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Evaluation of the Pharmacokinetic Interaction between Repeated Doses of Rifapentine or Rifampin and a Single Dose of Bedaquiline in Healthy Adult Subjects

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This study assessed the effects of rifapentine or rifampin on the pharmacokinetics of a single dose of bedaquiline and its M2 metabolite in healthy subjects using a two-period single-sequence design. In period 1, subjects received a single dose of bedaquiline (400 mg), followed by a 28-day washout. In period 2, subjects received either rifapentine (600 mg) or rifampin (600 mg) from day 20 to day 41, as well as a single bedaquiline dose (400 mg) on day 29. The pharmacokinetic profiles of bedaquiline and M2 were compared over 336 h after the administration of bedaquiline alone and in combination with steady-state rifapentine or rifampin. Coadministration of bedaquiline with rifapentine or rifampin resulted in lower bedaquiline exposures. The geometric mean ratios (GMRs) and 90% confidence intervals (CIs) for the maximum observed concentration (C_{max}), area under the concentration-time curve to the last available concentration time point (AUC_{0-t}), and AUC extrapolated to infinity (AUC_{0-inf}) of bedaquiline were 62.19% (53.37 to 72.47), 42.79% (37.77 to 48.49), and 44.52% (40.12 to 49.39), respectively, when coadministered with rifapentine. Similarly, the GMRs and 90% CIs for the C_{max}, AUC_{0-t}, and AUC_{0-inf} of bedaquiline were 60.24% (51.96 to 69.84), 41.36% (37.70 to 45.36), and 47.32% (41.49 to 53.97), respectively, when coadministered with rifampin. The C_{max}, AUC_{0-t}, and AUC_{0-inf} of M2 were also altered when bedaquiline was coadministered with rifapentine or rifampin. Single doses of bedaquiline, administered alone or with multiple doses of rifapentine or rifampin, were well tolerated, with no safety concerns related to coadministration. Daily administration of rifapentine to patients with tuberculosis presents the same drug interaction challenges as rifampin and other rifamycins. Strong inducers of the cytochrome P450 isoenzyme CYP3A4 should be avoided when considering the use of bedaquiline. (This study is registered at clinicaltrials.gov under identifier NCT02216331.)

Bedaquiline (formerly TMC207 and R207910) is a diarylquinoline antitubercular compound that specifically inhibits ATP synthase in *Mycobacterium tuberculosis* (1). It was approved by the U.S. FDA as part of combination therapy for the treatment of multidrug-resistant pulmonary tuberculosis (TB) on 28 December 2012 (2). The U.S. FDA-approved bedaquiline drug label has a black box highlighting an increased risk of death and QT prolongation (3). *In vitro*, bedaquiline potently inhibits both drug-sensitive and drug-resistant *M. tuberculosis* isolates (4, 5) and is also bactericidal against nonreplicating tubercle bacilli (6). In the murine model of tuberculosis, bedaquiline alone showed improved clearance of bacilli over the combination of isoniazid, rifampin, and pyrazinamide, while bedaquiline and pyrazinamide in combination revealed a synergistic interaction that accelerated the clearance of bacilli (7). Since rifampin is currently considered one of the most important so-called sterilizing TB drugs, it was critical to further understand whether a bedaquiline-rifamycin combination should be considered for improved therapeutic efficacy.

CYP3A4 is the major cytochrome P450 (CYP450) isoenzyme involved in the metabolism of bedaquiline and the formation of its major *N*-monodesmethyl metabolite, M2, which is 4 to 6 times less active in terms of antimycobacterial potency. *In vitro*, bedaquiline does not significantly inhibit the activity of the CYP450 enzymes CYP1A2, CYP2A6, CYP2C8, -9, -10, and -19, CYP2D6, CYP2E1, CYP3A4 and -5, and CYP4A, nor does it induce CYP1A2, CYP2C9 or -19, or CYP3A4 activities (3). Rifampin and rifapentine are both inducers of a variety of enzymes, including CYP3A4, CYP1A2, CYP2C9, and CYP2D6. Other proteins induced are glucuronyl transferase and *p*-glycoprotein. The relative ranking of commonly used rifamycins in terms of CYP3A4 enzyme induction potential is rifampin, followed by rifapentine, and finally, rifabutin (8). Given that bedaquiline is metabolized mainly via CYP3A, there is a potential for drug interactions during coadministration of bedaquiline with CYP3A inducers or inhibitors (9). A previous clinical drug interaction study of a single dose of 300 mg of bedaquiline and steady-state 600-mg dosing of rifampin in healthy subjects found that the exposure (area under the concentration-time curve [AUC]) to bedaquiline was reduced by 52% (90% confidence interval [CI], 46 to 57) (9).

