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ARTICLE

A modeling-based proposal for safe and efficacious reintroduction of bedaquiline after dose interruption: A population pharmacokinetics study

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Abstract

Bedaquiline (BDQ) is recommended for treatment of multidrug-resistant tuberculosis (MDR-TB) for the majority of patients. Given its long terminal half-life and safety concerns, such as QTc-prolongation, re-introducing BDQ after multiple dose interruption is not intuitive and there are currently no existing guidelines. In this simulation-based study, we investigated different loading dose strategies for BDQ re-introduction, taking safety and efficacy into account. Multiple scenarios of time and length of interruption as well as BDQ re-introduction, including no loading dose, 1- and 2-week loading doses (200 mg and 400 mg once daily), were simulated from a previously published population pharmacokinetic (PK) model describing BDQ and its main metabolite M2 PK in patients with MDR-TB. The efficacy target was defined as 95.0% of the average BDQ concentration without dose interruption during standard treatment. Because M2 is the main driver for QTc-prolongation, the safety limit was set to be below the maximal average M2 metabolite concentration in a standard treatment. Simulations suggest that dose interruptions between treatment weeks 3 and 72 (interruption length: 1 to 6 weeks) require a 2-week loading dose of 200 mg once daily in the typical patient. If treatment was interrupted for longer than 8 weeks, a 2-week loading dose (400 mg once daily) was needed to reach the proposed efficacy target, slightly exceeding the safety limit. In conclusion, we here propose a strategy for BDQ re-introduction providing guidance to clinicians for safe and efficacious BDQ dosing.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Bedaquiline (BDQ) pharmacokinetics and efficacy have earlier been characterized, but guidance on BDQ re-introduction after treatment interruption is lacking.

WHAT QUESTION DID THIS STUDY ADDRESS?

This simulation-based study is aimed at establishing a strategy for safe and efficacious BDQ re-introduction.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study suggests dosing recommendations for BDQ re-introduction. According to the simulations in the typical patient, a 2-week loading dose (200 mg daily) was sufficient to raise BDQ concentrations to a proposed efficacy target while keeping concentrations of its M2 metabolite below a proposed safety limit when the interruption occurred between treatment weeks 3 and 72 and was no longer than 6 weeks. In case of an interruption greater than 8 weeks, a 2-week loading dose (400 mg once daily) was necessary for the efficacy target, but the safety limit might be exceeded. The approach was applied to a clinical case in Sweden during 2021 and found to be safe.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

This work proposes guidelines for resumption of BDQ dosing after interruption. Further clinical study of these guidelines is necessary to confirm their validity.

INTRODUCTION

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is one of the most common causes of death due to a single infectious agent, with about 10 million new cases and 1.5 million deaths in 2020 globally,[1] surpassed only by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) last year. Multidrug-resistant TB (MDR-TB) is increasing worldwide and is more difficult to treat with higher morbidity and mortality.[2] In 2020, roughly 160,000 new cases of drug-resistant TB were diagnosed and the cure rate was merely 59% globally.[1] Treatment of MDR-TB is between 9 and 20 months long (i.e., considerably longer than the 6 months that are sufficient for treatment of drug-sensitive TB), and requires treatment with recommended three to five drugs in total, depending on the drug regimen (e.g., BPaL, standardized shorter or longer MDR-TB regimen).[2] A new important addition to the treatment arsenal is bedaquiline (BDQ),[3] a diarylquinoline, selectively inhibiting mycobacterial ATP synthase.[4–6] BDQ exhibits complex pharmacokinetics (PK), with an effective half-life of 24 h,[4,7] and a terminal half-life of ~ 5.5 months,[4,8,9] caused by BDQ amphiphilic properties and subsequent peripheral intracellular ion trapping.[4] The decline in BDQ and M2 plasma concentration is driven by the dissociation from phospholipids and the tissue elimination rate,[4,10] which leads to detectable BDQ and M2 metabolite plasma concentrations even 96 weeks after treatment cessation in the majority of patients.[11] In order to reach therapeutic plasma concentrations faster, the approved BDQ dosing regimen consists of a 2-week loading dose (400 mg once daily) and a three times weekly maintenance dose (200 mg).[3] The recommended total treatment length varies between 6 months based on the label recommendations,[3] and 9–20 months according to the World Health Organization (WHO) guidelines,[2] depending on the setting and the patient's eligibility for shorter or longer MDR-TB regimens.[2] The drug has been shown to reduce time to sputum culture conversion and increase cure rates,[3,11–13] and is thus currently recommended for all patients with MDR-TB (given bacterial susceptibility) in combination with two to four other drugs (e.g., fluoroquinolones, linezolid, and often clofazimine).[2] However, resistance development to BDQ has been observed shortly after the drug was introduced.[14] Drug resistance is a problem arising from irregular drug intake or administration, monotherapy, and/or insufficient drug concentrations.[15] An increasing number of studies highlight the importance of adequate drug concentrations, partly to avoid the development of resistance, but also to improve treatment outcomes.[16–18]

