

Population Pharmacokinetic Analysis of Bedaquiline-Clarithromycin for Dose Selection Against Pulmonary Nontuberculous Mycobacteria Based on a Phase I, Randomized, Pharmacokinetic Study

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Abstract

Based on the in vitro profile of bedaquiline against mycobacterial species, it is being investigated for clinical efficacy against pulmonary nontuberculous mycobacteria (PNTM). Being a cytochrome P450 3A substrate, pharmacokinetic interactions of bedaquiline are anticipated with clarithromycin (a cytochrome P450 3A inhibitor), which is routinely used in pulmonary nontuberculous mycobacteria treatment. This phase I, randomized, crossover study assessed the impact of steady-state clarithromycin (500 mg every 12 hours for 14 days) on the pharmacokinetics of bedaquiline and its metabolite (M2) after single-dose bedaquiline (100 mg; n = 16). Using these data, population pharmacokinetic modeling and simulation analyses were performed to determine the effect of clarithromycin on steady-state bedaquiline exposure. Although no effect was observed on maximum plasma concentration of bedaquiline and time to achieve maximum plasma concentration, its mean plasma exposure increased by 14% after 10 days of clarithromycin coadministration, with slower formation of M2. Simulations showed that bedaquiline plasma trough concentration at steady state was higher (up to 41% until week 48) with clarithromycin coadministration as compared to its monotherapy (400 mg once daily for 2 weeks, followed by 200 mg 3 times a week for 46 weeks; reference regimen). The overall exposure of a simulated bedaquiline regimen (400 mg once daily for 2 weeks, followed by 200 mg twice a week for 46 weeks) with clarithromycin was comparable (<15% difference) to the monotherapy. Overall, combination of bedaquiline (400 mg once daily for 2 weeks, followed by 200 mg twice a week for 46 weeks) with clarithromycin seems a suitable regimen to be explored for efficacy and safety against pulmonary nontuberculous mycobacteria.

Keywords

bedaquiline, clarithromycin, CYP3A inhibitors, drug interaction, pharmacokinetics, pulmonary nontuberculous mycobacteria disease

Nontuberculous mycobacteria (NTM) are known to cause pulmonary and extrapulmonary infections in humans.¹ Pulmonary NTM (PNTM) diseases (majorly caused by *Mycobacterium avium* complex [MAC], *Mycobacterium kansasii*, and *Mycobacterium abscessus*) are the leading causes of significant morbidity and mortality¹ and are increasing in prevalence (at an estimate of 2.5%-8% per year).² These diseases are more common in women, elderly, alcoholics, and patients with diseases such as cystic fibrosis, immunosuppression, lung diseases, diabetes mellitus, and cancer. The incidence of pulmonary nontuberculous mycobacteria disease is underestimated, and challenges in its differential diagnosis from tuberculosis add a significant disease burden to the economy.^{1,2}

The recommended treatment for pulmonary nontuberculous mycobacteria disease is a combination therapy of azithromycin/clarithromycin (macrolides),

rifampicin/rifabutin (rifamycins), and ethambutol until 12 months of negative sputum cultures; amikacin (intravenous or liposome inhalation suspension) and streptomycin are indicated for cavitary, advanced

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bronchiectatic, macrolide-resistant, or refractory MAC pulmonary disease.³⁻⁵ These treatments are known to be associated with suboptimal efficacy, potential side effects, emerging resistance, and poor patient compliance.⁶⁻¹³ There is also a lack of supporting data for the use of amikacin and streptomycin, thereby not warranting their routine use and highlighting the need of new treatment options for pulmonary nontuberculous mycobacteria disease.^{3,4}

Bedaquiline (Sirturo, Janssen Pharmaceutica NV, Beerse, Belgium), a diarylquinoline antibiotic that inhibits adenosine triphosphate synthetase, is globally approved for the treatment of pulmonary multidrug-resistant tuberculosis (MDR-TB).¹⁴ Bedaquiline may be a potential treatment for pulmonary nontuberculous mycobacteria disease based on its bactericidal activity found in in vitro studies against mycobacterial species such as *M avium*, *M intracellulare*, *M chimaera*, *M kansasii*, *M xenopi*, and *M abscessus*.¹⁵⁻²¹ Further, preclinical studies have shown antimicrobial activity of bedaquiline against some NTM species (such as MAC, *M bovis*, *M kansasii*, and *M abscessus*), and a possible clinical effect has been observed in patients with advanced pulmonary nontuberculous mycobacteria disease (caused by *M avium* or *M abscessus*).^{22,23} However, limited data are available on the use of bedaquiline against NTM infections.^{4,7}

Bedaquiline is metabolized by cytochrome P450 (CYP) 3A to form the *N*-monodesmethyl metabolite (M2); thus, CYP3A modulators can alter its pharmacokinetics (PK).²⁴ Of the currently recommended regimen of macrolides, rifamycins, and ethambutol for pulmonary nontuberculous mycobacteria disease,³⁻⁵ rifamycins are CYP3A inducers that have shown to substantially reduce the plasma concentrations of bedaquiline and are not recommended for concomitant use.^{25,26} A drug-drug interaction is also anticipated with CYP3A inhibitors such as clarithromycin (Clarithromycin Sandoz, Sandoz NV, Vilvoorde, Belgium).²⁴ Thus, this phase 1 study was conducted to assess the PK interactions of bedaquiline and clarithromycin when administered together.

The primary objective of the study was to assess the effect of steady-state clarithromycin exposure on the PK of bedaquiline and its metabolite (M2) after single-dose bedaquiline. The secondary objectives were to describe the steady-state PK of clarithromycin and its active metabolite (14-OH-clarithromycin) in the presence of single-dose bedaquiline, and to evaluate the short-term safety and tolerability of bedaquiline with and without clarithromycin. Based on the bedaquiline concentrations in the study, population PK (popPK) modeling was performed to assess the effect of clarithromycin on bedaquiline exposure after repeated bedaquiline dosing. This model was then used

to simulate steady-state bedaquiline PK under different dosing regimens to select the optimal dosing regimen of bedaquiline for use in combination with clarithromycin for long-term treatment (48 weeks) of pulmonary nontuberculous mycobacteria disease.

