Assessing Prolongation of the Corrected QT Interval with Bedaquiline and Delamanid Coadministration to Predict the Cardiac Safety of Simplified Dosing Regimens

Lénaïg Tanneau1, Mats O. Karlsson1, Susan L. Rosenkranz2, Yoninah S. Cramer2, Justin Shenje3, Caryn M. Upton4, Joel Morganroth5, Andreas H. Diacon4, Gary Maartens6, Kelly E. Dooley7 and Elin M. Svensson1,8,*

Delamanid and bedaquiline are two drugs approved to treat drug-resistant tuberculosis, and each have been associated with corrected QT interval (QTc) prolongation. We aimed to investigate the relationships between the drugs’ plasma concentrations and the prolongation of observed QT interval corrected using Fridericia’s formula (QTcF) and to evaluate their combined effects on QTcF, using a model-based population approach. Furthermore, we predicted the safety profiles of once daily regimens. Data were obtained from a trial where participants were randomized 1:1:1 to receive delamanid, bedaquiline, or delamanid + bedaquiline. The effect on QTcF of delamanid and/or its metabolite (DM-6705) and the pharmacodynamic interactions under coadministration were explored based on a published model between bedaquiline’s metabolite (M2) and QTcF. The metabolites of each drug were found to be responsible for the drug-related QTcF prolongation. The final drug-effect model included a competitive interaction between M2 and DM-6705 acting on the same cardiac receptor and thereby reducing each other’s apparent potency, by 28% (95% confidence interval (CI), 22–40%) for M2 and 33% (95% CI, 24–54%) for DM-6705. The generated combined effect was not greater but close to “additivity” in the analyzed concentration range. Predictions with the final model suggested a similar QT prolonging potential with simplified, once-daily dosing regimens compared with the approved regimens, with a maximum median change from baseline QTcF increase of 20 milliseconds in both regimens. The concentrations-QTcF relationship of the combination of bedaquiline and delamanid was best described by a competitive binding model involving the two main metabolites. Model predictions demonstrated that QTcF prolongation with simplified once daily regimens would be comparable to currently used dosing regimens.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Bedaquiline and delamanid use has been associated with corrected QT interval (QTc) prolongation. Combining the two drugs led to a no more than additive effect on the QTc interval.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ What is the relation between drugs’ concentrations and QTc prolongation?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ The respective metabolites were found to be responsible for the QTcF prolongation. The pharmacodynamic interaction was described by a competitive agonist model, indicating no synergic toxicity for the combination of bedaquiline and delamanid.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ Alternative dosing regimens can be explored with this quantitative model-based approach. The newly more-practical-to-use once-daily regimen for these drugs was explored through the developed model, and was predicted not to lead to a higher risk of safety events.

1Department of Pharmacy, Uppsala University, Uppsala, Sweden; 2Frontier Science Foundation, Brookline, Massachusetts, USA; 3South African Tuberculosis Vaccine Initiative, University of Cape Town, Cape Town, South Africa; 4TASK Applied Science, Cape Town, South Africa; 5Clario, Inc., Philadelphia, Pennsylvania, USA; 6Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa; 7Center for Tuberculosis Research, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; 8Department of Pharmacy, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands. *Correspondence: Elin M. Svensson (elin.svensson@farmaci.uu.se)

Received April 19, 2022; accepted May 30, 2022. doi:10.1002/cpt.2685
Mycobacterium tuberculosis is one of the leading causes of mortality globally, with about 1.5 million reported deaths in 2019. Drug-resistant tuberculosis (TB) has poor treatment outcomes and, until recently, required prolonged therapy, including injectables, with considerable toxicity. Fortunately, since 2020, all-oral shorter regimens (9–12 months) have been recommended by the World Health Organization (WHO) for the treatment of drug-resistant TB. To further refine treatment, mismatching dosing schedules could be aligned within the multidrug regimens and once-daily dosing is preferred to simplify use and improve adherence.

Bedaquiline and delamanid are two registered antituberculosis drugs with new and distinct mechanisms of action, making them good candidates for inclusion in shorter, all-oral, once-daily regimens. With bedaquiline targeting adenosine triphosphate synthase and delamanid acting on mycolic acid synthesis, the combination shows promising results in terms of efficacy to enhance culture conversion. However, both drugs have been associated with the cardiotoxic potential of prolonging the QTc interval, a risk factor for sudden death. While no pharmacokinetic interaction between bedaquiline and delamanid is anticipated, the pharmacodynamic interaction requires further study. Prior observational studies have been reassuring with regard to QTc prolongation when bedaquiline and delamanid are given together under compassionate use.