However, the extent of the drug interaction between rifampin and bedaquiline was considered to be underestimated, as the enzyme induction effect of rifampin was not maintained by contin-

Received 26 August 2014 **Returned for modification** 25 September 2014
Accepted 28 November 2014

Accepted manuscript posted online 15 December 2014

Citation Winter H, Egizi E, Murray S, Erondu N, Ginsberg A, Rouse DJ, Severynse-Stevens D, Pauli E. 2015. Evaluation of the pharmacokinetic interaction between repeated doses of rifapentine or rifampin and a single dose of bedaquiline in healthy adult subjects. Antimicrob Agents Chemother 59:1219–1224. doi:10.1128/AAC.04171-14.

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doi:10.1128/AAC.04171-14

Period 1 – Bedaquiline Single Dose (Groups 1 (n = 16) and 2 (n=16))		Period 2 – Rifapentine (Group 1 (n =16)) and Rifampin (Group 2 (n=13))	
Screening and Checking	Single Dose of Bedaquiline (400 mg) on Day 1	Screening and Checking	Daily Doses of Rifapentine (600 mg) or Rifampin (600 mg) and on Day 29 a Single dose of Bedaquiline (400 mg)
Day -1	Days 1-18	Day 19	Days 20-41

FIG 1 Study design and subject disposition.

ued dosing during the long terminal elimination phase of bedaquiline (terminal elimination half-life, 5.5 months [3]). Thus, the present study was designed to assess the effect of repeated daily doses of rifapentine or rifampin on the pharmacokinetics (PK) of a single dose of bedaquiline and its "M2" metabolite and to compare whether rifapentine affected the PK of bedaquiline to a lesser extent than rifampin (the study is registered at clinicaltrials.gov under identifier NCT02216331).

The FDA-approved drug label for bedaquiline stipulates that bedaquiline coadministration with strong CYP3A4 inducers used systemically should be avoided (3). Rifampin has been regarded as a more potent enzyme inducer than rifapentine in the clinic (8), even though both drugs have similar binding affinities (50% effective concentration [EC_{50}]) for human pregnane X receptor (hPXR) transcription activator (EC_{50} of 1.19 μM and 1.63 μM, respectively) and a similar ability to maximally transactivate hPXR *in vitro* (10). In contrast, while rifabutin has a similar affinity for hPXR (EC_{50} of 0.76 μM), it has a lower potential to maximally activate hPXR and requires much lower plasma concentrations for efficacy relative to the EC_{50} than rifampin and rifapentine, all of which likely account for a lack of reports consistent with significant enzyme induction by rifabutin in the clinic (8, 10). The predicted induction potencies when rifampin, rifapentine, and rifabutin are ranked according to their reported efficacious maximum observed concentration (C_{max}) are 100%, 82%, and 50%, respectively (11). Rifapentine is a recognized inducer of CYP3A4 and CYP2C8 and -9, and the extent of induction observed is dependent on both dose and dose frequency (12). The FDA-approved rifapentine dose administration for the treatment of tuberculosis, as part of a multidrug regimen, is 600 mg administered twice weekly for the first 2 months of therapy, followed by 600 mg administered once weekly for an additional 4 months (12). However, as part of efforts to optimize drug therapy for tuberculosis, rifapentine daily dosing regimens are also being explored (13, 14).

MATERIALS AND METHODS

Study design. This was a phase 1, open-label, single-center, two-period, single-sequence, drug interaction study performed in two groups to evaluate the safety, tolerability, and effect of repeated doses of rifapentine or rifampin on the PK of a single dose of bedaquiline. Healthy adult subjects were chosen to avoid the multiple issues associated with the administration of ineffective therapy to patients. Single doses of bedaquiline were administered in a fixed-sequence design in order to minimize safety concerns that might arise from the administration of a drug with such a long terminal half-life. The clinical study was conducted by Celerion, Inc. (formerly MDS Pharma Services, Inc.), in Lincoln, NE. Figure 1 outlines the study design and subject disposition.

