquiline (BDQ) and M2 concentrations (dots) and the
95% CIs (shaded areas) of the same percentiles from model-simulated data for bedaquiline administered alone, bedaquiline with rifampicin (RIF) and
bedaquiline with rifapentine (RPT).

Figure 3. PK profiles for bedaquiline (continuous lines) and M2 (broken lines) during the first 4 weeks of bedaquiline treatment alone (black), with
rifampicin (dark grey) or with rifapentine (light grey). Profiles are representative of a 70 kg healthy volunteer. The concentrations are depicted on a
logarithmic scale. BDQ, bedaquiline; RIF, rifampicin; RPT, rifapentine.
decisions regarding the composition of regimens to study further in TB patients, potential dose adjustments needed, and trial design. Other limitations of this work include the lack of varied rifamycin doses and measured rifamycin concentrations, which makes it impossible to investigate the effect of rifamycin levels on the magnitude of the interaction effect. No PK sampling was conducted between the start of rifamycin administration and the time of assumed full induction and it is therefore futile to characterize the time course of the induction process. The simplistic on–off effect implemented in the developed model is sufficient for estimation of the full induction effect of the administered dose, which was the aim of this work, but cannot be used directly to describe the effect of other rifamycin doses or a situation in which rifamycin co-administration is started during ongoing treatment with bedaquiline.

In this work we have characterized the interaction effects of rifamycins on the concentrations of bedaquiline and its main metabolite, M2, using population PK analysis. We provide the first predictions of the impact of continuous co-administration of rifampicin or rifapentine on bedaquiline exposure. The results showed that significant reductions in bedaquiline and M2 are expected if bedaquiline is given together with rifampicin or rifapentine. We investigated potential dose adjustments to mitigate the impact of the interaction, but the doses required to achieve the desired concentrations of bedaquiline would be costly and would result in high M2 peaks during the early phase of treatment, with unclear safety implications. In line with the bedaquiline product label and the current strategy for the composition of bedaquiline-containing regimens under investigation for the treatment of drug-susceptible TB, we do not recommend concomitant use of bedaquiline and rifampicin or rifapentine before the therapeutic window of bedaquiline has been fully established and the safety profile of M2 is better known.

**Acknowledgements**

The data and a non-compartmental analysis have previously been published as an abstract at the Nineteenth International AIDS Conference, Washington, DC, 2012 (MOAB0304).

The computations were partly performed on resources provided by the Swedish National Infrastructure for Computing (SNIC) at UPPMAX. Martin Agback at UPPMAX is acknowledged for assistance concerning technical aspects in making NONMEM run on the UPPMAX resources. PK data were kindly provided by the Global Alliance for TB Drug Development.

**Funding**

This modelling work was supported by: the Swedish Research Council (grant number 521-2011-3442 to E. M. S. and M. O. K.); the Innovative
Rifampicin and rifapentine significantly reduce concentrations of bedaquiline

Medicines Initiative Joint Undertaking (www.imi.europa.eu) (grant agreement 115537 to E. M. S. and M. O. K.) for the PreDiCT-TB consortium, resources of which are composed of a financial contribution from the European Union’s Seventh Framework Programme (FP7/2007–2013) and EFPIA companies’ in-kind contribution; and by the US National Institutes of Health (grant number K23AI080842 to K. E. D.).

Transparency declarations
S. M. is an employee of the Global Alliance for TB Drug Development. M. O. K. has received research grants from Janssen Pharmaceuticals. E. M. S. and K. E. D.: none to declare.