The DELIBERATE (Delamanid Bedaquiline for Resistant Tuberculosis) clinical trial was a phase II randomized, controlled study that aimed to precisely quantify the effect of bedaquiline, delamanid, or both on the QTcF interval. Given the long terminal half-lives of the studied TB drugs and their metabolites, leading to slow accumulation over time, the effect on QTcF interval was assessed over 6 months of multidrug treatment. The trial included 84 participants, of whom 80 proceeded to receive study treatment, and none of whom experienced absolute QTcF values over 500 milliseconds. The change from baseline QTcF of the combined arm vs. the sum of changes on bedaquiline alone plus delamanid alone arms had a mean QTcF of ~0.1 milliseconds (95% CI, −8.0 to 7.7). The authors concluded that combining bedaquiline and delamanid should have a no more than additive effect on the QTc interval.

Our objective in this analysis was to characterize the relationships between plasma concentrations of bedaquiline, its M2 metabolite, delamanid, its DM-6705 metabolite, and QTcF interval, using a population pharmacokinetic–pharmacodynamic model. Then we simulated the effect of daily dosing regimens of bedaquiline and delamanid on QTcF interval prolongation, at doses proposed for ongoing and future clinical trials.

**MATERIALS AND METHODS**

**Data**

Data were obtained from the DELIBERATE clinical trial, which was a phase II, open-label, randomized controlled study in adults with multidrug-resistant TB (ClinicalTrials.gov number NCT 02583048). The trial was approved by local ethics committees at each site, and participants gave written informed consent.

Participants were randomized 1:1:1 to either bedaquiline, delamanid, or bedaquiline plus delamanid, together with a multidrug background treatment (28 participants in each group). Clofazimine and moxifloxacin, both of which cause significant QT prolongation, were not permitted in the background regimen. Delamanid was dosed 100 mg twice daily with food for 24 weeks, and bedaquiline was administered 1 hour after the meal together with other anti-TB drugs at 400 mg daily for 2 weeks then 200 mg three times a week for 22 weeks. QT intervals were assessed by electrocardiogram (ECG) and corrected for the effect of heart rate using Fridericia’s formula (QTcF). ECGs were performed in triplicate at baseline and every 2 weeks until Week 24, ~4–6 hours post dose, before lunch. Rich pharmacokinetic (PK) sampling was performed at Weeks 2, 8, and 24, (according to the schedule displayed in Table S1), and sparse sampling was drawn, concurrent to ECG measurements, every 2 weeks.

**Model selection and evaluation**

Model selection was based on significant drops in objective function value (OFV) or Bayesian information criteria (BIC), goodness-of-fit plots, precision in parameter estimates, and scientific plausibility. For nested models, a significant drop in OFV for one added parameter (i.e., 1 degree of freedom) was 3.84 points, corresponding to a P value <0.05. Non-nested models were compared with BIC for nonlinear mixed-effect models, accounting for the numbers of subjects, observations, fixed effects, and random effects in the calculation of the OFV’s penalty. Parameter precision was obtained with the R covariance (Hessian) matrix. Models were qualified using visual predictive checks (1,000 replicates), stratified by study arms. All triplicate ECG measurements were included (i.e., no averaging of data was carried out). Missing covariate values (see Table 1) were imputed by replacing them with the population median for continuous covariates, and with the most common category for categorical covariates.

**Pharmacokinetic models**

Parent and metabolite drug concentrations at the time of the ECG measurements for each individual were obtained by predictions with previously developed models, based on individual dosing information, demographics, and observed drug concentrations. Diagnostic plots between observed concentrations and individual predicted concentrations were generated to assess the predictability of the models. Similar to the previously published evaluation of bedaquiline and/or M2 effects on delamanid/DM-6705 PK, the effect of delamanid and/or DM-6705 on bedaquiline/M2 PK was investigated by evaluating a possible arm effect on disposition parameters.

