

Safety, Tolerability, and Pharmacokinetic Interactions of the Antituberculous Agent TMC207 (Bedaquiline) With Efavirenz in Healthy Volunteers: AIDS Clinical Trials Group Study A5267

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Background: Drug–drug interactions complicate management of coinfection with HIV-1 and *Mycobacterium tuberculosis*. Bedaquiline (formerly TMC207), an investigational agent for the treatment of tuberculosis, is metabolized by cytochrome P450 (CYP) 3A which may be induced by the antiretroviral drug efavirenz.

Methods: This was a phase 1 pharmacokinetic drug interaction trial. Each healthy volunteer received two 400 mg doses of bedaquiline, the first alone and the second with concomitant steady-state efavirenz. Plasma pharmacokinetic sampling for bedaquiline and its N-monodesmethyl metabolite was performed over 14 days after each bedaquiline dose. Steady-state efavirenz pharmacokinetics were also determined. Efavirenz metabolizer status was based on *CYP2B6* composite 516/983 genotype.

Results: Thirty-three of 37 enrolled subjects completed the study. Geometric mean of ratios for bedaquiline with efavirenz versus bedaquiline alone were 0.82 [90% confidence interval (CI): 0.75 to 0.89] for the 14-day area under the concentration–time curve ($AUC_{0-336\text{ h}}$) and 1.00 (90% CI: 0.88 to 1.13) for the maximum concentration (C_{\max}). For N-monodesmethyl metabolite, the geometric mean of ratios was 1.07 (90% CI: 0.97 to 1.19) for $AUC_{0-336\text{ h}}$ and 1.89 (90% CI: 1.66 to 2.15) for C_{\max} . There were no grade 3 or 4 clinical adverse events. One subject developed asymptomatic grade 3 serum transaminase elevation, prompting study drug discontinuation. Efavirenz concentrations stratified by *CYP2B6* genotype were similar to historical data.

Conclusions: Single-dose bedaquiline was well tolerated alone and with steady-state efavirenz. The effect of efavirenz on bedaquiline concentrations is unlikely to be clinically significant.

Key Words: bedaquiline, efavirenz, CYP3A, HIV, pharmacokinetics, TMC207, tuberculosis

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INTRODUCTION

Of the 9.4 million patients with incident tuberculosis (TB) annually, 1.4 million are coinfecting with HIV-1, and globally, TB is the leading cause of death among HIV-infected individuals.¹ Recent studies have demonstrated that survival among coinfecting individuals is improved by initiating antiretroviral therapy early during TB treatment rather than waiting to complete TB therapy.^{2–5} Such antiretroviral therapy is particularly beneficial in coinfecting individuals with lower CD4 counts. Concomitant treatment for HIV and TB is, thus, common and is becoming the standard of care in many settings. However, concurrent treatment of TB and HIV is complicated by drug–drug interactions and overlapping drug toxicities.⁶ There is an urgent need for new anti-TB medications that can be given safely with antiretrovirals (ARVs).

The novel diarylquinoline bedaquiline (formerly TMC207) is active against both drug-sensitive and drug-resistant TB and has the potential to shorten treatment

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duration.^{7,8} Bedaquiline inhibits the proton pump of *M. tuberculosis*, ATP synthase, a novel mechanism of action.^{7,9} Bedaquiline has demonstrated bactericidal and sterilizing activity in mouse models, and it is synergistic with first-line and second-line TB drugs and TB compounds in development.^{10–13} In a phase 2 placebo-controlled trial among patients with multidrug-resistant (MDR) TB, 48% of those randomized to receive bedaquiline together with a 5-drug MDR regimen became sputum culture negative by 8 weeks of treatment compared with 9% who received just the 5-drug MDR regimen.¹⁴ By 6 months, 79% of patients who received bedaquiline plus standard MDR treatment became culture negative compared with 58% who received standard MDR treatment.¹⁵ Clinical trials are ongoing to identify optimal bedaquiline-containing regimens for drug-sensitive TB and MDR-TB.