Period 1 examined the PK of bedaquiline and M2 in the absence of rifapentine and rifampin. On day 1, subjects received a single 400-mg dose of bedaquiline (four 100-mg tablets) with food following an overnight fast. Subjects were confined to the clinic from the morning of day −1 through the morning of day 2 and visited the clinic for a daily blood draw on days 3 through 15. On day 15, the subjects had an additional blood draw for safety assessments, urinalysis and urine drug screen, triplicate electrocardiograms (ECGs), and screening of vital signs. Period 2 examined the effects of repeated doses of either rifapentine or rifampin on the PK of bedaquiline and M2. After returning to the clinic on day 19 (study day 20), subjects began their 600-mg (four 150-mg tablets) intake of rifapentine (group 1) or rifampin (group 2) once daily for 22 days. In compliance with the label and to ensure maximum exposure, rifapentine was administered with food, whereas rifampin was administered fasted except on day 29, when it was administered with food due to coadministration with the single 400-mg dose of bedaquiline. The subjects were discharged on day 30 and returned to the clinic daily for a blood draw on days 31 through 43. On days 30, 36, and 43, the subjects had an additional blood draw for safety assessments, urinalysis, and urine drug screen (days 36 and 43), triplicate ECGs, and vital sign screening.

Subjects. Healthy male and female adult volunteers were recruited and separated equally into groups 1 and 2. Subjects were medically healthy based on a prescreening medical evaluation and history that revealed the absence of any clinically relevant abnormality. The prescreening medical evaluation included a physical examination, ECG, vital sign screening, blood biochemistry results, hematology tests, and urinalysis. At both screening and check-in, subjects were to have negative urine test results for alcohol and other drugs of abuse.

Subjects were excluded if they had laboratory abnormalities noted based on the adult toxicity table of the Division of Microbiology and Infectious Disease, National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIAID, NIH) (15), which included the following: serum creatinine grade 1 or greater (>1.0 times the upper limit of normal [ULN]), pancreatic lipase grade 1 or greater (>1.0 times ULN), hemoglobin grade 1 or greater (≤10.5 g/dl), platelet count grade 1 or greater (≤99,000/mm^3), absolute neutrophil count grade 1 or greater (≤1,500/mm^3), aspartate aminotransferase (AST) or alanine aminotransferase (ALT) grade 1 or greater (>1.0 times ULN), total bilirubin grade 1 or greater (>1.0 times ULN), and any other toxicity of grade 2 or above, including proteinuria (spot urine) >1 plus and gross hematuria.

At screening, subjects were also excluded if their QTcF interval (QT interval with Fredericia correction) was >450 ms (based on the average of the triplicate ECGs) or if any other ECG abnormalities, such as arrhythmia, ischemia, or evidence of heart failure, were evident. Furthermore, subjects were excluded if there was the use of concomitant medication, including over-the-counter products and dietary supplements, except for ibuprofen and paracetamol, up to 7 days before the first dose of trial medication, and all prescribed medication must have been discontinued at least 14 days before the first intake of trial medication. Female subjects were excluded except if postmenopausal for more than 2 years, posthysterectomy, or postsurgical sterilization.

All subjects provided written informed consent prior to participation in the study. The study protocol and consent forms were reviewed and approved by Celerion's Institutional Review Board and were constituted and conducted in accordance with U.S. Code of Federal Regulations (21 CFR Parts 50, 56, and 312) principles and requirements and International Conference on Harmonisation guidelines (ICH E6).

Sampling. For period 1, blood samples for bedaquiline and M2 PK were collected predose and at 1, 2, 3, 4, 5, 6, 8, 12, and 24 h and every 24 h thereafter from day 3 (48 h after bedaquiline) through day 15 (336 h after

bedaquiline). For period 2, blood samples for PK were collected on days 20, 27, 28, and 29 prior to receiving a dose of either rifapentine or rifampin, with an additional sample collected predose on day 20 for bedaquiline. On day 29, the day bedaquiline was coadministered with either rifapentine or rifampin, PK blood sampling for bedaquiline and M2 was performed predose and at 1, 2, 3, 4, 5, 6, 8, 12, and 24 h and every 24 h thereafter from day 31 (48 h after bedaquiline) through day 43 (336 h after bedaquiline).

Bioanalytical methods. Blood samples were collected and centrifuged, and plasma was separated and stored at −20°C for bedaquiline and M2 and at −70°C for rifapentine, desacetyl rifapentine, rifampin, and desacetyl rifampin prior to analysis. Plasma samples were analyzed for bedaquiline, M2, rifapentine, desacetyl rifapentine, rifampin, and desacetyl rifampin using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods developed at PRA International Early Development Services Bioanalytical Laboratory, The Netherlands. The lower limit of quantitation for bedaquiline and M2 was 1.00 ng/ml; for rifapentine and rifampin, it was 0.200 μg/ml; and for desacetyl rifapentine and desacetyl rifampin, it was 0.100 μg/ml. The accuracy and precision for each bioanalytical method was ≤15.0% (20% at the lower level of quantification).