**Pharmacokinetic–pharmacodynamic model**

A previously developed model describing the relation between M2 concentration and QTcF interval was used as the base model. In addition to the drug effect (DE), this model included several components that influenced the QTcF interval, such as participants’ characteristics (age, sex, race, electrolyte levels) on baseline QTcF, the circadian rhythm, and the effect of time on treatment (see Figure S1). No covariate search was performed on top of the base model, given that no new potential covariates were available in the analysis data set, compared with the base model.

Our analysis consisted of three steps. First, with data from the bedaquiline arm only, the base model was fitted using priors. Given the similarity of the participants’ population, the PRIOR functionality in NONMEM uses information from the base model (developed with 430 participants) to stabilize the estimation process of a smaller data set, such as the current data set with 28 participants in the bedaquiline arm. The drug QTcF effect was also confirmed to be driven only by M2 concentrations, and not bedaquiline concentrations. Secondly, the impact of delamanid and/or DM-6705 concentrations on QTcF prolongation was analyzed on top of the base model, via step, linear, or maximal drug effect (Emax) functions. Data from the delamanid arm only were first fitted to define delamanid/DM-6705 drug effect, then applied to the entire data set. Thirdly, pharmacodynamic drug interactions between bedaquiline and delamanid, or their metabolites, using the entire data set, were explored via an empirical approach by estimating an interaction parameter β (Eq. 1) and a more mechanistic approach using a competitive interaction model (Eq. 2).
DE stands for drug effect. A represents bedaquiline or M2, and B represents delamanid or DM-6705.

The competitive interaction model relies on the assumption that the analytes bind to a common receptor and have a common mechanism of action to induce QT prolongation.

\[
DE_{AB} = \frac{E_{\text{max},A} \cdot \text{Conc}_A}{EC_{50,A} \cdot \left(1 + \frac{\text{Conc}_A}{EC_{50,A}}\right) + \text{Conc}_A} + \frac{E_{\text{max},B} \cdot \text{Conc}_B}{EC_{50,B} \cdot \left(1 + \frac{\text{Conc}_B}{EC_{50,B}}\right) + \text{Conc}_B}
\]

\[(2)\]

DE stands for drug effect, \(E_{\text{max}}\) for maximal drug effect, Conc for concentration, and \(EC_{50}\) for the concentration needed to achieve half of the \(E_{\text{max}}\). A represents bedaquiline or M2, and B represents delamanid or DM-6705.

Tested interindividual variability (IIV) on added parameters was assumed to be log-normally distributed, with the exception of the interaction parameter \(\beta\) where a normal distribution was tested, so that positive and negative values were permitted.

To account for a possible relation between albumin concentrations and potency, through parent drug or metabolite-binding, a directly proportional relation between albumin concentration and potency was tested. This relation can be motivated as all four entities explored have a high protein binding.

Simulations

The final model was used to simulate the drug-induced QTcF interval prolongation expected if bedaquiline and delamanid were to be administered together with once-daily regimens currently tested in...
clinical trials (200 mg once daily (q.d.) for 8 weeks then 100 mg q.d. for bedaquiline, and 300 mg q.d. for delamanid). This analysis focused only on the drug effect component of the model (different from the total change from baseline QTcF interval, as already reported in the clinical reference publication 13), to more precisely address the change in dosing regimens. One thousand profiles of the drug-induced QTcF prolongation were generated, considering IIV in the pharmacokinetic and pharmacodynamic parameters. The participants’ characteristics for the simula were 35 years old, 54 kg, non-Black race, corresponding to the typical individual in the DELIBERATE trial. The PK model of delamanid/DM-6705 includes an adherence component and a morning/evening effect on relative bioavailability that were not included in the simulations (centering the simulations around the daily average relative bioavailability). The nonlinear bioavailability of delamanid with increasing doses was accounted for by a fixed effect on bioavailability extracted from the literature.23

Software
Data analysis was performed with the nonlinear mixed-effects modeling software NONMEM version 7.4.4 (ICON plc, Gaithersburg, MD), with the first-order conditional estimation method with interaction.24 Model diagnostics were supported by Perl-speaks-NONMEM (PsN, version 5.2.6)25,26 and R software version 4.1.0 (R Core Team, Vienna, Austria).27

RESULTS
Data
A total of 80 participants with drug-resistant TB were included in the analysis, out of the 84 planned per protocol. Four participants were excluded from the analysis as they did not receive any doses of study treatment. The demographic characteristics at baseline are summarized in Table 1.