Methods

This was a phase 1, single-center, 2-sequence, open-label, randomized, 2-way crossover study to assess the PK interaction between single-dose bedaquiline and steady-state clarithromycin (NCT03800550). Before the study initiation, approval was obtained from Commissie voor Medische Ethiek ZNA, Belgium (Approval number 5184), and informed consents were obtained from all volunteers before enrollment at 1 site in Belgium. The study was conducted in accordance with the principles defined in the Declaration of Helsinki, International Council for Harmonization guidelines (Good Clinical Practices), and the local regulatory guidelines.

Study Population

Healthy adults, aged 18 to 55 years (extremes included) with body mass index (BMI) between 18.0 and 30.0 kg/m² and body weight ≥ 50 kg at screening were enrolled. Subjects were healthy based on physical examination, medical history, vital signs, electrocardiogram (ECG), and laboratory tests. Women were either of non-childbearing potential or had a negative serum pregnancy test at screening and on day 1 in each treatment period; effective contraceptive methods were used by men and women of childbearing potential. Subjects meeting any of the following criteria were excluded: history or current clinically significant medical illness such as cardiac, respiratory, hepatic, gastrointestinal, renal, infectious, hormonal, or hematologic diseases; laboratory abnormalities at screening as defined by the World Health Organization Toxicity Grading Scale (such as grade ≥ 1 serum creatinine, grade ≥ 1 bilirubin, grade ≥ 1 hemoglobin, grade ≥ 2 lipase, etc); history of smoking or drug or alcohol abuse; and hypersensitivity or intolerance to study drugs (bedaquiline and/or clarithromycin).

Study Treatment

Subjects were assigned to the following treatment groups based on a computer-generated randomization schedule:

- *Treatment A*: A single oral dose of 100-mg bedaquiline (1 \times 100-mg commercial tablet formulation F001) on the morning of day 1, taken with a standardized breakfast.
- *Treatment B*: Oral doses of 500-mg clarithromycin every 12 hours from day 1 to day 14 (1 \times 500-mg film-coated commercial tablet formulation), taken with a

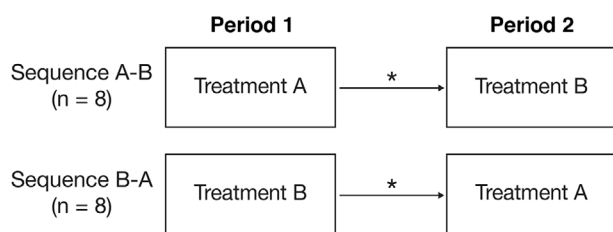


Figure 1. Overview of study design. *Washout period for bedaquiline of at least 28 days. In case subjects received treatment A in period 1, the washout period started after bedaquiline administration on day 1. In case subjects received treatment B in period 1, the washout period started after bedaquiline administration on day 5.

standardized breakfast on day 1 and on the mornings of day 2 and day 4 to day 8 at the study site (other self-administrations at home could be with or without food); and a single oral dose of 100-mg bedaquiline on the morning of day 5, taken with a standardized breakfast.

Each subject received both treatments sequentially as sequence A-B or sequence B-A, with a washout period of at least 28 days after bedaquiline administration. The study duration for each subject was at least 62 days, excluding screening. The study design is depicted in Figure 1.

Pharmacokinetic Evaluations

For determination of plasma concentrations of bedaquiline and M2, blood samples were collected at 2 hours before dosing of bedaquiline until 240 hours after administration (at 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 120, 168, and 240 hours) of treatments A and B.

For determination of plasma concentrations of clarithromycin and 14-OH-clarithromycin, blood samples were collected at 30 minutes before dosing of bedaquiline and clarithromycin until 12 hours after administration (at 1, 2, 3, 4, 5, 6, 8, and 12 hours) on day 5 of treatment B.

Bioanalytical Methods. Plasma samples were analyzed to determine the concentrations of bedaquiline, M2, clarithromycin, and 14-OH-clarithromycin using a validated liquid chromatography–tandem mass spectrometry in the sponsor's bioanalytical laboratory (PRA Health Sciences, Groningen, the Netherlands, for bedaquiline; and PPD Laboratories, Richmond, Virginia, for clarithromycin measurements). The quantification ranges were 1 to 2000 ng/mL for bedaquiline and M2; 20 to 10 000 ng/mL for clarithromycin; and 5 to 2500 ng/mL for 14-OH-clarithromycin.

Pharmacokinetic Parameters. Based on the individual plasma concentration–time data, the following PK parameters were determined for bedaquiline and

M2 on day 1 of treatment A and day 5 of treatment B: maximum observed analyte concentration (C_{\max}), actual sampling time to reach C_{\max} (t_{\max}), area under the analyte concentration–time curve (AUC) from 0 to 72 hours (AUC_{0-72h}), and AUC from 0 to 240 hours (AUC_{0-240h}). The PK parameters of C_{\max} , t_{\max} , minimum observed analyte concentration, and AUC from 0 to 12 hours (AUC_{0-12h}) were calculated for clarithromycin and 14-OH-clarithromycin on day 5 of treatment B. The metabolite to parent (M/P) ratios of the following PK parameters were also determined for bedaquiline: M/P ratio C_{\max} , M/P ratio AUC_{0-72h} , and M/P ratio AUC_{0-240h} .

Safety Evaluations

Safety and tolerability were evaluated from signing of the informed consent until the subject's last activity in the study, the subject was lost to follow-up, or the consent was withdrawn. Safety was evaluated on the basis of the assessment of adverse events (AEs), physical examinations, vital signs, ECG, clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis), and other toxicities.

Statistical Evaluation

No formal hypothesis testing was done.

Sample Size Determination. The sample size was determined on the basis of the data from a previous study of bedaquiline 100-mg single-dose administration.²⁷ Assuming a within-subject coefficient of variation of $\approx 27\%$ for bedaquiline AUC in the fed state and a sample size of 14 subjects, the point estimate of geometric mean ratio of the AUC of bedaquiline with or without clarithromycin coadministration was expected to fall between 84% and 120% of the true value, with 90% confidence. To account for dropouts, it was planned to recruit 16 subjects.