Pharmacokinetic analysis. Bedaquiline and M2 PK parameters were calculated for each subject when bedaquiline was dosed alone and in combination with either rifampin or rifapentine by applying a noncompartmental approach using WinNonlin professional version 5.2 (Pharsight Corp., Mountain View, CA). The key PK parameters calculated for bedaquiline and M2 were C_{max}, time at which C_{max} occurs (T_{max}), terminal elimination rate constant (k_{el}), elimination half-life ($t_{1/2}$), area under the concentration-time curve to the last available concentration time point (AUC_{0-t}), and AUC extrapolated to infinity (AUC_{0-inf}).

Descriptive statistics were calculated for PK parameters. The PK endpoints C_{max}, AUC_{0-t}, and AUC_{0-inf} for bedaquiline and M2 were compared between bedaquiline dosed alone and bedaquiline administered with either rifampin or rifapentine using an analysis of variance (ANOVA) model. The ANOVA model using the SAS PROC mixed procedure included treatment as a fixed effect and subject as a random effect. It was planned that 16 subjects be enrolled in each treatment group (rifampin or rifapentine) to ensure that 14 subjects completed treatment in each group. The geometric least-squares means (LS means) were calculated by exponentiation of the LS means from the ANOVA, and the exponentiated differences between LS means are presented as geometric mean ratios (GMRs). Consistent with the 2 one-sided tests approach to the assessment of relative bioavailability, the endpoints for each of the designated treatments were the 90% confidence intervals (CIs) for the GMRs that are derived from the analyses of the ln-transformed PK parameters C_{max}, AUC_{0-t}, and AUC_{0-inf}. If the GMRs (rifapentine effect over rifampin effect) for bedaquiline AUC and C_{max} were 1.26 and 1.38, respectively, then the study had 80% power to yield a 90% CI for each GMR (for AUC and for C_{max}) that would be >1.0. This would have indicated statistically significantly greater bedaquiline AUC and C_{max} during coadministration of rifapentine than during coadministration of rifampin (alpha = 0.05, one sided).

Safety evaluation. Safety assessments included physical examinations, vital signs, ECGs, hematology, serum chemistry, coagulation, and urinalysis. Laboratory samples were collected at screening and on days −1, 2, and 15 of period 1 to assess bedaquiline alone. For period 2, laboratory samples for safety assessments were collected on days 19, 21, 23, and 28 (rifapentine or rifampin alone), days 30, 36, and 43 (bedaquiline with rifapentine or bedaquiline with rifampin), and day 57 (follow-up). Twelve-lead ECGs were performed in triplicate, with the inter-ECG intervals being 30 to 180 s for each subject, at screening and days 1, 2, and 15 in period 1 and days 24, 29, 30, 36, 43, and 57 for period 2. On days 1 and 29, ECGs were collected predose (within 30 min before start of breakfast) and at 4 h postdose.