References
1 WHO. Global Tuberculosis Report 2013. http://apps.who.int/iris/bitstream/10665/91355/1/9789241564656_eng.pdf?ua=1.
2 Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council Tuberculosis Units, 1946–1986, with relevant subsequent publications. Int J Tuberc Lung Dis 1999; 3: 5231–79.
3 Munro SA, Lewin SA, Smith HJ et al. Patient adherence to tuberculosis treatment: a systematic review of qualitative research. PLoS Med 2007; 4: e238.
4 Pablos-Mendez A, Knirsch CA, Barr RG et al. Nonadherence in tuberculosis treatment: predictors and consequences in New York City. Am J Med 1997; 102: 164–70.
5 Volmink J, Garner P. Directly observed therapy for treating tuberculosis. Cochrane Database Syst Rev 2007; issue 4: CD003343.
6 TB Alliance. Our Pipeline. http://www.tballiance.org/pipeline/pipeline.php.
7 Andres K, Verhasellt P, Guillemont J et al. A diarylquinoline drug active on the ATP synthase of Mycobacterium tuberculosis. Science 2005; 307: 223–7.
8 Kaul A, Dendouga N, Vergauwen K et al. Diarylquinolines target subunit c of mycobacterial ATP synthase. Nat Chem Biol 2007; 3: 323–4.
9 Diacon AH, Donald PR, Pym A et al. Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence of drug resistance. Antimicrob Agents Chemother 2012; 56: 3271–6.
10 European Medicines Agency. CHMP Assessment Report: SIRTURO. http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002614/WC500158728.pdf.
11 Diacon AH, Pym A, Grobusch MP et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med 2014; 371: 723–32.
12 Niemi M, Bockman JT, Fromm MF et al. Pharmacokinetic interactions with rifampicin: clinical relevance. Clin Pharmacokinet 2003; 42: 819–50.
13 Burman DWJ, Gallicano K, Peloquin C. Comparative pharmacokinetics and pharmacodynamics of the rifamycin antibacterials. Clin Pharmacokinet 2001; 40: 327–41.
14 Williamson B, Dooley KE, Zhang Y et al. Induction of influx and efflux transporters and cytochrome P450 3A4 in primary human hepatocytes by rifampicin, rifabutin, and rifapentine. Antimicrob Agents Chemother 2013; 57: 6366–9.
15 Li AP, Reith MK, Rasmussen A et al. Primary human hepatocytes as a tool for the evaluation of structure-activity relationship in cytochrome P450 induction potential of xenobiotics: evaluation of rifampin, rifabutin and rifapentine. Chem Biol Interact 1997; 107: 17–30.
16 Dooley KE, Bliven-Sizemore EE, Weiner M et al. Safety and pharmacokinetics of escalating daily doses of the antituberculosis drug rifapentine in healthy volunteers. Clin Pharmacal Ther 2012; 91: 881–8.
17 Everitt D, Winter H, Egizi E. Pharmacokinetic interaction between the investigational anti-tuberculosis agent TMC207 and rifampicin or rifapentin. In: Abstracts of the Nineteenth International AIDS Conference, Washington, DC, 2012. Abstract MOAB0304. http://www.iiasociety.org/Abstracts/A2007/46786.aspx.
18 Winter H, Egizi E, Murray S et al. Evaluation of the pharmacokinetic interaction between repeated doses of rifapentine or rifampicin and a single dose of bedaquiline in healthy adult subjects. Antimicrob Agents Chemother, in press.
19 Svensson EM, Aweke F, Park J-G et al. Model-based estimates of the effects of efavirenz on bedaquiline pharmacokinetics and suggested dose adjustments for patients coinfected with HIV and tuberculosis. Antimicrob Agents Chemother 2013; 57: 2780–7.
20 Anderson BJ, Holford NHG. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol 2008; 48: 303–32.
21 Beal S, Sheiner LB, Boeckmann A et al. NONMEM User’s Guides (1989–2009). Ellicott City, MD, USA: Icon Development Solutions, 2009.
22 Lindbom L, Pihlgren P, Jonsson EN et al. PsN-Toolkit—a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Programs Biomed 2005; 79: 241–57.
23 Jonsson EN, Karlsson MO. Xpose—an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. Comput Methods Programs Biomed 2005; 101: 72–9.
24 Keizer RJ, van Benten M, Beijnen JH et al. Piraha and PCCluster: a modeling environment and cluster infrastructure for NONMEM. Comput Methods Programs Biomed 2011; 101: 72–9.
25 Dooley KE, Park J-G, Swindells S et al. Safety, tolerability, and pharmacokinetic interactions of the antituberculous agent TMC207 (bedaquiline) with efavirenz in healthy volunteers: AIDS Clinical Trials Group Study A5267. J Acquire Immune Defic Syndr 1999; 25: 455–62.
26 van Heeswijk RPG, Dannerman B, Hoetelmans RMW. Bedaquiline: a review of human pharmacokinetics and drug–drug interactions. J Antimicrob Chemother 2014; 69: 2310–8.
27 Janssen Pharmaceuticals. Sirturo, United States Product Insert. http://www.sirturo.com/sites/default/files/pdf/sirturo-pi.pdf.
28 Acharya C, Hooker AC, Jonsson S et al. A diagnostic tool for population models using non-compartmental analysis: nca_pcc functionality for R. In: Abstracts of the Annual Meeting of the Population Approach Group in Europe, 2014. Abstract 3103. www.page-meeting.org?abstract=3103.
29 Yano Y, Beal SL, Sheiner LB. Evaluating pharmacokinetic/pharmacodynamic models using the posterior predictive check. J Pharmacokinet Pharmacodyn 2001; 28: 171–92.
30 FDA. Center for Drug Evaluation and Research, Application Number: 204384Orig1s0000, Pharmacology Review(s). http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/204384Orig1s000Pharmr.pdf.
31 FDA. Center for Drug Evaluation and Research, Application Number: 204384Orig1s0000, Clinical Pharmacology and Biopharmaceutics Review(s). http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/204384Orig1s000ClinPharmr.pdf.
32 Mesens N, Steemans M, Hansen E et al. Screening for phospholipidosis induced by central nervous drugs: Comparing the predictivity of an in vitro assay to high throughput in silico assays. Toxicol In Vitro 2010; 24: 1417–25.
33 Mesens N, Verbeek J, Rouan M. Elucidating the role of M2 in the preclinical safety profile of TMC207. In: Proceedings of the Thirty-eighth World Conference on Lung Health of the International Union Against Tuberculosis, Cape Town, South Africa, 2007. Abstract PS-71358–11, p. S167. International Union Against Tuberculosis and Lung Disease, Paris, France.