Bedaquiline is largely metabolized by cytochrome P450 (CYP) 3A to a less-active N-monodesmethyl metabolite (M2). Bedaquiline undergoes triphasic elimination, and although the average half-life over a dosing interval is about 24 hours, its terminal half-life is approximately 5 months.^{7,16,17} Administration with food increases bioavailability by about 95%. Efavirenz, one of the most widely prescribed ARVs globally, may induce CYP3A, raising the possibility that efavirenz might adversely lower bedaquiline concentrations. In addition, efavirenz is metabolized primarily by CYP2B6, and genetic variants in *CYP2B6* confer marked interindividual variability in efavirenz pharmacokinetics (PK).^{18,19}

We conducted a phase 1 open-label clinical trial in healthy volunteers to evaluate the effects of efavirenz on the PKs of bedaquiline and its M2 metabolite and to describe the safety and tolerability of single doses of bedaquiline coadministered with steady-state efavirenz. We also compared the PKs of efavirenz in this study with historical control values, taking into account *CYP2B6* genotype.

METHODS

Study Population

Healthy adults 18–65 years of age were recruited at 5 NIH-funded AIDS Clinical Trials Group sites in the United

States. Eligible subjects had negative HIV antibody tests and normal serum aspartate aminotransferase, alanine aminotransferase, amylase, and lipase values. Subjects were excluded for hemoglobin ≤ 12.0 g/dL (men) or ≤ 11.0 g/dL (women), white blood cell count < 4000 cells per cubic millimeter, platelets $< 100,000$ cells per cubic millimeter, electrocardiogram (ECG) with QT interval corrected for heart rate > 440 or PR interval > 200 milliseconds, or clinical evidence of active TB. Other exclusion criteria included breastfeeding, active illicit drug use or dependence, recent use of drugs that inhibit or induce CYP3A, chronic illness, and current use of prescription medications. Women of reproductive potential were excluded because of the lack of adequate and well-controlled studies of bedaquiline in pregnant women. The study was approved by the institutional review boards of participating sites, and all subjects provided written informed consent. The trial was registered at clinicaltrials.gov (NCT00992069).

Experimental Protocol

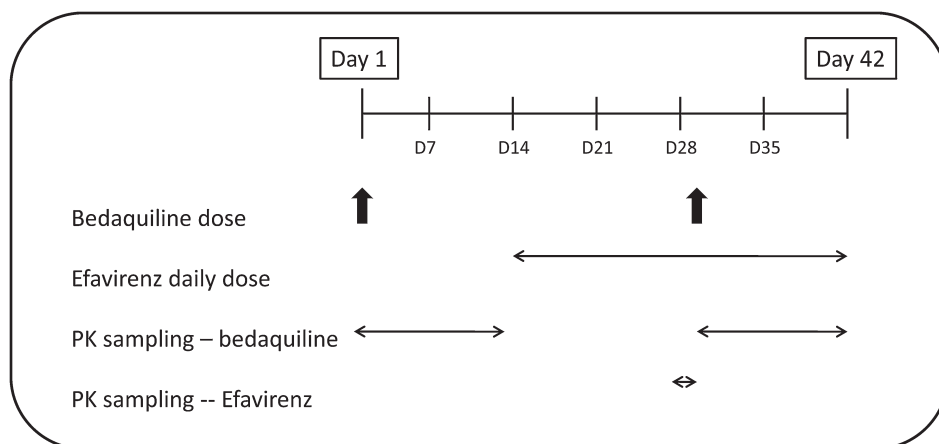
Study Design

This was a 2-period sequential design PK study (Fig. 1). Subjects received a single 400 mg oral dose of bedaquiline on study day 1. Plasma samples for bedaquiline and M2 PK analysis were collected predose, then at 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 120, 168, 216, 264, and 336 hours postdose (days 1–14, PK period 1). On study days 15–28, subjects received efavirenz 600 mg orally once nightly. Plasma samples for steady-state efavirenz PK analysis were collected predose, then at 1, 2, 3, 4, 8, 12, and 24 hours postdose on day 28. On day 29, a second 400-mg dose of bedaquiline was administered. PK sampling was performed for bedaquiline and M2, again over 336 hours (days 29–43, PK period 2). Efavirenz 600 mg once nightly was continued throughout the bedaquiline/M2 sampling period. Bedaquiline was given after a standard breakfast (670 kcal, 33% fat), and efavirenz was taken on an empty stomach.

Safety Monitoring

Subjects underwent safety evaluations approximately once weekly during the study. ECG evaluations were performed at baseline and 4–6 hours after each bedaquiline dose.

FIGURE 1. Schematic of the dosing regimen and pharmacokinetic sample collection.