Analysis Sets. All subjects who received at least 1 dose of the study drug (either bedaquiline or clarithromycin) were included in the safety analysis set; subjects having at least 1 postbaseline plasma-concentration statistic were included in the PK analysis set.

Statistical Analyses. Descriptive statistics (median, minimum, and maximum) were measured for age, BMI, weight, and height. Sex, race, and ethnicity were listed and tabulated.

For PK analyses, descriptive statistics (sample size [n], mean, standard deviation [SD], coefficient of variation, geometric mean with 90% confidence interval [CI], median, minimum, and maximum) were calculated for plasma concentrations of bedaquiline, clarithromycin, their metabolites, and for the derived

PK parameters (for t_{\max} , only n, median, minimum, and maximum were presented). Graphs of the mean plasma concentration–time profiles were produced for each subject and per treatment.

Statistical analyses were performed for bedaquiline and M2 PK parameters comparing treatment B with treatment A. The least squares means of the log-transformed primary PK parameters were estimated with a linear mixed-effects model for each treatment, controlling for treatment, sequence, and period as fixed effects, and subject as a random effect. The differences between least squares means and 90% CIs were retransformed to the original scale to provide relative bioavailability estimates with corresponding CIs.

All safety parameters were analyzed using descriptive statistics as actual values and changes from baseline. The number and percentage of subjects who experienced at least 1 occurrence of any AE were summarized by treatment.

Analysis Software. The noncompartmental PK analyses were performed using a validated computer software, Phoenix WinNonlin (version 8.0; Certara LP, Princeton, New Jersey); SAS (version 9.4; SAS Institute Inc, Cary, North Carolina) was used for the creation of PK tables and figures, estimation of M/P ratios, and inferential statistical analysis.

For safety analyses, AEs were coded using the Medical Dictionary for Regulatory Activities (version 21.1). All reported AEs that started after the first study drug administration (ie, treatment-emergent AEs [TEAEs]) were included in the analysis and tabulated by system organ class and preferred terms.

Population PK Modeling and Simulation Analyses

Using the concentration data of bedaquiline, popPK modeling and simulation analyses were performed. These analyses were conducted based on a previously developed popPK model, which was a 4-compartment model with dual zero-order output for healthy subjects and patients with tuberculosis after bedaquiline monotherapy.²⁸ In the previous popPK model, the following covariates were included: route of administration for bioavailability (F), Black race and subject status for apparent clearance (CL/F), and sex for apparent central volume of distribution. The detailed information is provided in Table S1. No formal covariate analysis was performed in the present study.

The previous model was evaluated for its applicability to the data collected from treatment A (using a maximum a posteriori estimation in nonlinear mixed-effects modeling software [NONMEM; ICON plc, Hanover, Maryland]; visual predictive check [VPC] and goodness-of-fit [GOF] plots were used for model evaluation). The structural model and the covariate

model parameters were then applied to the current data (updated model). While the previous popPK model described the plasma concentration profiles of bedaquiline after its monotherapy in healthy subjects and tuberculosis patients, the updated model estimated the effect of clarithromycin on bedaquiline PK using the data of treatments A and B from the present study. The details of the model parameters are listed in Table S1.²⁸

The effect of clarithromycin on CL/F of bedaquiline was then estimated using combined PK data from treatments A and B. The first-order conditional estimation method was used for parameter estimation, and the following equation was employed:

$$CL/F = CL_{pop} \cdot (1 + \theta)^{CLR_i}$$

where CL/F is model-predicted apparent bedaquiline clearance for the typical individual with or without clarithromycin coadministration, depending on the clarithromycin coadministration status value (CLR_i ; no coadministration = 0 or coadministration = 1); CL_{pop} is the population central tendency for CL/F without clarithromycin coadministration; and θ is the change in apparent bedaquiline clearance when clarithromycin was coadministered. VPC and GOF plots were used for evaluation.

Subsequently, using the updated model, bedaquiline PK profile was simulated to assess the impact of clarithromycin coadministration on steady-state bedaquiline exposure, based on the assumptions of 1000 non-Black subjects (male:female = 1:1) and similar disease status of MDR-TB and NTM. A similar bedaquiline exposure level achieved by the MDR-TB regimen (duration, 24 weeks) was targeted for the pulmonary nontuberculous mycobacteria treatment (duration, 48 weeks), but with clarithromycin coadministration. The plasma bedaquiline trough concentration (C_{trough}) profile of the standard MDR-TB dose regimen with longer treatment duration (ie, 400-mg bedaquiline once daily for 2 weeks followed by 200 mg 3 times a week for 46 weeks) was simulated with or without clarithromycin coadministration (500 mg every 12 hours for 48 weeks as a standard NTM treatment). The MDR-TB regimen (without clarithromycin coadministration) was chosen as a reference regimen based on the similar minimum inhibitory concentration of bedaquiline for NTM and MDR-TB shown in a previous study.²⁹

The reference regimen was compared to 4 regimens of bedaquiline (with clarithromycin coadministration): regimen A (400 mg once daily for 2 weeks followed by 200 mg twice a week for 46 weeks), regimen B (400 mg once daily for 2 weeks followed by 100 mg 3 times a week for 46 weeks), regimen C (400 mg once daily for

Table 1. Demographic and Baseline Characteristics

Analysis Set	Treatment A-B	Treatment B-A	All Subjects
Number	8	8	16
Sex, n (%)			
Female	5 (62.5)	4 (50.0)	9 (56.3)
Male	3 (37.5)	4 (50.0)	7 (43.8)
Age, y			
Median (range)	40.0 (31-52)	48.5 (24-55)	43.0 (24-55)
Race and ethnicity			
White, n (%)	8 (100)	8 (100)	16 (100)
Weight, kg			
Median (range)	69.90 (56.8-83.6)	63.55 (58.2-100.0)	65.65 (56.8-100.0)
Height, cm			
Median (range)	170.60 (162.2-179.1)	173.35 (165.2-187.2)	170.85 (162.2-187.2)
BMI, kg/m ²			
Median (range)	23.80 (19.4-26.9)	22.08 (18.9-29.5)	22.44 (18.9-29.5)

BMI, body mass index.