Downloaded from https://academic.oup.com/jac/article-abstract/70/4/1106/802795 by guest on 29 July 2018
34 Reinach B, de Sousa G, Dostert P et al. Comparative effects of rifabutin and rifampicin on cytochromes P450 and UDP-glucuronosyl-transferases expression in fresh and cryopreserved human hepatocytes. *Chem Biol Interact* 1999; **121**: 37–48.

35 Weber A, Kaplan M, Chughtai SA et al. CYP3A inductive potential of the rifamycins, rifabutin and rifampin, in the rabbit. *Biopharm Drug Dispos* 2001; **22**: 157–68.

36 Pinheiro VGF, Ramos LMA, Monteiro HSA et al. Intestinal permeability and malabsorption of rifampin and isoniazid in active pulmonary tuberculosis. *Braz J Infect Dis* 2006; **10**: 374–9.

37 Zhu M, Namdar R, Stambough JJ et al. Population pharmacokinetics of ethionamide in patients with tuberculosis. *Tuberculosis* 2002; **82**: 91–6.

38 Peresi E, Silva SMUR, Calvi SA et al. Cytokines and acute phase serum proteins as markers of inflammatory regression during the treatment of pulmonary tuberculosis. *J Bras Pneumol* 2008; **34**: 942–9.

39 Ramakrishnan K, Shenbagarathai R, Kavitha K et al. Serum zinc and albumin levels in pulmonary tuberculosis patients with and without HIV. *Jpn J Infect Dis* 2008; **61**: 202–4.

40 McLeay SC, Vis P, van Heeswijk RPG et al. Population pharmacokinetics of bedaquiline (TMC207), a novel antituberculosis drug. *Antimicrob Agents Chemother* 2014; **58**: 5315–24.

41 Svensson EM, Dooley KE, Karlsson MO. Impact of lopinavir-ritonavir or nevirapine on bedaquiline exposures and potential implications for patients with tuberculosis-HIV coinfection. *Antimicrob Agents Chemother* 2014; **58**: 6406–12.