Signs and symptoms, laboratory events, and ECG events were graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0 (December 2004, August 2009 clarification).²⁰

Drug Concentration Analysis

Plasma Assay for Bedaquiline and Its M2 Metabolite

Bedaquiline and its M2 metabolite were quantified using a reversed phase high-performance liquid chromatographic method with tandem mass spectrometric detection. Bedaquiline and its M2 metabolite and the assay internal standard, halofantrine, were isolated from plasma by a simple acetonitrile precipitation of plasma proteins followed by centrifugation. The clear supernatants were then directly injected onto an ACE-5 C18-AR reverse phase column and eluted with a linear gradient of ammonium formate buffer and acetonitrile containing 0.1% formic acid as the mobile phase. The ion pairs 555.7/58.0 for bedaquiline, 539.8/481.5 for its M2 metabolite, and 500/482 for the internal standard were selected for tandem mass spectrometry detection in multiple reaction monitoring mode. The method was linear over the range from 10–2500 ng/mL for bedaquiline and M2 ($R = 0.9986$). For measurements of bedaquiline, the interassay precision [% coefficient of variation, (CV)] and deviation [% relative error, (RE)] were, respectively, 4.3% to 6.1% and –6.2% to 2.4%. The intra-assay CV and RE were, respectively, 2.4% to 10.5% and –9.3% to 8%. For measurements of M2, the interassay CV and RE were, respectively, 4.7% to 6.3% and –1.8% to 8.2%, and the intra-assay CV and RE were, respectively, 2.4% to 10.5% and –9.3 to 8.0%. The lower limit of quantification was 10 ng/mL for both bedaquiline and M2.

Plasma Assay for Efavirenz

Efavirenz was quantified using an isocratic reverse phase high-performance liquid chromatographic method with ultraviolet detection. Efavirenz and the internal standard reserpine were extracted from plasma by acetonitrile protein precipitation followed by centrifugation.²¹ The organic supernatant was then evaporated to dryness under nitrogen and reconstituted with mobile phase. The reconstituted efavirenz and internal standard were injected onto a Waters Symmetry Shield-C8 reverse phase column and eluted with an isocratic mobile phase of sodium phosphate and acetonitrile. Detection was performed using a photodiode-array detector, scanning at a wavelength of 247 nm. The method was linear over the range from 100 to 10,000 ng/mL for efavirenz concentrations ($R = 0.9995$). For measurements of efavirenz, the interassay CV and RE were, respectively, 2.4% to 4.5% and –0.4% to 3.3% and the intra-assay CV and RE were, respectively, 0.6% to 3.0% and –0.4% to 0.8%. The lower limit of quantification was 100 ng/mL.

CYP2B6 Metabolizer Status

Genomic DNA was extracted from whole blood. Genotyping of known functional polymorphisms *CYP2B6* 516G→T (rs3745274, *CYP2B6**6) and 983T→C (rs28399499, *CYP2B6**18) and of infrequent variants with uncertain effects

including rs35303484 (*CYP2B6**11), rs35773040 (*CYP2B6**14), rs2279343 without rs3745274 (*CYP2B6**4), rs35979566 (*CYP2B6**15), and rs3211371 (*CYP2B6**5) was accomplished using TaqMan assays, and the ABI Prism 7900 HT Sequence Detection System. Because few individuals carried the latter variants, genetic analyses were limited to 516G→T and 983T→C. Composite *CYP2B6* genotypes were assigned as follows: “extensive metabolizer” denoted no variant allele at either position 516 or 983; “intermediate metabolizer,” a single variant allele at either position 516 or 983; “slow metabolizer,” 2-variant alleles (ie, either 516 TT, 983 CC, or 516 GT with 983 TC).¹⁸

PK and Statistical Analyses

Sample Size

It was estimated that a sample size of 28 volunteers would achieve 80% power to test whether or not coadministration of efavirenz resulted in a single-dose bedaquiline area under the time-concentration curve (AUC) that differed from that observed with bedaquiline alone by $\geq 20\%$, assuming a bedaquiline coefficient of variance of 35% and a significance level of 0.05 using a 2-sided paired-sample *t* test. Sample size was increased to 35 to account for inefficiencies associated with using nonparametric tests and the possibility of unusable assay results after study closure.