Pharmacokinetic models
The previously published PK models displayed good performance at predicting observed concentrations (Figure 1). The summary of the model-predicted PK data at ECG timepoints for each analyte can be found in Table 1.

No PK drug–drug interactions were identified between bedaquiline and delamanid: neither bedaquiline on delamanid PK,17 nor delamanid on bedaquiline PK (see Table S2).

Pharmacokinetic–pharmacodynamic model
As a first step, the evaluation of the base model with bedaquiline arm data, using the PRIOR functionality, resulted in parameter estimates and precision in line with published results (see Table 2 and Ref.18). The exploration of bedaquiline’s contribution to the drug effect resulted in a nonsignificant improvement of the data fit, either as a single agent or as a combination with M2 (see Table S3). Those results confirmed the previously published relationship.

Secondly, analysis of the contribution of delamanid and DM-6705 concentrations to the drug effect, with delamanid arm data only, demonstrated that only DM-6705 (and not delamanid) played a significant role in QTcF prolongation. A model accounting for the effects of both delamanid and DM-6705 concentrations was not better at describing the data. The function that described best the drug-induced QTcF prolongation by DM-6705 concentrations in the delamanid arm data was a linear function (see Table S3), with a slope coefficient estimated to 7.91 milliseconds per 100 ng/mL of DM-6705 (90% CI, 4.2 to 11.6). Those results are in line with a published linear model, defined with pediatric data, where the slope was estimated to 6.13 milliseconds per 100 ng/mL (90% CI, 1.6 to 10.7).28

Thirdly, the characterization of the interaction between M2 and DM-6705 concentrations to the drug-induced QTcF prolongation was explored for the entire data set (80 individuals). Beforehand, the previously defined E_max function for M2 concentrations, and the linear function for DM-6705 concentrations, were turned into two E_max functions sharing the same maximal effect parameter (no difference in OFV and same number of parameters). This allowed us to normalize the drug effect (by dividing by the maximal effect) and to compare the empirical approach with the Bliss independence theorem. The latter

Figure 1. Diagnostic plots of the pharmacokinetic models showing observed concentrations vs. individual predicted concentrations for metabolites M2 and DM-6705. The gray dashed line represents the trendline across the data and the black full line represents the line of identity.
says that the interaction parameter $\beta = 1$ indicates Bliss independence (i.e., additive interaction), $\beta > 1$ antagonism and $\beta < 1$ synergy. In our analysis, $\beta$ was estimated to 2.72 (relative standard error: 32%), indicating antagonism. Also, a competitive interaction model was tested, with and without estimation of two separated maximal effects. Finally, the competitive interaction model with a common estimated maximal effect (Eq. 3) was selected, over the empirical more flexible model, to be the best to describe the data (BIC competitive = 15,491; BIC empirical = 15,497).

Addition of IIV on $E_{\text{max}}$ or $E_{\text{50,M2}}$ did not improve the fit of the data. Further investigations to account for a possible relation between albumin concentrations and potency were not significant.

Visual predictive checks of QTcF vs. time and change from baseline QTcF vs. time, showing adequate model fit to the data are depicted in Figure 2. The final model parameter estimates with their precision are summarized in Table 2. To note, although IIV parameters on maximal effect of time on treatment and $E_{\text{50,M2}}$ were large (166% and 155%, respectively), the uncertainty of these parameters was low (10.3% and 13.6%, respectively).

**Simulation of once-daily regimens**

The final model predicted similar QTcF prolongation with the approved regimens and the once-daily regimens, as depicted in Figure 3. It predicted median drug-induced QTcF increases at 2, 8, and 24 weeks of 8.4 milliseconds (95% CI, 4.2–22.0), 12.5 milliseconds (95% CI, 6.1–24.5), and 11.9 milliseconds (95% CI, 6.1–24.0) with once-daily regimens compared with 10.9 milliseconds (95% CI, 5–24.5), 12.1 milliseconds (95% CI, 6.2–24.5), and 12.4 milliseconds (95% CI, 6.2–24.2) with the approved regimens. At Week 24, 15.2 and 18.3% of the participants were simulated to have a change from baseline QTcF interval over 30 milliseconds with the once-daily and approved regimens, respectively. Similarly, 4.1% of the participants with both regimens were simulated to have an absolute QTcF interval over 450 milliseconds at Week 24.