Treatment with BDQ can cause severe adverse events, such as hepatotoxicity[8] and delayed ventricular repolarization (i.e., QTc-prolongation), which can lead to torsade de pointes and fatal arrhythmias.[3,8,19] Regular electrocardiogram monitoring is thus mandatory during BDQ treatment and the drug should be stopped if QTc is above 500 ms. The risk of cardiac arrhythmias is concentration-dependent and increases with increasing concentrations of the metabolite M2.[3,8,19] Furthermore, the risk for QTc-prolongation is increased when BDQ is administered in combination with other drugs known to cause QTc-prolongation (e.g., fluoroquinolones and clofazimine).

Interruptions of MDR-TB treatment are relatively common and can occur due to multiple reasons, such as severe adverse events, treatment adherence issues, or

lack of access to drugs. The proportion of patients with MDR-TB where treatment was interrupted at least once, varies from 6.1%[20] over 14.6%[21] to 93.0%[22] across different studies and settings. Due to the long terminal half-life and toxicity concerns, re-introducing BDQ after multiple dose interruption is not intuitive and there is a lack of guidelines addressing how treatment should be resumed. In this simulation-based study, we therefore aimed to derive model-based dosing recommendations for BDQ re-introduction after treatment interruption, taking both safety and efficacy into account.

METHODS

Population pharmacokinetic model

BDQ and M2 metabolite concentrations were simulated from a previously published population pharmacokinetic (PopPK) model.[9] The model was built on data from 335 patients with MDR-TB enrolled in the clinical trials C208 (ClinicalTrials.gov number NCT00449644) and C209 (ClinicalTrials.gov number NCT00910871). The model incorporates BDQ transit absorption, a three-compartmental distribution for BDQ, and a one-compartment model for the M2 metabolite. Covariates included in the PopPK model influencing BDQ and M2 metabolite exposures are age, race (Black or non-Black), bodyweight, and albumin plasma concentrations. Simulations were performed for the typical individual, which was non-Black, 32 years of age, with a bodyweight of 57 kg and an albumin plasma concentration of 3.7 g/dl at the start of treatment. Bodyweight and albumin concentrations were included as time-varying covariates and were 63 kg and 4.0 g/dl after 120 weeks of treatment, respectively.[9] In addition, different patient subpopulations with different covariate combinations were simulated to investigate if the BDQ re-introduction strategy derived for the typical level are applicable to patients across the covariate range. The 5th and 95th percentiles for continuous covariates, as well as the less common value for binary covariates, were simulated in addition to the typical patient. In order to derive the 5th and 95th percentiles for continuous covariates from the reported median and range,[9] the mean and standard deviation were approximated using the Box-Cox method.[23]

Simulations

Multiple treatment interruptions and BDQ re-introduction scenarios were explored, as summarized in Table 1. The simulated treatment interruption scenarios included interruptions occurring between 1 and 72 weeks of treatment for a length of 1–10 weeks (1-week increments). For BDQ re-introduction, no loading dose, a 1-week loading dose (400 mg once daily), and a 2-week loading dose (200 mg and 400 mg once daily) were simulated (see Table 1). Because simulating all possible combinations of the above-described scenarios would lead to 2880 simulations in the typical patient alone, we developed a workflow which enabled us to perform less simulations in total, while still being able to obtain dosing recommendations for each scenario (see Figure S1).