PK and Statistical Evaluation

Bedaquiline and efavirenz PK parameters, including AUC, maximum plasma concentration (C_{max}), half-life ($T_{1/2}$), and oral clearance (CL/F) were calculated using standard non-compartmental methods performed in SAS and confirmed using WinNonLin software, version 6.1 (Pharsight, Cary, NC). Specifically, CL/F was estimated as dose/AUC_{0–336 h}. Also, bedaquiline has triphasic elimination, so $T_{1/2}$ reported here represents average $T_{1/2}$ over the 336-hour PK sampling period; that is, $T_{1/2}$ was estimated using the best-fitting log-linear regression model in the drug elimination phase for each participant. Given the long terminal $T_{1/2}$ of bedaquiline, low residual concentrations before the intake of the second dose of bedaquiline were anticipated. Bedaquiline and M2 were non-zero at the time of the second single-dose administration, and corrections for residual concentrations in PK period 2 were performed before PK analysis by subtracting the estimated carryover concentrations from the observed concentrations in PK period 2. Estimated carryover concentrations were obtained by fitting a log-linear model to the concentrations observed during the terminal elimination phase of the first single dose. Statistical analyses for the study objectives were based on nonparametric tests, and the *P* values for these Wilcoxon signed-rank tests comparing PK of bedaquiline coadministered with efavirenz to bedaquiline alone are reported. Calculated geometric means of ratios (GMR) and 90% confidence interval (CI) were also used to compare PK parameter estimates of bedaquiline alone and in the presence of steady-state efavirenz. M2 PK estimation and comparisons were performed using similar procedures. Efavirenz PK parameters were estimated using standard noncompartmental

methods, and descriptive statistics of efavirenz PK parameters were summarized by *CYP2B6* genotype status.

RESULTS

Subjects

Thirty-seven subjects were enrolled and received the first dose of bedaquiline. The median age was 44 years (range 19–62), and 34 (92%) were male. The median weight and body mass index were 82.9 kg (range 57–119) and 26 (19–36), respectively. Twenty-six (70%) participants were white, non-Hispanic; 8 (22%) were black, non-Hispanic; 2 (5%) were Hispanic; and 1 (3%) was Asian. Of the 37, 1 was removed from the study for missing study visits, 1 withdrew for personal reasons (relocation), 1 was discontinued for study drug nonadherence, and 1 developed grade-3 serum transaminase elevations, prompting study drug discontinuation. Thirty-three participants were, thus, eligible for analysis of PK endpoints.

Effect of Efavirenz on Bedaquiline and M2 PKs

Figure 2 shows the mean (SE) single-dose bedaquiline and M2 log-transformed plasma concentration–time curves for single doses of bedaquiline 400 mg taken alone [pharmacokinetic period 1, (PK1)] or with steady-state efavirenz 600 mg daily [pharmacokinetic period 2, (PK2)]. The median bedaquiline $AUC_{0-336\text{ h}}$ was 58,155 $\text{ng}\cdot\text{hr}\cdot\text{mL}^{-1}$ for bedaquiline alone and 52,135 $\text{ng}\cdot\text{hr}\cdot\text{mL}^{-1}$ for bedaquiline coadministered with efavirenz ($P < 0.001$) (Table 1). The $AUC_{0-336\text{ h PK2}}$: $AUC_{0-336\text{ h PK1}}$ GMR was 0.82 (90% CI: 0.75 to 0.89). Oral clearance of bedaquiline was increased with concomitant efavirenz, whereas bedaquiline C_{max} was not significantly affected. The median M2 C_{max} was 42.4 ng/mL for bedaquiline alone and 83.3 ng/mL for bedaquiline coadministered with efavirenz ($P < 0.001$) (Table 1). The ratio of C_{maxPK2} to C_{maxPK1} GMR was 1.89 (90% CI: 1.65 to 2.15). The $AUC_{0-336\text{ h}}$ of M2, however, did not differ significantly between the 2 PK periods. Our analyses suggested a nonsignificant trend toward inverse correlations between efavirenz $AUC_{0-24\text{ h}}$ values and change from period 1 to period 2 in $AUC_{0-336\text{ h}}$ values for bedaquiline ($r = -0.34$, $P = 0.053$) and M2 ($r = -0.3$, $P = 0.089$; see **Figure, Supplemental Digital Content 1**, <http://links.lww.com/QAI/A238>).