**DISCUSSION**

In this work, we used a pharmacometric approach to characterize the QTcF prolongation and its relation to parent drug/metabolite

### Table 2 Parameters estimates and uncertainty of the final model

| Submodel                  | Parameters (unit) | Value (RSE%) | IIV % CV (RSE%) |
|---------------------------|-------------------|--------------|-----------------|
| Baseline                  | QTcF₀ (ms)        | 401 (0.312)  | 3.73 (7.52)     |
| Drug effect               | $E_{\text{max}}$ (ms) | 25.9 (14.4) |                |
|                           | $E_{\text{50,M2}}$ (ng/mL) | 695 (30.1) | 155 (13.6)     |
|                           | $E_{\text{50,DM-6705}}$ (ng/mL) | 205 (40.9) |                |
| Time effect               | QTₘₚ (ms)         | 7.09 (8.72)  | 166 (10.3)      |
|                           | $T_{1/2}$ (weeks) | 7.52 (13)    |                |
| Circadian rhythm          | A₂₄ (ms)          | 2.96 (40.9)  |                |
|                           | $\varphi₂₄$ (hours) | 4.76 (27.3) |                |
|                           | A₁₂ (ms)          | 1.51 (25.6)  |                |
|                           | $\varphi₁₂$ (hours) | 4.32 (24.1) |                |
| Covariates                | Effect of potassium levels (ms per IU/L) | -1.25 (36.2) | |
|                           | Effect of being a female (ms) | 6.67 (21) | |
|                           | Effect of being black (ms) | -7.14 (18.6) | |
|                           | Effect of age (ms per year) | 0.366 (15) | |
| Residual error model      | Additive RUV (ms) | 8.77 (3.98)  | 20.0 (8.9)      |
|                           | Box-Cox IIV² RUV  | 3.89 (21.5)  |                |
|                           | Additive RUV repl (ms) | 5.29 (3.13) | 23.5 (4.96)    |
|                           | Box-Cox IIV² RUV repl | 0.874 (34.7) | |

CV is reported as the square root of the variance. RSE of IIV and RUV is reported on the approximate standard deviation scale (standard error/variance estimate)/2.

$E_{\text{max}}$, amplitude for the 12-hour circadian rhythm cycles; $A_{\varphi24}$, amplitude for the 24-hour circadian rhythm cycles; CV, coefficient of variation; $E_{\text{50,M2}}$, concentration needed to achieve half of $E_{\text{max}}$; $E_{\text{50,DM-6705}}$, concentration of DM-6705, delamanid’s metabolite; $E_{\text{50,M2}}$, bedaquiline’s metabolite; $E_{\text{max}}$, maximal drug effect; IIV, interindividual variability; ms, milliseconds; QTcF₀, baseline QT interval corrected using Fridericia’s formula; QTₘₚ, maximal effect of time on treatment; RSE, relative standard error; RUV, residual unexplained variability; RUV repl, replicate-specific residual unexplained variability; $T_{1/2}$, time needed to achieve half of QTₘₚ; $\varphi₁₂$, acrophase for the 12-hour circadian rhythm cycles; $\varphi₂₄$, acrophase for the 24-hour circadian rhythm cycles.

*Same maximal effect parameter ($E_{\text{max}}$) for M2 and DM-6705. **IIV coded with a proportional model, whereas the others are coded with an exponential model. ***Absolute change in QTcF₀ (ms) per IU/L, different from the population median, 4.150 IU/L. ****Absolute change in QTcF₀ (ms) per year, different from the population median, 35 years. **Parameter estimate of the Box–Cox transformed distribution of IIV on $\varepsilon$ components.
exposures when bedaquiline and delamanid are administered together. Indeed, QTcF interval prolongation has been reported as an electrophysiologic effect of both drugs separately. To perform this work, we analyzed data from a trial that was designed to assess the pharmacodynamic interaction when both drugs were administered alone or together (on top of multidrug background

Figure 2 Visual predictive checks of the final models. Panel (a) represents QTcF interval over time after start of treatment per arm, and panel (b) represents change from baseline QTcF interval over time after start of treatment per arm. The solid and dashed lines represent the median, the 2.5th, and 97.5th percentiles of the observed data (black circles), respectively, and the shaded areas the simulation-based 95% confidence intervals for the corresponding percentiles. QTcF, QT interval corrected using Fridericia’s formula.