Treatment A: single dose of 100-mg bedaquiline on day 1; treatment B: 14 days of 500-mg clarithromycin every 12 hours (days 1-14), with a single dose of 100-mg bedaquiline on day 5.

2 weeks followed by 100 mg twice a week for 46 weeks), and regimen D (400 mg once daily for 2 weeks followed by 100 mg 5 times per week for 46 weeks).

The popPK analyses were performed using NONMEM 7.3 using Perl-speaks-NONMEM version 4.2.0. Data management, exploratory analyses, diagnostic graphics, postprocessing of data, and NONMEM outputs were performed using statistical software R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study Population

The study was conducted from March 2019 to June 2019 and enrolled 16 subjects (9 women and 7 men). All subjects were White, with a median age of 43 years (range, 24-55 years) and median BMI of 22.44 kg/m² (range, 18.9-29.5 kg/m²). The demographic and baseline characteristics are described in Table 1. All 16 subjects were included in the PK and safety analyses.

Of all subjects, 4 missed ≥ 1 doses of clarithromycin. One of these was reported as a major protocol deviation; the subject missed 3 doses of clarithromycin on the evening of day 13, and morning and evening of day 14. As no impact on PK analytes was anticipated, no action was taken.

Pharmacokinetic Findings

Bedaquiline and M2. Following a single-dose administration of bedaquiline in period 1 of sequence A-B and sequence B-A, the predose plasma concentrations of bedaquiline and M2 were quantifiable in period 2 in all subjects. The predose plasma concentrations of bedaquiline and M2 in period 2 were $<5\%$ and $>10\%$ of C_{\max} , respectively, associated with the second single dose of bedaquiline.

The bedaquiline mean plasma concentration was maximum at 5 hours after dosing in both treatment groups, after which it rapidly declined initially followed by a slower decline and was quantifiable until 240 hours. The M2 mean plasma concentration reached a peak at 12 hours after dosing in both treatment groups, after which it decreased slowly (a slight reincrease was noted after treatment B before the gradual decrease in plasma concentration); M2 was formed slowly but was quantifiable until 240 hours. Overall, bedaquiline plasma concentrations were slightly higher, with lower M2 levels on clarithromycin coadministration as compared to monotherapy (Figure 2 and Figure S1).

The PK parameters of bedaquiline and M2 and summary of statistical analysis are presented in Tables 2 and 3, respectively. Although mean t_{\max} and C_{\max} of bedaquiline were similar in both treatment groups, mean AUCs were slightly higher in treatment B compared to treatment A. Also, higher values were observed in period 2 compared to period 1 for both AUC_{0-72h} (5%-6% higher) and AUC_{0-240h} (8%-18% higher). M2 was formed more slowly in treatment B (median t_{\max} of 23.91 hours for treatment B vs 12 hours for treatment A), and C_{\max} and AUCs (including their M/P ratios) were markedly decreased. All M2 PK parameters were higher in period 2 as compared to period 1 (C_{\max} , AUC_{0-72h}, and AUC_{0-240h} were 36%, 41%, and 46% higher in treatment A and 2.2-, 2.1-, and 2.1-fold higher in treatment B, respectively).

Overall, clarithromycin, when coadministered with bedaquiline had no impact on t_{\max} and C_{\max} of bedaquiline but increased the AUCs (12% for AUC_{0-72h} [$P = .0011$] and 14% for AUC_{0-240h} [$P = .0002$]) along with a significant period effect for AUC_{0-240h} ($P = .0005$). The plasma exposures of M2 (52%, 51%, and

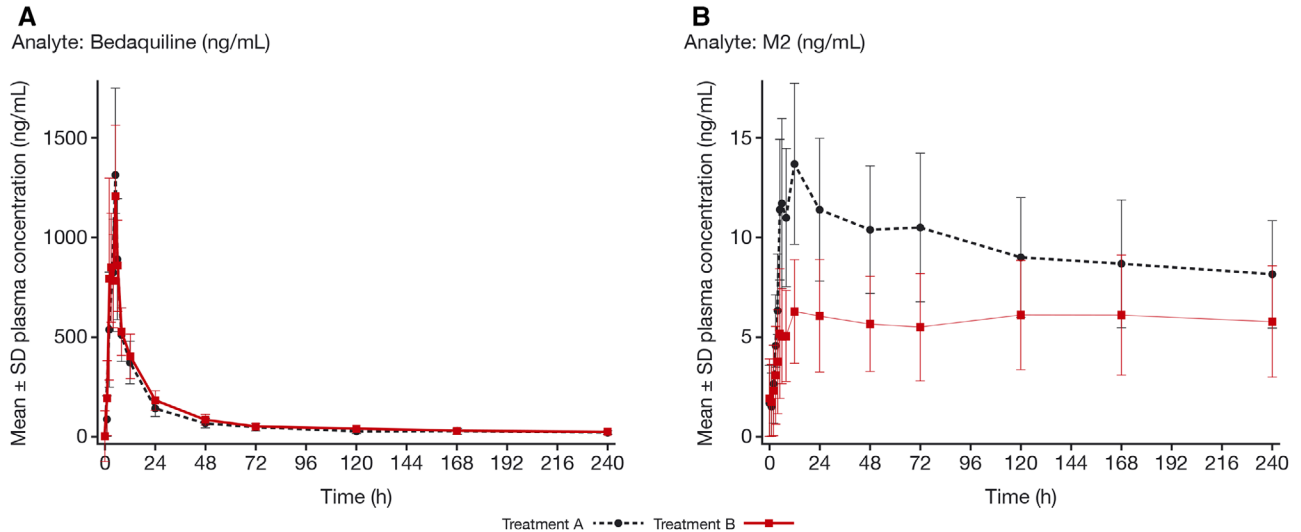


Figure 2. Mean plasma concentration–time profile of bedaquiline and M2. **(A) Mean plasma concentration–time profile of bedaquiline. (B) Mean plasma concentration–time profile of M2.** Linear scale: time scale up to 240 hours; treatment A: single dose of 100-mg bedaquiline on day 1; treatment B: 14 days of 500-mg clarithromycin every 12 hours (days 1–14), with a single dose of 100-mg bedaquiline on day 5. SD, standard deviation.