Efavirenz PKs

Median (IQR) $AUC_{0-24\text{ h}}$ for efavirenz was 56.87 $\mu\text{g}\cdot\text{hr}\cdot\text{mL}^{-1}$ (42.27–74.99), C_{max} was 3.98 $\mu\text{g/mL}$ (3.32–5.49), and C_{min} was 1.58 $\mu\text{g/mL}$ (1.04–2.06). These values are similar to mean steady-state parameters reported among HIV-infected adults (58.09 $\mu\text{g}\cdot\text{hr}\cdot\text{mL}^{-1}$, 4.07 $\mu\text{g/mL}$, and 1.77 $\mu\text{g/mL}$, respectively).²² Among the 33 study participants eligible for PK analysis, 3 (9%) had *CYP2B6* slow metabolizer genotypes (2 with 516TT, 1 with 516GT/983TC), 12 (36%) intermediate metabolizer genotypes (10 with 516GT, 2 with 983TC), and 18 (55%) extensive metabolizer genotypes. Median efavirenz concentrations stratified by *CYP2B6*

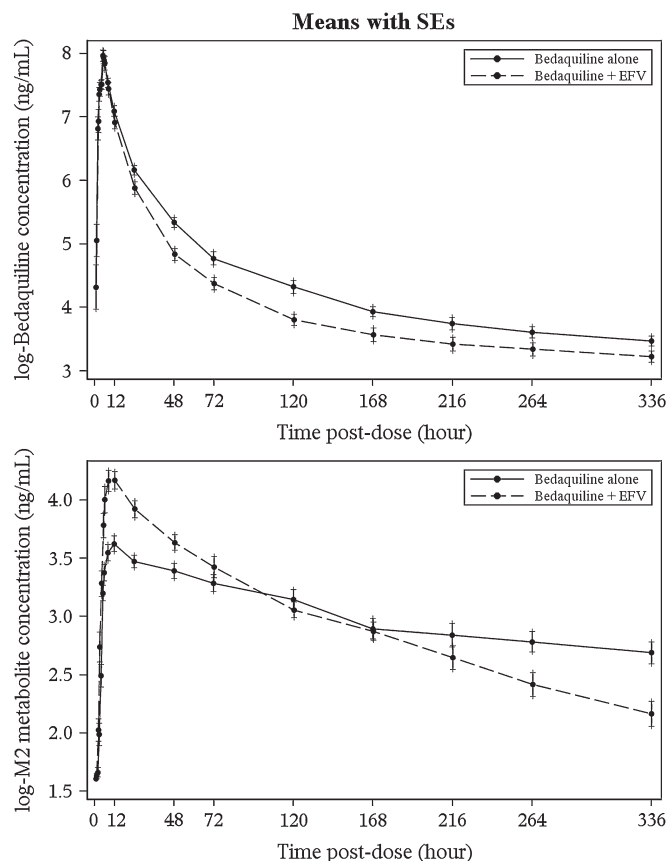


FIGURE 2. Mean bedaquiline (top panel) and M2 (bottom panel) plasma concentration versus time curve after single dose of bedaquiline dosed at 400 mg alone (solid line) and single-dose bedaquiline given together with steady-state efavirenz (dashed line). Values shown represent means with standard error.

genotype are shown in Table 2 and Figure 3. Efavirenz $C_{24\text{ h}}$ values among *CYP2B6* extensive, intermediate, and slow metabolizers in the present study were similar to previously described steady-state $C_{24\text{ h}}$ values stratified by *CYP2B6* metabolizer genotype among HIV-infected adults.²³

Safety and Tolerability of Single-dose TMC With Steady-State Efavirenz

Grade 2 or higher clinical or laboratory adverse events are reported in the supplemental Table (see **Supplemental Digital Content 2**, <http://links.lww.com/QAI/A239>). There were no serious adverse events and no clinical adverse events of grade 3 or higher. One subject developed grade-2 serum transaminase elevations 14 days after the first dose of bedaquiline that increased to grade 3 on the first day of efavirenz dosing, prompting discontinuation of study drug. Another developed grade-3 hypoglycemia, while taking efavirenz, which resolved without specific intervention. Mean increase in QT interval corrected for heart rate using Fridericia's formula (QTcF) from baseline to 4–6 hours after the first and second bedaquiline doses was 12.3 milliseconds (95% CI: 6.92 to 17.6) and 12.8 milliseconds (95% CI: 7.49 to 18.1),