Figure 3 Simulated drug-induced QTcF increase with approved regimens (400 mg daily for 14 days, then 200 mg thrice-weekly for bedaquiline, and 100 mg twice-daily for delamanid) and once-daily regimens (200 mg daily for 8 weeks then 100 mg daily for bedaquiline, and 300 mg daily for delamanid) for a typical participant (35 years old, 54 kg, non-Black). The solid line represents the median of the simulated data, and the limits of the shaded area represent the 2.5th and 97.5th percentiles of the simulated data. QTcF, QT interval corrected using Fridericia’s formula.
treatment). First, we confirmed the absence of a pharmacokinetic interaction between bedaquiline and delamanid, i.e., bedaquiline was not impacting delamanid’s pharmacokinetics, and delamanid was not impacting bedaquiline’s pharmacokinetics. Then, after characterizing the effect of each drug individually and confirming the metabolites to be the drivers of the QTcF prolongations, the pharmacodynamic interaction between the two metabolites was explored. A flexible model allowing the interaction to be either additive, antagonistic, or synergistic, when compared with the Bliss independence theorem, indicated an antagonistic relationship between the metabolites. Thus, a competitive binding model was tested and selected as being the best to describe the data. It denotes that metabolites M2 and DM-6705 both act as agonists of the human ether-a-go-go-related gene (hERG) receptor (by binding and blocking the hERG potassium channel) but will act as antagonists for the other metabolite by competing to bind to the same receptor. Therefore, each metabolite reduces the other metabolite’s apparent potency (i.e., increasing apparent EC<sub>50</sub>, see Eq. 3). It results in a shift of the concentration–response curve to the right, meaning that a larger concentration of drug is required to give the same prolongation of the QTcF interval in the presence of the other metabolite. The ratios of median concentration to typical EC<sub>50</sub> for each metabolite were of the same magnitude (0.28 for M2 and 0.33 for DM-6705), depicting a similar extent of effect for both metabolites on each other’s potency, in the range of analyzed concentrations (Figure 4). Moreover, the low values

![Figure 4](image1.png)

**Figure 4** Drug-induced QTcF increase vs. metabolite M2 or DM-6705 concentrations, stratified by arm. For the bedaquiline + delamanid arm (black line), for each panel, while the concentration of one metabolite is increasing, the concentration of the other metabolite is constant (set to median of observed concentrations). QTcF, QT interval corrected using Fridericia’s formula.

![Figure 5](image2.png)

**Figure 5** Contribution of each metabolite (M2 or DM-6705) to the drug-induced QTcF increase over time after start of study. The solid line represents the median contribution among all participants and the dashed lines represent the individual contributions. QTcF, QT interval corrected using Fridericia’s formula.
of the ratios and the near-parallel plot lines (Figure 4) indicate that the combined effect was close to “additivity,” where the combined effect would be equal to the sum of two effects separately. However, the time course of each metabolite is different, so the contribution to the drug effect of each metabolite over time is illustrated in Figure 5.

The newly tested once-daily regimens for bedaquiline and delamanid are of key importance to improve patients’ quality of life as well as logistics for programs for provision of multidrug regimens. To assess the cardiotoxic risk of the newly offered once-daily regimens to TB patients, we performed simulations with the developed model to compare the drug-induced QTcF prolongation between the approved regimens and the newly proposed once-daily regimens (200 mg q.d. for 8 weeks then 100 mg q.d. for bedaquiline, and 300 mg q.d. for delamanid). The simulations suggested that once-daily regimens of bedaquiline and delamanid taken together are as safe as the approved regimens. Indeed, with the once-daily regimens, the predicted maximal QTcF increase over 24 weeks of treatment, as well as the prevalence of patients with change from baseline QTcF interval over 30 milliseconds at 24 weeks, were not higher than the predicted values with the current approved regimens. From a safety perspective, these results provide assurance in the use of all-oral once-daily regimens.