Table 2. Pharmacokinetic Results of Bedaquiline and Its Metabolite (M2)

Parameters (Mean [SD])	Treatment A		Treatment B	
	Period 1	Period 2	Period 1	Period 2
Number	8	8	8	8
Bedaquiline				
C_{max} , ng/mL	1387 (407)	1287 (432)	1295 (343)	1363 (351)
t_{max} , h ^a	5.00 (2.00–5.00)	5.00 (3.00–5.00)	5.00 (2.00–6.03)	3.48 (1.98–4.98)
AUC_{0-72h} , ng · h/mL	13 886 (2653)	14 646 (4469)	15 389 (4155)	16 357 (3289)
AUC_{0-240h} , ng · h/mL	17 641 (4052)	20 761 (6341)	20 869 (5738)	22 555 (5100)
M2				
C_{max} , ng/mL	12.0 (3.27)	16.3 (3.83)	4.66 (1.54)	9.89 (2.04)
t_{max} , h ^a	12.00 (5.00–239.77)	12.00 (6.00–72.28)	35.92 (11.92–120.20)	23.90 (11.92–220.62)
AUC_{0-72h} , ng · h/mL	637 (177)	898 (211)	260 (78.1)	543 (132)
AUC_{0-240h} , ng · h/mL	1839 (422)	2691 (715)	886 (268)	1884 (370)
M/P ratios				
M/P ratio C_{max}^b	0.00936 (0.00318)	0.0142 (0.00514)	0.00390 (0.00153)	0.00798 (0.00294)
M/P ratio AUC_{0-72h}^b	0.0481 (0.0154)	0.0670 (0.0190)	0.0183 (0.00639)	0.0347 (0.00872)
M/P ratio AUC_{0-240h}^b	0.110 (0.0299)	0.141 (0.0390)	0.0460 (0.0155)	0.0881 (0.0202)

AUC_{0-72h} , area under the analyte concentration–time curve from 0 to 72 hours; AUC_{0-240h} , area under the analyte concentration–time curve from 0 to 240 hours; C_{max} , maximum observed analyte concentration; C_{min} , minimum observed analyte concentration; M/P, metabolite/parent ratio; M/P ratio AUC_{0-72h} , AUC_{0-72h} for M2 divided by AUC_{0-72h} for bedaquiline; M/P ratio AUC_{0-240h} , AUC_{0-240h} for M2 divided by AUC_{0-240h} for bedaquiline; M/P ratio C_{max} , C_{max} for M2 divided by C_{max} for bedaquiline; SD, standard deviation; t_{max} , actual sampling time to reach the maximum observed analyte concentration.

Treatment A: single-dose of 100 mg bedaquiline on day 1; treatment B: 14 days of 500-mg clarithromycin every 12 hours (days 1–14), with a single-dose of 100-mg bedaquiline on day 5.

^a t_{max} is presented in median (range).

^b M/P ratios corrected for molecular weight (bedaquiline: 555.50 g/mol and M2: 541.47 g/mol).

42% for C_{max} , AUC_{0-72h} , and AUC_{0-240h} , respectively) and M/P (52%, 56%, and 49% for C_{max} , AUC_{0-72h} , and AUC_{0-240h} , respectively) were significantly reduced, along with a significant period effect for all PK parameters ($P < .0001$).

Clarithromycin and 14-OH-Clarithromycin. The mean plasma concentration–time profiles of clarithromycin

and 14-OH-clarithromycin are presented in Figure S2. On the morning of day 5, the predose mean plasma concentrations of clarithromycin and 14-OH-clarithromycin were 1281 ng/mL and 797 ng/mL, respectively; after reaching mean peak concentrations at 3 hours after dosing, the concentrations decreased to mean levels of 986 ng/mL and 650 ng/mL, respectively, at 12 hours after dosing (ie, before evening dose), which

Table 3. Statistical Analyses of the Pharmacokinetic Parameters of Bedaquiline and Its Metabolite (M2)

PK Parameters (n = 16)	Geometric Means		P Values			Treatment B Versus Treatment A	
	Treatment A	Treatment B	Treatment	Sequence	Period	Geometric Mean Ratio (90%CI)	Intrasubject CV (%)
Bedaquiline							
C _{max} , ng/mL	1277	1285	.9082	.6122	.8074	100.66 (91.22-111.08)	15.9
AUC _{0-72h} , ng • h/mL	13 831	15 458	.0011	.8307	.0781	111.77 (106.52-117.27)	7.7
AUC _{0-240h} , ng • h/mL	18 482	21 065	.0002	.8855	.0005	113.97 (108.88-119.30)	7.3
M2							
C _{max} , ng/mL	13.5	6.56	<.0001	.0774	<.0001	48.45 (42.63-55.07)	20.8
AUC _{0-72h} , ng • h/mL	732	362	<.0001	.1492	<.0001	49.47 (45.08-54.28)	15.0
AUC _{0-240h} , ng • h/mL	2165	1255	<.0001	.1053	<.0001	57.97 (53.26-63.10)	13.7
M/P ratios							
M/P ratio C _{max} ^a	0.0109	0.00 523	<.0001	.3567	<.0001	48.13 (40.72-56.90)	27.3
M/P ratio AUC _{0-72h} ^a	0.0543	0.0240	<.0001	.2855	<.0001	44.26 (40.37-48.52)	14.9
M/P ratio AUC _{0-240h} ^a	0.120	0.0611	<.0001	.1434	<.0001	50.86 (47.05-54.98)	12.6

AUC_{0-72h}, area under the analyte concentration–time curve from 0 to 72 hours; AUC_{0-240h}, area under the analyte concentration–time curve from 0 to 240 hours; C_{max}, maximum observed analyte concentration; CI, confidence interval; CV, coefficient of variation; M/P, metabolite/parent ratio; M/P ratio AUC_{0-72h}, AUC_{0-72h} for M2 divided by AUC_{0-72h} for bedaquiline; M/P ratio AUC_{0-240h}, AUC_{0-240h} for M2 divided by AUC_{0-240h} for bedaquiline; M/P ratio C_{max}, C_{max} for M2 divided by C_{max} for bedaquiline; PK, pharmacokinetic.