TABLE 1. PK Parameters of Bedaquiline and its M2 Metabolite When Bedaquiline is Administered Alone (Single Oral Dose of 400 mg) or Coadministered With Steady-State Efavirenz (Efavirenz at a Dose of 600 mg by Mouth Daily)

PK Parameter	Alone*	With Efavirenz*	GMR†	90% CI	P‡
Bedaquiline					
AUC _{0–336 h} (ng·hr·mL ⁻¹)	58155 (42222–78249)	52135 (39868–62528)	0.82	(0.75 to 0.89)	<0.001
C _{max} (ng/mL)	3390 (2420–4290)	3708 (2716–4529)	1.00	(0.88 to 1.13)	0.88
T _{max} (hr)	5.0 (5.0–6.0)	5.0 (5.0–5.0)	0.95	(0.85 to 1.07)	0.25
T _{1/2} (hr)	51.1 (48.7–55.3)	47.5 (43.5–53.0)	0.92	(0.88 to 0.97)	0.006
CL/F (L/hr)	6.88 (5.11–9.47)	7.67 (6.40–10.03)	1.22	(1.12 to 1.33)	<0.001
M2 metabolite					
AUC _{0–336 h} (ng·hr·mL ⁻¹)	7432 (6189–9753)	8542 (6274–10589)	1.07	(0.97 to 1.19)	0.295
C _{max} (ng/mL)	42.4 (34.9–50.3)	83.3 (56.2–107.9)	1.89	(1.66 to 2.15)	<0.001
T _{max} (hr)	12 (8.0–12)	8.0 (8.0–12)	0.73	(0.55 to 0.97)	0.080
T _{1/2} (hr)	231.3 (207.6–321.1)	100.44 (87.8–142.8)	0.50	(0.38 to 0.53)	<0.001
CL/F (L/hr)	53.9 (41.0–64.6)	46.8 (37.8–63.8)	0.93	(0.84 to 1.03)	0.295

*Values are medians (IQR).

†GMR of PKs of bedaquiline coadministered with efavirenz to bedaquiline alone.

‡The P value of Wilcoxon signed-rank test comparing PKs of bedaquiline coadministered with efavirenz to bedaquiline alone.

respectively. One subject had a QTcF that was 450 milliseconds after the second bedaquiline dose, and another had a QTcF that was 452 after the first dose and 450 after the second dose (all were grade-1 toxicities), but all other postdose QTcF were below the upper limit of normal (450 milliseconds by Fredericia). There were no statistically significant associations between bedaquiline or M2 C_{max} and changes in QTcF for either bedaquiline dose administration period.

DISCUSSION

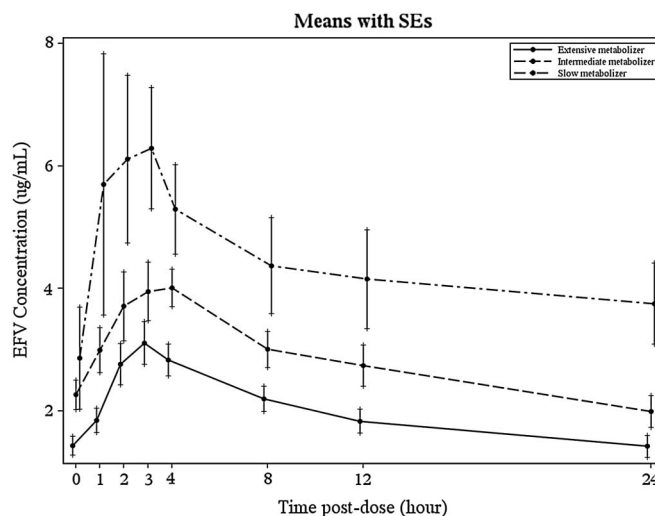
Coinfection with HIV-1 and *M. tuberculosis* is common, and concurrent treatment is now recommended.^{24,25} The widely prescribed ARV efavirenz can induce CYP3A isoforms, and the promising investigational agent for TB, bedaquiline, is a CYP3A substrate. The most important finding from the present study is that steady-state efavirenz

reduced the AUC of bedaquiline by only a median of about 20%. Although the C_{max} of the M2 metabolite was increased almost 90%, the AUC of M2 was unchanged. That efavirenz coadministration results in only a modest decrease in bedaquiline exposure is reassuring, given that drug–drug interactions can be problematic during treatment of TB/HIV coinfection and limit therapeutic options for HIV-infected patients with TB. Safety implications of higher peak concentrations of the M2 metabolite, however short-lived, are unclear.