Due to the lack of a thoroughly clinically validated target for BDQ efficacy and safety, we defined targets for clinical efficacy and safety based on the BDQ and M2 metabolite exposure in the typical patient during standard treatment without any dose interruption, because the standard BDQ dosing has been shown to be efficacious and safe in the majority of patients.[3] The efficacy target was the 95.0% average BDQ plasma concentration (C_{avg}) as it would have been at the given time point during treatment if no interruption occurred (i.e., a time-varying target). Because the BDQ C_{avg} is much higher during the loading dose phase and then drastically decreases during the maintenance phase, the efficacy was evaluated 3 weeks after BDQ re-introduction, thus avoiding overestimation of BDQ exposure. The safety limit was to not exceed the maximal M2 metabolite C_{avg} seen during standard treatment. To derive dosing recommendations for each scenario, typical average daily (during loading dose phase) and weekly (during maintenance phase) BDQ and M2 metabolite plasma concentrations (C_{avg}) were simulated from the PopPK model, using the typical patient covariates (see Table S1) as input. Interindividual variability, interoccasion variability, and residual error were excluded from

TABLE 1 Simulated re-introduction scenarios

Interruption at treatment week	Length of interruption, weeks	Loading dose
1–72	1–10	No loading dose
		2-week 200 mg o.d.
		1-week 400 mg o.d.
		2-week 400 mg o.d.

TABLE 2 Simulated average BDQ and M2 plasma concentrations following different loading dose strategies for the typical patient