Treatment A: single dose of 100-mg bedaquiline on day 1; treatment B: 14 days of 500-mg clarithromycin every 12 hours (days 1-14), with a single dose of 100-mg bedaquiline on day 5.

^aM/P ratios corrected for molecular weight (bedaquiline: 550.50 g/mol; M2: 541.47 g/mol).

were close to the predose morning levels, indicating that steady state was achieved. The mean C_{max} and minimum observed analyte concentration were 2972 ng/mL and 976 ng/mL for clarithromycin, and 1152 ng/mL and 636 ng/mL for 14-OH-clarithromycin, respectively. The detailed PK results of clarithromycin and 14-OH-clarithromycin after 5 days of clarithromycin administration are presented in Table 4.

Safety Findings

No deaths, serious AEs, or TEAEs leading to study drug discontinuation or termination of study participation were reported.

The number of subjects who experienced at least 1 TEAE were 6 of 16 (37.5%) who received treatment A, 10 of 16 (62.5%) who received treatment B1 (ie, pre-bedaquiline period of treatment B), and 9 of 16 (56.3%) who received treatment B2 (ie, post-bedaquiline period of treatment B). All TEAEs were of grade 1 severity, except 4 TEAEs of grade 2 headache (n = 3 who received treatment A and n = 1 who received treatment B2). The number of subjects with TEAEs possibly related to study drug were 3 of 16 (18.8%; bedaquiline related) with treatment A, 10 of 16 (62.5%; clarithromycin related) with treatment B1, and 7 of 16 (43.8%; all 7 subjects had clarithromycin-related TEAEs, and 2 subjects had additional bedaquiline-related TEAEs) with treatment B2. The summary of overall TEAEs is presented in Table S2. None of the laboratory, ECG, vital signs, and physical examination findings were reported as TEAEs.

Table 4. Pharmacokinetic Results of Clarithromycin and Its Metabolite (14-OH-Clarithromycin)

Parameters (Mean [SD])	Treatment B (Bedaquiline 100 mg + Clarithromycin at 500 mg Every 12 Hours for 14 Days - Day 5)
Clarithromycin	
N	16
C _{predose} , ng/mL	1281 (353)
C _{0-3h} , ng/mL	2619 (988)
C _{0-12h} , ng/mL	986 (277)
C _{max} , ng/mL	2972 (1061)
t _{max} , h ^a	3.00 (1.00-8.03)
C _{min} , ng/mL	976 (280)
AUC _{0-12h} , ng • h/mL	22 866 (6676)
14-OH-Clarithromycin	
N	16
C _{predose} , ng/mL	797 (194)
C _{0-3h} , ng/mL	1071 (340)
C _{0-12h} , ng/mL	650 (193)
C _{max} , ng/mL	1152 (326)
t _{max} , h ^a	2.00 (0.00-4.00)
C _{min} , ng/mL	636 (183)
AUC _{0-12h} , ng • h/mL	10 849 (3050)

AUC_{0-12h}, area under the analyte concentration–time curve from 0 to 12 hours; C_{max}, maximum observed analyte concentration; C_{min}, minimum observed analyte concentration; C_{predose}, predose analyte concentration; C_{0-3h}, analyte concentration at 3 hours; C_{0-12h}, analyte concentration at 12 hours; SD, standard deviation; t_{max}, actual sampling time to reach the maximum observed analyte concentration.

^at_{max} is presented in median (range).

Population PK Modeling Analysis Findings

Updated Model and Effect of Steady-State Clarithromycin on Bedaquiline PK. The GOFs and VPCs plotted for the previously developed model (Figure S3 and Figure S4)

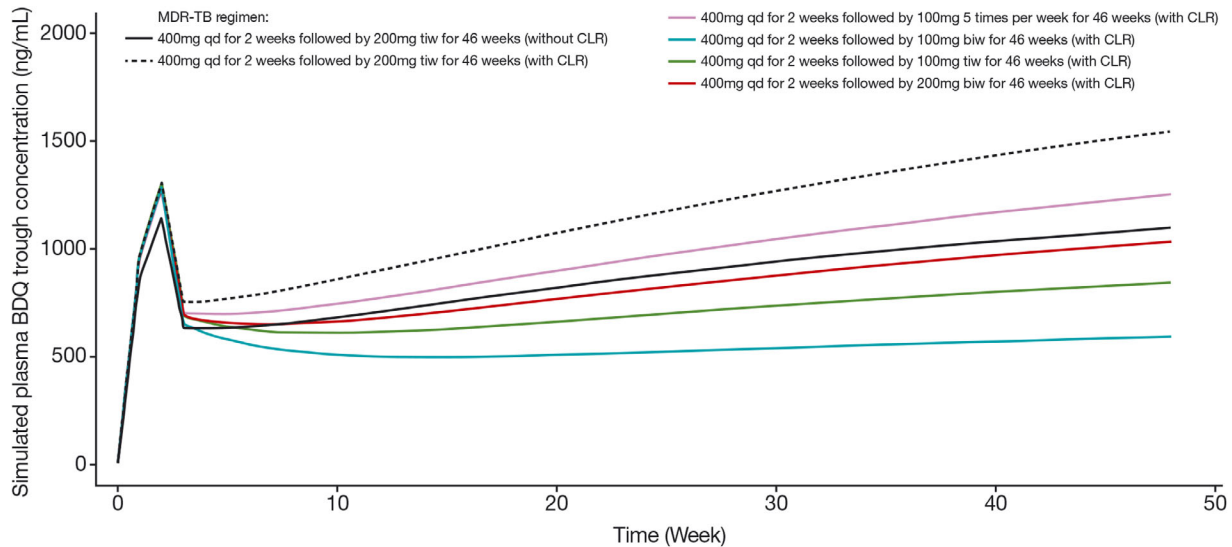


Figure 3. Simulated mean plasma bedaquiline trough concentrations in standard and alternative regimens based on the updated population pharmacokinetic model. BDQ, bedaquiline; biw, twice a week; CLR, clarithromycin; MDR-TB, multidrug-resistant tuberculosis; qd, once daily; tiw, 3 times a week.

indicated their applicability for describing the data of treatment A. Further, the updated model adequately described the present data and captured the central tendency and variability; the predictive performance of the model was confirmed by the VPC (Figure S5 and Figure S6).