There are several limitations to the model developed. One is that the estimation of two separate E\text{max} parameters for M2 and DM-6705 in the competitive interaction model was not supported by the data. It would mean that at high concentrations (higher than the analyzed concentrations range), the two metabolites would share the same maximal possible toxicity. So, extrapolation outside the range of analyzed exposures could be uncertain; however, in the analysis, the simulated concentrations were in the same range as the concentrations used for the model development. Another limitation is that the simulations only account for the bedaquiline and delamanid coadministration, as they reproduce the DELIBERATE trial design where there was no coadministration of drugs with drug–drug interaction with bedaquiline or delamanid (e.g., antiretroviral drugs such as lopinavir/ritonavir), and no coadministration of drugs with QT liability (e.g., clofazimine). So, to fully assess the drug-induced QTcF prolongation in new clinical trials with once-daily regimens, other drug–drug interactions should be accounted for in the simulations.

In conclusion, we established the PK-QTcF relationship of the combination of bedaquiline and delamanid. The metabolites, M2 and DM-6705, were found to be responsible for the drug-induced QTcF prolongation, and the pharmacodynamic interaction was best described by a competitive agonist model, indicating no synergic toxicity for the combination of bedaquiline and delamanid. Predictions from the model support the use of these drugs together in once-daily regimens currently being tested in clinical trials, as the predicted QTcF prolongation is comparable to what is seen with currently used dosing regimens.

ACKNOWLEDGMENTS
We would like to thank the participants and their families for participating in the study. We acknowledge all members of the A5343 DELIBERATE study team and ViV Healthcare for the conduct of the clinical study. Open access funding enabled and organized by ProjektDEAL.

FUNDING
This analysis was supported by AIDS Clinical Trials Group (ACTG), National Institutes of Health (NIH).

CONFLICT OF INTEREST
Study bedaquiline and delamanid provided to NIH by Janssen and Otsuka, respectively, for the parent study. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS
All authors wrote the manuscript. L.T., M.O.K., S.L.R., Y.S.C., J.S., C.M.U., A.H.D., G.M., K.E.D., and E.M.S. designed the research. L.T. performed the research. L.T., M.O.K., J.M., and E.M.S. analyzed the data.

© 2022 The Authors. Clinical Pharmacology & Therapeutics published by Wiley Periodicals LLC on behalf of American Society for Clinical Pharmacology and Therapeutics.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

1. World Health Organization. Global tuberculosis report 2020 <https://www.who.int/publications/i/item/9789240013131> (2020).
2. Infographic: Drug-resistant TB: How many pills does it take? Médecins Sans Frontières Access Campaign <https://msfaccess.org/infographic-drug-resistant-tb-how-many-pills-does-it-take>.
3. World Health Organization, Consolidated Guidelines on Tuberculosis, Module 4: Treatment – Drug-Resistant Tuberculosis Treatment. <https://www.who.int/publications-detail-redirect/9789240007048> (2020).
4. Franke, M. F. et al. Culture conversion in patients treated with Bedaquiline and/or Delamanid. A prospective multicountry study. Am. J. Respir. Crit. Care Med. 203, 111–119 (2021).
5. Hafkin, J., Hittel, N., Martin, A. & Gupta, R. Compassionate use of delamanid in combination with bedaquiline for the treatment of multidrug-resistant tuberculosis. Eur. Respir. J. 53, 1801154 (2019).
6. Ferlazzo, G. et al. Early safety and efficacy of the combination of bedaquiline and delamanid for the treatment of patients with drug-resistant tuberculosis in Armenia, India, and South Africa: a retrospective cohort study. Lancet. Infect. Dis. 18, 536–544 (2018).
7. Sarin, R. et al. Early efficacy and safety of Bedaquiline and Delamanid given together in a “salvage regimen” for treatment of drug-resistant tuberculosis. Indian J. Tuberc. 66, 184–188 (2019).
8. Diacon, A.H. et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N. Engl. J. Med. 360, 2397-2405 (2009).
9. Gler, M.T. et al. Delamanid for multidrug-resistant pulmonary tuberculosis. N. Engl. J. Med. 366, 2151–2160 (2012).
10. Migliori, G.B. et al. Combined use of Delamanid and Bedaquiline to treat multidrug-resistant and extensively drug-resistant tuberculosis: a systematic review. Int. J. Mol. Sci. 18, E341 (2017).
11. Kim, C.T. et al. Bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis: a multicentre cohort study in Korea. Eur. Respir. J. 51, 1702467 (2018).