	Average BDQ concentration, ng/ml, 3 weeks after treatment re-introduction					Maximal average M2 concentration, ng/ml, after treatment re-introduction			
Interruption scenario	**Without interruption**	**No loading dose**	**1-week loading dose (400 mg o.d.)**	**2-week loading dose (400 mg o.d.)**	**2-week loading dose (200 mg o.d.)**	**Without interruption**	**1-week loading dose (400 mg o.d.)**	**2-week loading dose (400 mg o.d.)**	**2-week loading dose (200 mg o.d.)**
1 week in, 1-week dose interruption[a]	*871.3*	632.8	**850.9**	**1140.9**	824.0	*358.2*	**317.6**	448.1	**268.0**
1 week in, 2-week dose interruption	*869.5*	610.2	**828.3**	**1118.5**	801.4	*358.2*	**293.6**	431.5	**254.5**
1 week in, 3-week dose interruption	*872.5*	592.3	810.4	**1100.7**	783.6	*358.2*	**280.2**	419.9	**244.8**
2 weeks in, 1-week dose interruption	*869.5*	819.4	**1037.5**	**1327.7**	**1010.6**	*358.2*	408.0	522.0	**343.6**
2 weeks in, 6-week dose interruption	*910.8*	680.3	**898.4**	**1189.0**	**871.7**	*358.2*	**299.8**	439.4	**265.5**
2 weeks in, 7-week dose interruption	*937.1*	665.6	883.7	**1174.4**	857.0	*358.2*	**291.2**	432.1	**259.0**
3 weeks in, 1-week dose interruption	*872.5*	822.4	**1040.5**	**1330.8**	**1013.6**	*358.2*	390.5	512.8	**334.6**
3 weeks in, 2-week dose interruption	*878.9*	784.8	**1003.0**	**1293.3**	**976.1**	*358.2*	358.3	489.8	**311.8**
3 weeks in, 6-week dose interruption	*923.7*	693.4	**911.4**	**1202.1**	**884.8**	*358.2*	**301.4**	441.4	**267.9**
3 weeks in, 7-week dose interruption	*937.1*	679.2	**897.2**	**1188.0**	870.7	*358.2*	**294.2**	434.6	**261.8**
3 weeks in, 8-week dose interruption	*950.8*	667.1	885.1	**1175.9**	858.6	*358.2*	**288.2**	428.6	**256.7**
6 weeks in, 1-week dose interruption	*898.7*	848.7	**1066.8**	**1357.3**	**1040.1**	*358.2*	372.3	506.6	**329.1**
6 weeks in, 6-week dose interruption	*964.6*	734.7	**952.7**	**1243.6**	**926.2**	*358.2*	**309.4**	449.2	**265.6**
6 weeks in, 7-week dose interruption	*978.3*	721.0	**938.9**	**1229.8**	912.5	*358.2*	**303.1**	443.3	**271.1**
6 weeks in, 8-week dose interruption	*991.8*	708.9	926.8	**1217.7**	900.4	*358.2*	**297.6**	438.0	**266.2**
24 weeks in, 6-week dose interruption	*1165.7*	938.5	**1155.4**	**1446.2**	**1129.7**	*358.2*	**356.6**	493.7	**322.4**
24 weeks in, 7-week dose interruption	*1173.7*	919.7	**1136.4**	**1427.2**	1110.8	*358.2*	**349.1**	486.9	**316.1**
24 weeks in, 8-week dose interruption	*1181.5*	902.3	1119.0	**1409.7**	1093.4	*358.2*	**343.3**	480.7	**310.3**
31 weeks in, 6-week dose interruption	*1216.2*	990.1	**1206.2**	**1496.7**	**1180.9**	*358.2*	367.9	503.9	**333.2**
31 weeks in, 7-week dose interruption	*1222.4*	969.6	**1185.6**	**1476.0**	1160.3	*358.2*	360.7	473.1	**326.2**
31 weeks in, 8-week dose interruption	*1228.4*	950.5	1166.6	**1456.8**	1141.3	*358.2*	**353.9**	466.9	**320.5**
32 weeks in, 7-week dose interruption	*1228.4*	975.7	**1191.7**	**1482.0**	**1166.4**	*358.2*	361.5	498.0	**327.8**
32 weeks in, 8-week dose interruption	*1234.1*	956.5	**1172.4**	**1462.6**	1147.1	*358.2*	**355.2**	491.5	**321.7**
32 weeks in, 9-week dose interruption	*1239.6*	938.6	1154.4	**1444.5**	1129.2	*358.2*	**349.1**	485.2	**316.1**
52 weeks in, 6-week dose interruption	*1307.1*	1083.6	**1297.5**	**1586.2**	**1273.1**	*358.2*	386.4	519.9	**351.3**
52 weeks in, 7-week dose interruption	*1309.8*	1060.0	**1273.8**	**1562.3**	**1249.4**	*358.2*	378.6	512.3	**344.2**

TABLE 2 (continued)

Interruption scenario	Average BDQ concentration, ng/ml, 3 weeks after treatment re-introduction					Maximal average M2 concentration, ng/ml, after treatment re-introduction			
	Without interruption	No loading dose	1-week loading dose (400 mg o.d.)	2-week loading dose (400 mg o.d.)	2-week loading dose (200 mg o.d.)	Without interruption	1-week loading dose (400 mg o.d.)	2-week loading dose (400 mg o.d.)	2-week loading dose (200 mg o.d.)
52 weeks in, 8-week dose interruption	*1312.4*	1038.1	**1251.8**	**1540.2**	1227.4	*358.2*	370.5	505.4	**336.6**
52 weeks in, 9-week dose interruption	*1314.9*	1017.5	1231.1	**1519.4**	1206.7	*358.2*	364.9	498.9	**331.6**
52 weeks in, 10-week dose interruption	*1317.3*	998.1	1211.5	**1499.8**	1187.2	*358.2*	**357.3**	493.1	**324.4**

Note: The maximal M2 metabolite C_{avg} is 358.2 ng/ml. BDQ and M2 average concentrations are calculated based on weekly AUC_{0-168h}. Bold numbers indicate that the efficacy/safety target is met. Non-bold numbers indicate that the efficacy/safety target is not met. Italic numbers indicate the BDQ/M2 metabolite exposure as it would have been without dose interruption for comparison. The characteristics of the typical patient were non-Black race, 32 years of age, 57 kg bodyweight, and an albumin concentration of 3.7 g/dl. The maximal average M2 metabolite concentration (ng/ml) after treatment re-introduction for no loading dose is not shown as this scenario always meets the safety target.