The detailed popPK parameters of the previous and the updated model are listed in Table S1. The effect of clarithromycin on CL/F of bedaquiline (1.81 L/h) relative to its clearance as monotherapy (2.78 L/h) was estimated to be $-37%$ (95%CI, $-45%$ to $-29%$; $P < .001$).

Although the updated model captured the data well, some outliers (ie, conditional weighted residuals >6) were identified in this analysis, especially for the data in the absorption phase (1-2 hours after bedaquiline dosing). No additional/formal covariate analysis was done; however, a sensitivity analysis was performed to investigate the influence of these outliers. It was identified that those outliers had no influence on the estimation of the effect of clarithromycin on bedaquiline (data not shown).

Simulations of Steady-State Bedaquiline PK. Based on the updated model, the simulated plasma bedaquiline C_{trough} with clarithromycin coadministration in MDR-TB regimen was found to be higher at week 24 (33%; 1154 ± 576 ng/mL vs 869 ± 481 ng/mL) and week 48 (41%; 1542 ± 832 ng/mL vs 1095 ± 661 ng/mL) as compared to its monotherapy (as the reference regimen).

The reference regimen was then compared with 4 regimens of bedaquiline with clarithromycin coadministration. Although regimens B and C showed lower

mean plasma bedaquiline C_{trough} profiles (21% and 46%, respectively), the C_{trough} profiles were comparable for regimens A and D ($<14%$ difference), relative to the reference regimen (Figure 3). On comparing regimens A and D for C_{max} , AUC_{0-24h} , and AUC_{0-168h} at weeks 2, 24, and 48 with the reference regimen, their exposure profiles were similar ($<15%$ difference), except for C_{max} at week 24 in regimen D ($>20%$ difference) (Table 5).

Discussion

Since bedaquiline may be a potential treatment against pulmonary nontuberculous mycobacteria disease, it is imperative to understand its PK interactions with other drugs of the pulmonary nontuberculous mycobacteria regimen. Being a CYP3A substrate, the drug interaction of bedaquiline is obvious with rifamycins (CYP3A inducers), and is well proven.^{25,26,30,31} In a clinical study, rifabutin was suggested to lower the clinical efficacy of bedaquiline when given together and cause microbiological relapse; however, the sample size was small ($n = 16$), and further investigation is needed to assess the impact of companion drugs (used for NTM) on bedaquiline efficacy.³² No PK interactions of bedaquiline have been observed with ethambutol,³³ and the present study is the first human trial to assess the PK interaction between bedaquiline and clarithromycin.

Following administration of bedaquiline alone or with clarithromycin in period 1, predose plasma concentrations of bedaquiline and M2 were noted in period 2 for all subjects ($<5%$ and $>10%$, respectively, of C_{max} associated with the second single dose for bedaquiline). The plasma concentrations of bedaquiline and M2 were

Table 5. Simulated Bedaquiline Exposure of MDR-TB Regimen Without Clarithromycin, Regimen A and Regimen D

	MDR-TB Regimen			Regimen A			Regimen D		
	Week 2	Week 24	Week 48	Week 2	Week 24	Week 48	Week 2	Week 24	Week 48
C_{trough} , ng/mL									
Mean (SD)	1125 (523)	850 (489)	1069 (667)	1262 (567)	794 (420)	1009 (576)	1258 (529)	944 (463)	1230 (653)
Ratio ^a	1.12	0.93	0.94	1.12	1.11	1.15
C_{max} , ng/mL									
Mean (SD)	3274 (1657)	2013 (1059)	2233 (1212)	3372 (1695)	1919 (1002)	2137 (1138)	3358 (1537)	1596 (740)	1884 (918)
Ratio ^a	1.03	0.95	0.96	1.03	0.79	0.84
AUC ^b (ng · h/mL)									
Mean (SD)	42 652 (19 684)	180 526 (96 964)	217 615 (126 252)	45 900 (20 487)	161 430 (81 712)	197 865 (107 552)	45 780 (19 023)	191 203 (89 638)	239 657 (121 020)
Ratio ^b	1.08	0.89	0.91	1.07	1.06	1.10

AUC, area under the analyte concentration–time curve; C_{max} , maximum observed analyte concentration; C_{trough} , trough concentration; MDR-TB, multidrug-resistant tuberculosis; SD, standard deviation.

MDR-TB regimen: 400-mg bedaquiline once daily for 2 weeks followed by 200 mg 3 times a week (without clarithromycin); regimen A: 400 mg once daily for 2 weeks followed by 200 mg twice a week for 46 weeks with clarithromycin; regimen D: 400 mg once daily for 2 weeks followed by 100 mg 5 times per week for 46 weeks with clarithromycin.

^aMean exposure in regimen A or D/mean exposure in MDR-TB regimen.

^bAUC_{0-24h} for week 2, AUC_{0-168h} for weeks 24 and 48.

quantifiable up to 240 hours in both treatments, and a carryover effect was noted in period 2 (bedaquiline: higher AUC_{0-72h} and AUC_{0-240h}; M2: higher C_{max} , AUC_{0-72h}, and AUC_{0-240h}). This was expected considering the relatively short washout period between both treatment periods compared to the very long terminal elimination half-life of bedaquiline (5.5 months), owing to its cationic amphiphilic characteristics.²⁴ The results were consistent with the previous randomized trial of an 8-week bedaquiline regimen in patients with MDR-TB, where bedaquiline and M2 were quantifiable even after 96 weeks of finishing the treatment, with the mean terminal elimination half-lives of 164 and 159 days, respectively.³⁴ Bedaquiline reached a maximum concentration within 5 hours after dosing, which is consistent with the previous studies where C_{max} was reached within 4 to 6 hours of drug administration.^{22,35,36}