The clinical consequences of diminished bedaquiline concentrations for patients receiving bedaquiline-containing multidrug therapy for the treatment of TB are not known, but the change associated with efavirenz coadministration is modest and unlikely to be clinically relevant. Pharmacodynamic targets for bedaquiline have not been well established, but preclinical and clinical data do suggest dose-response relationships. In dose-ranging monotherapy studies in the

TABLE 2. Summary of Efavirenz PK Parameters for A5267 Study Participants, by CYP2B6 Metabolizer Status

PK parameter	Metabolizer Status	N	Median (IQR)
AUC _{0–24 hr} (μg/mL)	Extensive	18	46.50 (32.78–57.99)
	Intermediate	12	65.31 (49.48–84.36)
	Slow	3	99.50 (74.99–143.3)
C ₂₄ (μg/mL)	Extensive	18	1.33 (0.89–1.72)
	Intermediate	12	3.06 (1.47–2.46)
	Slow	3	3.71 (2.62–4.93)
C _{max} (μg/mL)	Extensive	18	3.84 (2.36–40.2)
	Intermediate	12	4.66 (3.59–5.81)
	Slow	3	5.94 (4.88–9.95)
CL/F (L/hr)	Extensive	18	12.9 (10.3–18.3)
	Intermediate	12	9.19 (7.11–12.2)
	Slow	3	6.03 (4.19–8.00)
T _{1/2} (hr)	Extensive	18	15.0 (13.2–19.7)
	Intermediate	12	16.6 (14.5–23.9)
	Slow	3	25.5 (25.3–32.8)

**FIGURE 3.** Mean (SE) efavirenz plasma concentrations versus time curves, stratified by CYP2B6 metabolizer genotype.

mouse acute infection model, bedaquiline at 6.5 mg/kg delivered 5 times per week was bacteriostatic, and a dose increase from 12.5 mg/kg to 25 mg/kg yielded a one-log decline in lung colony-forming units after 4 weeks.^{7,26} More recent dose-fractionation studies in the mouse acute infection model have shown a dose-response relationship between bedaquiline dose and lung colony-forming unit counts when doses from 8 to 64 mg/kg were tested, and the effects appeared to be concentration-dependent (personal communication, Dr Koen Andries, August 31, 2011). The optimal effect of bedaquiline in the mouse model was at plasma concentrations of approximately 0.3 mcg/mL, achieved with about 100 mg/kg per week.⁷ However, in mice, 80% of bedaquiline is converted to the M2 metabolite, whereas in humans, the circulating M2 to bedaquiline ratio is 1:4. Given that M2 is 3-fold to 6-fold less active against *M. tuberculosis* than bedaquiline, PK/pharmacodynamic targets may differ in mice and humans. In a 7-day early bactericidal activity study of bedaquiline monotherapy in humans, doses up to 200 mg daily showed no demonstrable activity, but 400 mg daily resulted in late declines in daily sputum colony counts.²⁷ When given in multidrug regimens for MDR-TB, a dose of 400 mg once daily for 2 weeks followed by 200 mg thrice weekly achieved plasma concentrations above 600 ng/mL throughout the dosing interval, a target that may achieve therapeutic efficacy similar to 25 mg/kg in mice.¹⁴ No correlation between average bedaquiline concentration and outcomes, however, was seen in this phase 2 study, so target concentrations in humans remain uncertain.

Bedaquiline is a cationic amphiphilic drug, as defined by a hydrophobic ring structure plus a hydrophilic side chain with a charged cationic amine group. Cationic amphiphilic drugs can cause phospholipidosis, characterized by the accumulation of phospholipids in cells.²⁸ Phospholipidosis is thought to be an adaptive response rather than a manifestation of direct cellular toxicity, but phospholipidosis can have clinical consequences, including prolonged QT interval, myopathy, hepatotoxicity, nephrotoxicity, or pulmonary dysfunction.²⁹ These effects are generally reversible with drug discontinuation. There is no reliable biomarker predictive of drug-related phospholipidosis, and animal models do not seem to predict human responses well, posing regulatory challenges.³⁰ In vitro, M2 was a stronger inducer of phospholipidosis than amiodarone, and M2 induced phospholipidosis at lower concentrations than bedaquiline (1.2 μ M vs. 7.3 μ M, respectively).³¹ Concentrations of M2 in our study were far lower than those that produced phospholipidosis in in vitro models (C_{\max} of 83.3 ng/mL = 0.154 μ M), but these were not steady-state concentrations. In the current study, ECGs were performed 4–6 hours after each single dose of bedaquiline. In a post hoc analysis in this small dataset, there was no correlation between change in QTcF from baseline and either AUC or C_{\max} for bedaquiline or M2. Although QT interval corrected for heart rate was slightly prolonged with both doses of bedaquiline, all but 2 subjects had ECGs with intervals within the normal range (<450 milliseconds).