SUPPORTING INFORMATION
Supplementary information accompanies this paper on the Clinical Pharmacology & Therapeutics website (www.cpt-journal.com).
12. Mohr, E., Ferlazzo, G., Hewison, C., De Azevedo, V. & Isaakidis, P. Bedaquiline and delamanid in combination for treatment of drug-resistant tuberculosis. Lancet Infect. Dis. 19, 470 (2019).
13. Dooley, K. E. et al. QT effects of bedaquiline, delamanid, or both in patients with rifampicin-resistant tuberculosis: a phase 2, open-label, randomised, controlled trial. Lancet Infect. Dis. 21, 975–983 (2021).
14. Boston University. Efficacy and Tolerability of Bedaquiline, Delamanid, Levofloxacin, Linezolid, and Clofazimine to Treat MDR-TB (DRAMATIC). ClinicalTrials.gov Identifier: NCT03828201. <https://clinicaltrials.gov/ct2/show/NCT03828201> (2021).
15. Delattre, M., Lavielle, M. & Poursat, M.-A. A note on BIC in mixed-effects models. Electron. J. Statist. 8, 456–475 (2014).
16. Svensson, E., Dagne, A. & Karlsson, M. Population pharmacokinetics of Bedaquiline and metabolite M2 in patients with drug-resistant tuberculosis: the effect of time-varying weight and albumin. CPT Pharmacometrics Syst. Pharmacol. 5, 682–691 (2016).
17. Tanneau, L. et al. Population pharmacokinetics of delamanid and its main metabolite DM-6705 in patients with multidrug resistant tuberculosis. <https://www.page-meeting.org/?abstract=9673> (2021).
18. Tanneau, L., Svensson, E.M., Rossenu, S. & Karlsson, M.O. Exposure-safety analysis of QTc interval and transaminase levels following bedaquiline administration in patients with drug-resistant tuberculosis. CPT Pharmacometrics Syst. Pharmacol. 10, 1538–1549 (2021).
19. Ariëns, E.J., van Rossum, J.M. & Simonis, A.M. Affinity. Intrinsic Activity and Drug Interactions Pharmacol. Rev. 9, 218–236 (1957).
20. Holford, N.H.G. & Sheiner, L.B. Kinetics of pharmacologic response. Pharmacol. Ther. 16, 143–166 (1982).
21. van Heeswijk, R.P.G., Dannemann, B. & Hoetelmans, R.M.W. Bedaquiline: a review of human pharmacokinetics and drug-drug interactions. J. Antimicrobial Chemother. 69, 2310–2318 (2014).
22. Sasahara, K. et al. Pharmacokinetics and metabolism of Delamanid, a novel anti-tuberculosis drug, in animals and humans: importance of albumin metabolism in vivo. Drug Metab. Dispos. 43, 1267–1276 (2015).
23. Wang, X., Mallikaarjun, S. & Gibiansky, E. Population pharmacokinetic analysis of Delamanid in patients with pulmonary multidrug-resistant tuberculosis. Antimicrob. Agents Chemother. 65, e01202-20 (2020).
24. Beal, S.L., Sheiner, L.B., Boeckmann, A.J. & Bauer, R.J. NONMEM 7.4 Users Guides (ICON plc, Gaithersburg, MD, 1989-2019). https://nonmem.iconplc.com/nonmem744.
25. Lindbom, L., Pihlgren, P. & Jonsson, E.N. PsN-toolkit—A collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput. Methods Programs Biomed. 79, 241–257 (2005).
26. Karlsson, M.O., Hooker, A., Nordgren, R., Harling, K. & Freiberga, S. Perl-speaks-NONMEM (PsN) <https://uupharmaometrics.github.io/PsN/> (2016).
27. R Core Team R: A language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria, 2021). https://www.r-project.org/.
28. Sasaki, T. et al. Population pharmacokinetic and concentration-QTc analysis of delamanid in pediatric participants with multidrug-resistant tuberculosis. Antimicrob. Agents Chemother. 66, e0160821 (2022).
29. European Medicines Agency. CHMP assessment report: sirturo <https://www.ema.europa.eu/en/documents/assessment-report/sirturo-epar-public-assessment-report_en.pdf> (2013).
30. European Medicines Agency. Assessment report: deltyba <https://www.ema.europa.eu/en/documents/assessment-report/deltyba-epar-public-assessment-report_en.pdf> (2013).
31. Gabrielsson, J. & Weiner, D. Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications Fourth edn. (Swedish Pharmaceutical Press, Stockholm, Sweden, 2007).