Abbreviations: AUC_{0-168h}, area under the concentration versus time curve weekly; BDQ, bedaquiline; C_{avg}, average plasma concentration.

[a]"X weeks in" refers to that the interruption occurred after X weeks of treatment.

the simulations. BDQ and M2 metabolite C_{avg} were derived from model-based areas under the concentration versus time curve from 0–24 h (AUC_{0-24h}) and weekly AUC (AUC_{0-168h}). In the simulations, the standard dosing regimen[3] was replicated (i.e., a 2-week loading dose of 400 mg once daily followed by 200 mg 3 times weekly). Thus, during the loading dose phase the AUC_{0-24h}, and during the maintenance phase the weekly AUC_{0-168h} were simulated. Based on the simulated AUC_{0-24h} and AUC_{0-168h}, the average BDQ and M2 metabolite plasma concentrations (C_{avg}) were computed as described in Equation 1:

$$C_{avg} = \frac{AUC_{0-Xh}}{\tau} \quad (1)$$

where Xh is either 24 h or 168 h, and τ is 24 h for AUC_{0-24h} and 168 h for AUC_{0-168h}.

To derive dosing recommendations, the loading dose strategy leading to BDQ and M2 metabolite exposures both meeting the efficacy and safety target was selected. In scenarios where it was not possible to reach both the safety and the efficacy target, efficacy was prioritized, but a warning regarding safety was given. In case several scenarios would lead to exposures meeting the proposed efficacy and safety target, the most common dosing strategy across all scenarios was selected in order to keep the final recommendations as easy-to-use as possible.

Example of clinical utility – patient case

The developed model-based approach was applied in clinical use in Sweden in 2021. A patient case is given here to illustrate the clinical utility of the model-based approach for re-introduction of BDQ after dose interruption. A 60-year-old patient with pulmonary MDR-TB of Black race, weighing 44 kg, and an observed albumin concentration of 3.1 g/dl underwent treatment interruption due to hepatotoxicity. The interruption occurred after 11 weeks of treatment and lasted for 8 weeks when liver values were normalized. An optimized re-introduction strategy for the patient was evaluated by simulating BDQ and M2 metabolite exposures following different loading doses or no loading dose taking the patient's covariate information into account.

Software

All simulations were performed in NONMEM version 7.3.0 (Icon Development Solutions, Hanover, MD, USA)[24] assisted by PsN version 5.0.0 (Department of Pharmacy,

Uppsala University, Uppsala, Sweden).[25] Dataset creation and creation of graphs were performed in R statistical software version 4.1.1.[26]

RESULTS

Simulations

The simulated profile for the typical patient following a standard BDQ treatment is shown in Figure S2 for a total treatment length of 18 months (72 weeks), as recommended for longer treatment regimens.[2] Figure S2 also illustrates the efficacy and safety targets. In total, 284 interruption and re-introduction scenarios were simulated following the workflow described in Figure S1. The simulation model code can be found in Material S1.

The model-predicted BDQ and M2 metabolite C_{avg} for different interruption scenarios are summarized in Table 2 and exemplary illustrated in Figures 1–3 for the typical patient. The safety limit for the typical patient (non-Black, 32 years, weighing 57 kg, with an albumin plasma concentration of 3.7 g/dl) was derived to be a maximal M2 metabolite C_{avg} of 358.2 ng/ml. The time-varying efficacy target is summarized in Table 2 for different interruption scenarios.

In addition, BDQ and M2 metabolite exposures in patient subpopulations with different covariates were simulated for the 5th and 95th percentiles of the continuous covariates and the less common value for binary covariates in the population (Table S1). The results are presented in Table S2 for selected extreme scenarios, including the safety and time-varying efficacy targets.