Bedaquiline is primarily metabolized via oxidative N-demethylation to M2, and this biotransformation is largely catalyzed by CYP3A. M2 can be further N-demethylated to

M3 or, alternatively, oxidized to M4. In this study, when efavirenz was coadministered with bedaquiline, M2 concentrations were initially increased resulting in a higher C_{\max} , but clearance of M2 also seemed to be enhanced, leading to similar overall M2 exposures, or $AUC_{0-336\text{ h}}$. This could be explained by increased velocity and capacity of enzymatic transformation of bedaquiline to M2 in the setting of efavirenz coupled with induction of further biotransformation of M2 to a secondary metabolite. M3 or M4 concentration–time data would be needed to confirm this. If M2 is both formed and cleared more rapidly with concomitant efavirenz, steady-state M2 C_{\max} is unlikely to be higher when bedaquiline is given with efavirenz than when bedaquiline is given alone. To test this assumption, nonlinear mixed effects modeling is underway to estimate steady-state M2 parameters using these single-dose data and taking into account triphasic bedaquiline elimination and M2 metabolite kinetics.

Efavirenz is a substrate of CYP2B6 and CYP3A and also induces these metabolizing enzymes, resulting in auto-induction of metabolism and diminished efavirenz concentrations with multiple dosing.³² The *CYP2B6* polymorphisms 516G \rightarrow T and 983T \rightarrow C predict decreased plasma clearance and increased steady-state efavirenz exposure.¹⁸ In the present study, as expected, plasma efavirenz exposure was strongly associated with *CYP2B6* metabolizer genotype. The PKs of efavirenz should not be affected by bedaquiline. It is therefore reassuring that, within each *CYP2B6* genotype group, efavirenz PK parameters were similar to previously reported values.²² In drug–drug interaction studies that involve efavirenz, it is important to determine *CYP2B6* metabolizer genotypes of study participants so as to more accurately interpret efavirenz PK parameters. In addition, results from participants with *CYP2B6* slow, intermediate, and extensive metabolizer genotypes suggest that our findings are generalizable regardless of *CYP2B6* genotype. This is important because *CYP2B6* slow metabolizer genotypes vary in frequency depending on geographic region of ancestry and are most frequent among populations of African descent.³³ There is a correlation between efavirenz AUC and hepatic CYP3A induction, but the dose or clinical exposure at which maximal induction is achieved is unknown.³⁴

There are several limitations of this study. Because bedaquiline was given as 2 single doses, the full safety and tolerability profile of bedaquiline with efavirenz could not be assessed. Although M2 is eliminated more rapidly when bedaquiline is given with efavirenz, it is unknown whether this represents increased metabolism of M2 to a secondary metabolite or another process because we did not measure other metabolites. Rifampin reduces bedaquiline concentrations by 50%.³⁵ Because the mechanism by which efavirenz induces CYP3A has not been fully elucidated,³⁶ it is unclear whether efavirenz would further diminish bedaquiline concentrations among patients who are also receiving concomitant rifampin. Finally, although we found no clear association between efavirenz concentrations and change in bedaquiline exposures, we studied relatively few individuals with *CYP2B6* slow metabolizer genotypes; trends seen in our analyses would need to be confirmed in a larger group of patients.

In conclusion, bedaquiline concentrations were only modestly reduced when bedaquiline was given together with efavirenz, a decrease that is unlikely to be clinically significant. Peak concentrations of the M2 metabolite were increased in this single-dose study, but once formed, M2 seems to be more rapidly cleared in the setting of efavirenz, and this will likely result in steady-state concentrations of M2 that do not significantly differ when bedaquiline is given with or without efavirenz. The present study indicates that efavirenz should not compromise the therapeutic efficacy of bedaquiline against TB. Further analyses will be needed to understand the implications, if any, of the effects of efavirenz on M2 metabolite PK.

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