Although C_{max} and t_{max} of bedaquiline were not impacted by clarithromycin coadministration, the mean plasma concentration of bedaquiline was slightly higher (with decreased C_{max} and AUCs for M2 and M/P ratio). This increased plasma exposure of bedaquiline along with decreased clearance was tested considering clarithromycin is a CYP3A inhibitor, in view of literature evidence available for other CYP3A inhibitors (erythromycin, ciprofloxacin, fluconazole, ketoconazole, and lopinavir/ritonavir).^{24,37,38} The mean plasma concentration of clarithromycin (in combination with bedaquiline) reached a peak at 3 hours after dosing, followed by a gradual decrease until 12 hours after dosing, and steady-state was achieved in the study; the PK profile of clarithromycin is already well established.³⁹

Owing to its long half-life and highly lipophilic nature, bedaquiline is known to prolong the QT interval (mainly driven by metabolite M2); additionally, hepatotoxicity is one of its known adverse drug reactions.^{40,41} In the present study, no deaths, serious AEs, or TEAEs leading to discontinuation were reported. No laboratory or ECG abnormality was reported as a TEAE; however, the sample size was small and safety still needs to be assessed in the target population. In previous studies of bedaquiline for MDR-TB treatment and case series against pulmonary nontuberculous mycobacteria, bedaquiline was deemed to be generally safe in combination with macrolides and other drugs.^{23,34-36,42} Still, the clinical experience on bedaquiline use in pulmonary nontuberculous mycobacteria remains scarce.⁴³ Appropriately powered studies are necessary to establish the safety and efficacy of the combination regimen of bedaquiline with clarithromycin in pulmonary nontuberculous mycobacteria disease.

Model-based analysis of drug interactions has been suggested as a preferable method over noncompartmental analysis for drugs with long half-life, as the former is associated with accurate and unbiased predictions of drug-drug interactions, and dose adjustment simulations.⁴⁴ PopPK modeling is now widely used in integration with clinical studies to provide dosage optimization, efficacy, and safety information for the drug labels and helps to estimate the range of concentrations from the dose administration strategies when combined with simulation analysis.⁴⁵ This approach is helpful to study the drug-drug interactions and determine the dosage recommendations in cases

where the study drug is a substrate.^{46,47} During phase I studies, popPK plays an important role to obtain the estimates of structural model parameters, understand the relationship between covariates and PK parameters, and determine the inter- and intrasubject variability.⁴⁵ Therefore, while planning this research, it was believed that the popPK approach can provide an estimate of the spread of the bedaquiline concentrations that would be achieved in the study, taking into account the inter- and intrasubject variability. In addition, the previously developed popPK model of bedaquiline successfully predicted the bedaquiline concentration at steady state (ie, over 24 weeks) and reported some covariates. Overall, popPK was considered suitable to predict the drug-drug interaction of bedaquiline and clarithromycin under the long-term administration in the future trial for pulmonary nontuberculous mycobacteria. Thus, to study the effect of clarithromycin on bedaquiline PK, a popPK modeling approach was used.²⁸ This model was then employed to simulate steady-state bedaquiline PK under different dosing regimens so as to determine the optimal dosing regimen for the treatment of pulmonary nontuberculous mycobacteria.

Based on the popPK modeling, the effect of clarithromycin on CL/F of bedaquiline relative to its clearance as monotherapy was estimated to be -37%. Further, simulated C_{trough} of bedaquiline with clarithromycin coadministration was found to be higher at weeks 24 and 48 as compared to its monotherapy, suggesting that an adjustment of the bedaquiline dose, especially in the maintenance period, would be warranted to avoid the potential increase of safety risk for patients with pulmonary nontuberculous mycobacteria having a longer treatment duration (ie, 48 weeks) compared to MDR-TB (ie, 24 weeks) according to their standard of care.^{3,4,33} This was considered due to inhibition of bedaquiline clearance by clarithromycin, in view of literature evidence available for other CYP3A inhibitors.^{24,37,38,48} Thus, to achieve a similar bedaquiline exposure with pulmonary nontuberculous mycobacteria treatment as that of the currently used regimen in MDR-TB, a combination of bedaquiline (400 mg once daily for 2 weeks, followed by 200 mg twice a week for 46 weeks, regimen A) and clarithromycin was found to be an optimal dosing regimen that can be further evaluated in the treatment of pulmonary nontuberculous mycobacteria; safety and efficacy of this regimen will be confirmed in a future study.

Conclusions

Clarithromycin coadministration with single-dose bedaquiline had no impact on the C_{max} and t_{max} of bedaquiline; however, the plasma exposure of bedaquiline was increased, with reduced plasma exposure of M2.

Overall, single-dose bedaquiline appears to be safe and well tolerated, either alone or with clarithromycin; however, this needs to be assessed in long-term trials. Furthermore, popPK modeling and simulation analyses showed higher C_{trough} of bedaquiline with clarithromycin coadministration at weeks 24 and 48 as compared to its monotherapy, indicating the need for bedaquiline dose adjustment, especially in the maintenance period. It is suggested that a combination regimen of bedaquiline (400 mg once daily for 2 weeks followed by 200 mg twice a week for 46 weeks) with clarithromycin can be further studied for the treatment of pulmonary nontuberculous mycobacteria disease, based on similar bedaquiline exposure found for pulmonary nontuberculous mycobacteria treatment as seen with the MDR-TB regimen.

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Conflicts of Interest

All authors are employees of Janssen Pharmaceutical Companies of Johnson and Johnson. Further, Ken Kurosawa, Stefaan Rossenu, Sivi Ouwerkerk-Mahadevan, Wouter Willems, and Chrispin Kambili are potential stockholders of Johnson and Johnson.

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Author Contributions

All authors were involved in the design and conduct of the research; W.W. and E.E. performed the statistical analysis for phase I study, while population pharmacokinetic modeling and simulation analyses were done by K.K. and S.R. All authors reviewed the manuscript for important intellectual content, approved the final manuscript, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Sharing

The data-sharing policy of Janssen Research and Development is available at <https://www.janssen.com/clinical-trials/transparency>. Any requests for access to the study data can be submitted via Yale Open Data Access (YODA) Project (<https://yoda.yale.edu/>).

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Supplemental Information

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