Re-introduction recommendations

The predictions of BDQ and M2 metabolite exposures for the typical patient suggest that most dose interruption scenarios (i.e., interruption between treatment weeks 3 and 72,

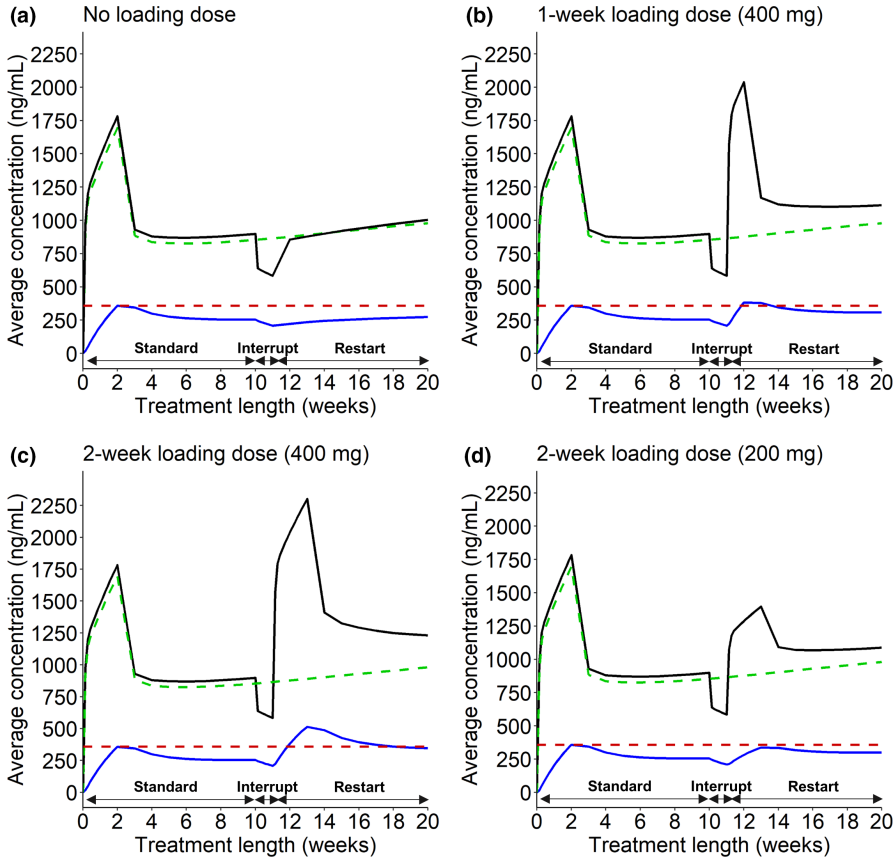

FIGURE 1 Model-based predictions of average daily (during week 0–2 and week 10–11) and weekly (remaining weeks) bedaquiline (BDQ; black solid line) and M2 metabolite (blue solid line) concentrations in the typical patient following a dose interruption at week 10 for a duration of 1 week. The green dashed line represents the time-varying efficacy target (average BDQ concentration) and the lower red dashed line is the safety target (maximal average M2 concentration in a scenario without dose interruption). (a) Scenario where no loading dose is administered. (b) Scenario where a 1-week loading dose of 400 mg once daily is administered. (c) Scenario where a 2-week loading dose of 400 mg once daily is administered. (d) Scenario where a 2-week loading dose of 200 mg once daily is administered. It becomes evident that a 2-week loading dose of 200 mg once daily is necessary to reach the efficacy target, while being safe