The frequency and severity of adverse events (AEs) were assessed on a

TABLE 1 Summary of plasma bedaquiline and M2 pharmacokinetic parameters

Parameter[a]	Arithmetic mean ± SD or median (minimum, maximum) for the indicated analyte in samples from:							
	Group 1				Group 2			
	Period 1, bedaquiline alone		Period 2, bedaquiline + rifapentine		Period 1, bedaquiline alone		Period 2, bedaquiline + rifampin	
	Bedaquiline	M2	Bedaquiline	M2	Bedaquiline	M2	Bedaquiline	M2
C_{max} (ng/ml)	3,500.6 ± 1,116.71 (*n* = 16)	35.25 ± 7.130 (*n* = 16)	2,192.5 ± 738.29 (*n* = 16)	65.06 ± 17.814 (*n* = 16)	3,828.0 ± 1,003.46 (*n* = 15)	33.55 ± 7.640 (*n* = 15)	2,335.4 ± 572.55 (*n* = 13)	67.62 ± 19.038 (*n* = 13)
T_{max} (h)	4.500 (2.00, 6.00) (*n* = 16)	12.001 (6.00, 168.00) (*n* = 16)	2.999 (2.00, 6.00) (*n* = 16)	8.000 (6.00, 23.92) (*n* = 16)	3.000 (2.00, 6.01) (*n* = 15)	11.999 (5.00, 48.00) (*n* = 15)	4.994 (2.00, 6.00) (*n* = 13)	5.999 (4.98, 12.00) (*n* = 13)
AUC_{0-t} (ng · h/ml)	67,192.8 ± 20,160.06 (*n* = 16)	7,086.4 ± 1,522.36 (*n* = 16)	28,517.9 ± 7,070.13 (*n* = 16)	6,060.1 ± 1,318.53 (*n* = 16)	62,866.6 ± 15,841.09 (*n* = 15)	6,551.1 ± 1,750.34 (*n* = 15)	26,165.2 ± 5,559.30 (*n* = 13)	5,136.6 ± 870.47 (*n* = 13)
AUC_{0-inf} (ng · h/ml)	78,626.8 ± 22,017.76 (*n* = 15)	13,960.2 ± 2,848.63 (*n* = 10)	34,758.3 ± 8,470.65 (*n* = 12)	7,837.4 ± 1,973.36 (*n* = 15)	68,733.8 ± 15,170.85 (*n* = 14)	13,199.9 ± 3,925.61 (*n* = 10)	33,046.9 ± 8,114.06 (*n* = 11)	6,497.4 ± 1,043.13 (*n* = 13)
k_{el} (h^{-1})	0.003669 ± 0.000868 (*n* = 15)	0.002137 ± 0.000374 (*n* = 10)	0.003253 ± 0.000552 (*n* = 12)	0.003966 ± 0.000739 (*n* = 15)	0.003914 ± 0.000642 (*n* = 14)	0.002285 ± 0.000457 (*n* = 10)	0.002787 ± 0.001110 (*n* = 11)	0.004330 ± 0.001063 (*n* = 13)
$t_{1/2}$ (h)	198.7 ± 48.60 (*n* = 15)	334.4 ± 65.38 (*n* = 10)	218.8 ± 37.18 (*n* = 12)	180.6 ± 34.90 (*n* = 15)	181.3 ± 28.37 (*n* = 14)	312.2 ± 50.47 (*n* = 10)	279.9 ± 94.06 (*n* = 11)	171.6 ± 53.68 (*n* = 13)
AUCR	0.8651 ± 0.03243	0.5008 ± 0.05056	0.8574 ± 0.04113	0.7668 ± 0.05874	0.8813 ± 0.01938	0.5304 ± 0.07161	0.8258 ± 0.07539	0.7920 ± 0.06949

[a] AUC_{0-t}, area under the concentration-time curve during the dosing interval; AUC_{0-inf}, AUC extrapolated to infinity; AUCR, ratio of AUC_{0-t} to AUC_{0-inf}; C_{max}, maximum observed concentration; $t_{1/2}$, elimination half-life; T_{max}, time at which C_{max} occurs (presented as median then minimum, maximum).

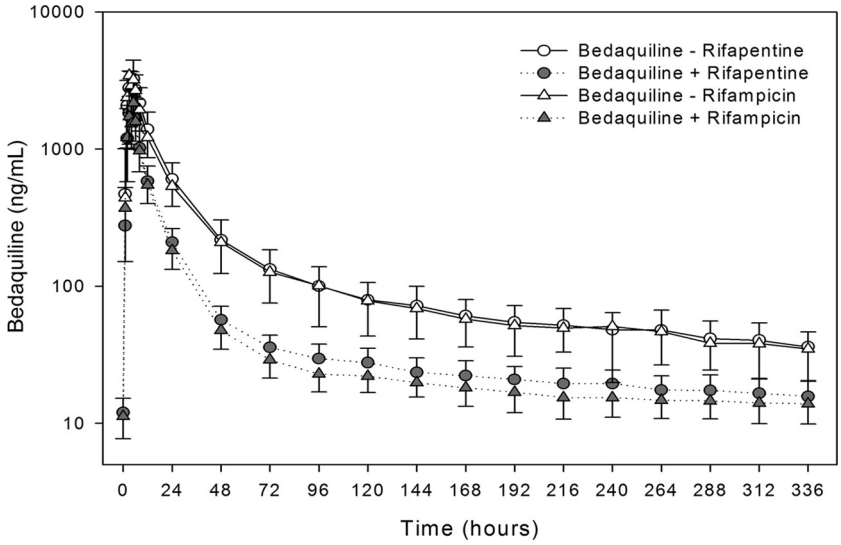

FIG 2 Mean plasma bedaquiline concentrations. Error bars indicate standard deviations (semilog scale).

continual basis throughout the study via safety assessments, observation, direct participant reporting, and specific AE inquiry. AEs were collected and coded using version 12.1 of the *Medical Dictionary for Regulatory Activities* (*MedDRA*) from the time the participant signed the informed consent form until the end of the follow-up visit (study day 57). The principal investigator (PI) reviewed each AE and assessed its relationship to drug treatment. Each sign or symptom reported was graded on a 3-point severity scale (mild, moderate, or severe) and a 3-point frequency scale (single episode, intermittent, or continuous). Additionally, the date and time of onset, time relationship to drug dosing, duration, action taken, and outcome of each AE were recorded.

RESULTS

The study sample consisted of healthy male ($n = 28$) and female ($n = 4$) subjects who were 19 to 55 years of age (mean ± standard deviation, 35.6 ± 11.40 years) and had a body mass index of 19.8 to 31.9 kg/m^2 (mean = 26.15 ± 3.77 kg/m^2). Twenty-eight subjects were white, 2 were black/African American, 1 was Asian, and 1 was American Indian/Alaskan Native.

Pharmacokinetics. Key PK parameters and mean plasma concentrations for bedaquiline and M2 are presented in Table 1. In group 1, the mean bedaquiline C_{max}, AUC_{0-t}, and AUC_{0-inf} were lower and the T_{max} was 1.5 h shorter following bedaquiline plus rifapentine administration than following bedaquiline alone. The mean M2 AUC_{0-t} and AUC_{0-inf} were lower but the C_{max} was greater and the T_{max} 4 h shorter for M2 following bedaquiline plus rifapentine administration than following bedaquiline alone. The mean $t_{1/2}$ of plasma bedaquiline appeared similar regardless of whether bedaquiline was administered alone or with rifapentine. The mean $t_{1/2}$ of M2 was approximately 46% shorter following bedaquiline plus rifapentine coadministration than following rifapentine alone. The mean AUCRs (ratio of AUC_{0-t} to AUC_{0-inf}) for bedaquiline were 0.86 for bedaquiline plus rifapentine and 0.87 for bedaquiline alone, indicating that approximately 14% and 13% of the AUC_{0-inf} calculations, respectively, were extrapolated on average. The mean AUCRs for M2 ranged from 0.77 for bedaquiline plus rifapentine to 0.50 for bedaquiline alone, indicating that approximately 23% and 50% of the AUC_{0-inf} calculations, respectively, were extrapolated on average.

In group 2, the mean bedaquiline C_{max}, AUC_{0-t}, and AUC_{0-inf} were lower and the T_{max} was 2.0 h longer following bedaquiline and rifampin coadministration than following bedaquiline alone. The M2 AUC_{0-t} and AUC_{0-inf} were lower, the C_{max} was greater, and the T_{max} 6.0 h shorter for M2 following bedaquiline and rifampin coadministration than following bedaquiline alone. The mean $t_{1/2}$ M2 was 45% shorter following bedaquiline and rifampin coadministration than following bedaquiline alone. The mean bedaquiline AUCR was 0.83 for bedaquiline and rifampin coadministration and 0.88 for bedaquiline alone, indicating that approximately 17% and 12% of the AUC_{0-inf} calculations, respectively, were extrapolated on average. The mean M2 AUCR ranged from 0.79 for bedaquiline plus rifampin coadministration to 0.53 for bedaquiline alone, indicating that approximately 21% and 47% of the AUC_{0-inf} calculations, respectively, were extrapolated on average.

In general, the mean changes in PK parameters of plasma bedaquiline and M2 following bedaquiline and rifapentine (group 1) were comparable to those following bedaquiline and rifampin (group 2). The results presented in Fig. 2 and 3 reveal the mean plasma bedaquiline and M2 concentrations in a semilog scale from predose through 336 h postdose for both groups and treatment periods.

The GMRs (90% CIs) for the bedaquiline ln-transformed C_{max}, AUC_{0-t}, and AUC_{0-inf} were 62.19% (53.17 to 72.47), 42.79% (37.77 to 48.49), and 44.52% (40.12 to 49.39), respectively, for the comparison of bedaquiline and rifapentine versus bedaquiline alone. The GMRs (90% CIs) for the M2 ln-transformed C_{max}, AUC_{0-t}, and AUC_{0-inf} were 181.71% (164.18 to 201.11), 85.33% (76.23 to 95.52), and 55.20% (48.86 to 63.36), respectively, for the comparison of bedaquiline plus rifapentine versus bedaquiline alone. Similarly, the GMRs (90% CIs) for the bedaquiline ln-transformed C_{max}, AUC_{0-t}, and AUC_{0-inf} were 60.24% (51.96 to 69.84), 41.36% (37.70 to 45.36), and 47.32% (41.49 to 53.97), respectively, for the comparison of bedaquiline and rifampin versus bedaquiline alone. The GMRs (90% CIs) for the M2 ln-transformed C_{max}, AUC_{0-t}, and AUC_{0-inf} were 197.77% (177.71 to 220.10), 79.35% (70.17 to 89.75), and 49.76%

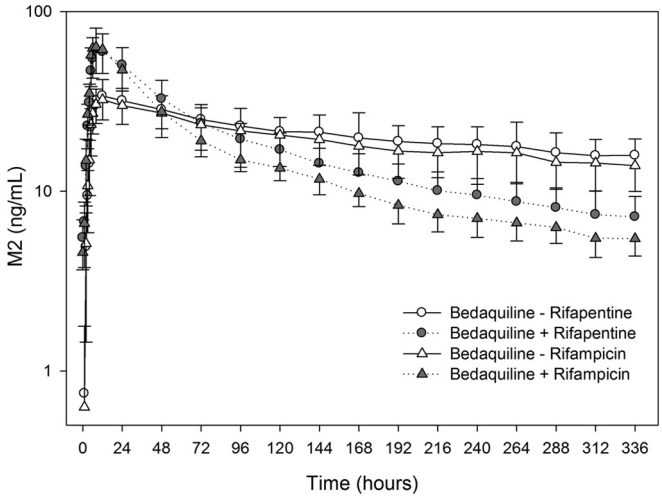

FIG 3 Mean plasma M2 concentrations. Error bars indicate standard deviations (semilog scale).

(42.70 to 57.98), respectively, for the comparison of bedaquiline plus rifampin versus bedaquiline alone. The comparisons of the C_{max}, AUC_{0-t}, and AUC_{0-inf} of bedaquiline when coadministered with rifapentine (group 1) or with rifampin (group 2) versus bedaquiline alone showed that the 90% CIs of the GMRs were outside the prespecified 80% to 125% equivalence range. This indicates that both rifamycins substantially affect the PK of bedaquiline (Table 2).

In comparing the effects of rifapentine and rifampin on bedaquiline and M2, the GMRs (90% CIs) for bedaquiline ln-transformed C_{max}, AUC_{0-t}, and AUC_{0-inf} were 103.89% (84.45 to 127.82), 104.08% (88.89 to 121.87), and 95.45% (80.53 to 113.12). The GMRs (90% CIs) for the rifapentine effect over the rifampin effect on M2 ln-transformed C_{max}, AUC_{0-t}, and AUC_{0-inf} were 92.15% (79.81 to 106.40), 108.33% (92.07 to 127.45), and 114.39% (95.12 to 137.57).

To confirm the attainment of steady state for rifapentine and rifampin, the individual and mean trough plasma levels of rifapentine, desacetyl rifapentine, rifampin, and desacetyl rifampin concentrations were determined on days 27 to 30 and 42. The mean trough rifapentine concentrations remained stable between study days 27 and 30, ranging from 10.60 to 12.04 μg/ml, and dropped to 4.18 μg/ml on study day 42. Similarly, the mean trough desacetyl rifapentine concentrations remained stable between days 27 and 30, ranging from 12.41 to 15.16 μg/ml, and dropped to 3.98 μg/ml on study day 42. The trough rifapentine and desacetyl rifapentine plasma concentrations indicated that, prior to coadministration with bedaquiline on day 29, steady-state levels of rifapentine and desacetyl rifapentine had been achieved. The pronounced drop in trough rifapentine and desacetyl rifapentine plasma concentrations on study day 42 may have been due to rifapentine autoinducing its own metabolism following repeated administration (16).

In the case of rifampin and desacetyl rifampin, the trough plasma concentrations on days 27 to 30 and 42 were undetectable, most likely due to autoinduction of rifampin's metabolism (17). Therefore, to confirm that subjects received rifampin, blood samples collected for bedaquiline and M2 analyses on study day 29 at the expected T_{max} of rifampin (i.e., 2 h postdose) were also assayed for rifampin and desacetyl rifampin. At T_{max}, the concentrations of both rifampin and desacetyl rifampin were above the limit of detection in 8 of the 13 subjects, confirming that rifampin was administered according to the protocol.

Safety and tolerability. There were no serious adverse events (SAEs) in group 1 or 2; one subject in group 2 was discontinued due to a skin reaction that the PI considered had a doubtful relationship to a study treatment. Throughout the study, there were four grade 2 treatment-emergent adverse events (TEAEs), which consisted of headache (rifapentine alone), lower abdominal pain (bedaquiline plus rifampin), and headache and nausea (in both cases, rifampin alone). Headache was the most common TEAE reported. All mean laboratory, vital sign, and ECG results remained within the reference range and were generally unremarkable. Two subjects in group 2 were discontinued due to failed drug/alcohol screens at the time of the period 2 check in.

DISCUSSION

This study was a phase 1, open-label, single-center, 2-period, single-sequence study in healthy volunteers to evaluate the effect of

TABLE 2 Effects of rifapentine and rifampin on bedaquiline pharmacokinetics

Analyte, treatment group	Parameter	Geometric least-squares mean		GMR	90% CI
		With inducer	Alone		
Bedaquiline					
Rifapentine group 1	C_{max} (ng/ml)	2,077	3,339	62.19	53.37–72.47
	AUC_{0-t} (ng · h/ml)	27,612	64,531	42.79	37.77–48.487
	AUC_{0-inf} (ng · h/ml)	33,765	75,848	44.52	40.12–49.39
Rifampin group 2	C_{max} (ng/ml)	2,240	3,718	60.24	51.96–69.84
	AUC_{0-t} (ng · h/ml)	25,314	61,209	41.36	37.70–45.36
	AUC_{0-inf} (ng · h/ml)	32,051	67,729	47.32	41.49–53.97
M2					
Rifapentine group 1	C_{max} (ng/ml)	62.7	34.5	181.71	164.18–201.11
	AUC_{0-t} (ng · h/ml)	5,918	6,936	85.33	76.23–95.52
	AUC_{0-inf} (ng · h/ml)	7,592	13,753	55.20	48.86–63.36
Rifampin group 2	C_{max} (ng/ml)	64.8	32.8	197.77	177.71–220.10
	AUC_{0-t} (ng · h/ml)	5,046	6,359	79.35	70.17–89.75
	AUC_{0-inf} (ng · h/ml)	6,392	12,846	49.76	42.70–57.98

repeated daily doses of rifapentine or rifampin on the PK of a single dose of bedaquiline. The PK parameters of bedaquiline and M2 are significantly altered to similar extents when combined with the same total daily dose of rifapentine or rifampin. Despite rifampin being regarded as the more potent inducer, the higher rifapentine plasma concentrations achieved in this study compared to those achieved with the less frequent dosing regimen approved in the U.S. FDA drug label led to enhanced enzyme induction equivalent to that produced by rifampin. Enzyme induction is not regarded as an issue when rifapentine is administered according to its label. Daily administration of rifapentine to patients with tuberculosis presents the same drug interaction challenges as are seen with rifampin with respect to inducing drug-metabolizing enzymes.

Despite the fact that the changes observed in bedaquiline C_{max} and AUC were consistent with the enzyme induction produced by rifampin and rifapentine, the terminal elimination half-life of bedaquiline did not appear to decrease. Significant induction of CYP3A4 would have been expected to lead to a decreased $t_{1/2}$ of a CYP3A4 substrate. The trend to a longer $t_{1/2}$ following induction may be a result of the sampling schedule, which included sampling until 336 h postdose. Given the long $t_{1/2}$ for bedaquiline, this schedule may not have allowed for a robust characterization of the true terminal elimination phase for bedaquiline. As such, the k_{el}, as well as the PK parameters dependent on the k_{el} ($t_{1/2}$ and $AUC_{0\text{-inf}}$), for both periods 1 and 2 should be interpreted with caution.

A single 400-mg dose of bedaquiline, administered alone or in combination with multiple doses of either rifapentine or rifampin, demonstrated an acceptable safety profile in the healthy male and female subjects in this study. However, considering the results of this study, bedaquiline should not be coadministered with rifamycins due to the decreased bedaquiline systemic exposure and likely decrease in therapeutic efficacy, as noted in the mouse murine model (7).

ACKNOWLEDGMENTS

This work was supported by grants from the Bill & Melinda Gates Foundation, United States Agency for International Development, Netherlands Ministry of Foreign Affairs, and United Kingdom Department for International Development.

We thank the staff of Celerion, Inc., and the study participants.

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