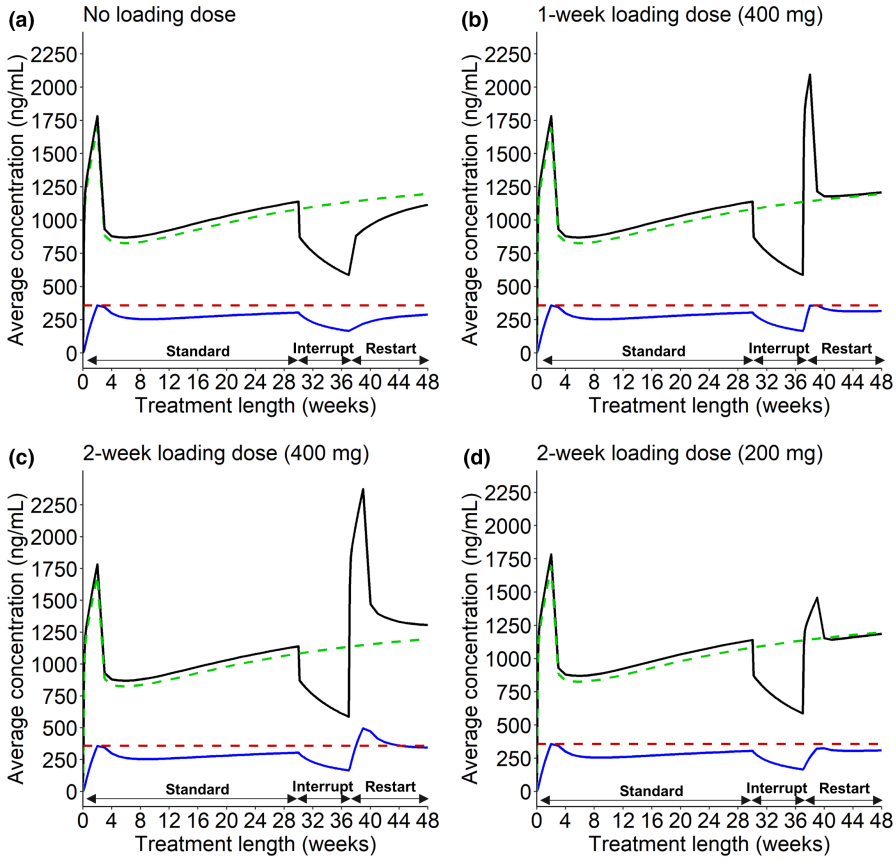

FIGURE 2 Model-based predictions of average daily (during week 0–2 and week 30–37) and weekly (remaining weeks) bedaquiline (BDQ; black solid line) and M2 metabolite (blue solid line) concentrations in the typical patient following a dose interruption at week 30 for a duration of 7 weeks. The green dashed line represents the time-varying efficacy target (average BDQ concentration) and the lower red dashed line is the safety target (maximal average M2 concentration in a scenario without dose interruption). (a) Scenario where no loading dose is administered. (b) Scenario where a 1-week loading dose of 400 mg once daily is administered. (c) Scenario where a 2-week loading dose of 400 mg once daily is administered. (d) Scenario where a 2-week loading dose of 200 mg once daily is administered. It becomes evident that a 1-week loading dose of 400 mg once daily is necessary to reach the efficacy target, while being safe

and interruption length: 1 to 6 weeks) require a 2-week loading dose of 200 mg once daily to reach the proposed efficacy target while being below the suggested safety limit (Tables 2, 3, and Figure 1). For a 7-week long interruption at weeks 3–31 and an 8-week long interruption at weeks 32–72, a 1-week loading dose of 400 mg once daily was best from an efficacy and safety perspective (Tables 2, 3, and Figure 2). Interruptions longer than 7 weeks (interruption at weeks 3–31) and 8 weeks (interruption at weeks 32–72) required a 2-week loading dose of 400 mg once daily to reach the proposed efficacy target, but the suggested safety limit might be exceeded depending on the timepoint and length of interruption (Tables 2, 3, and Figure 3). Interruptions at week 1 required either a 1-week loading dose (400 mg once daily) if the interruption was no longer than 2 weeks, or a 2-week loading dose (400 mg once daily) for an interruption longer than 2 weeks, which, however, led to average M2 metabolite concentrations above the safety limit (e.g., by 61.7 ng/ml for a 3-week long interruption; Table 2). The final dosing recommendations on a typical level are presented in Table 3.

These recommendations are true for the majority of the simulated patient subpopulations. For a few cases where both the patient covariate as well as the explored scenario was extreme (e.g., very early interruption for a very long or short time period), the optimal dosing strategy differed. In simulated patients with a high bodyweight, for example, the BDQ exposure after an 8-week interruption at treatment week 52 was insufficient for efficacy following a 1-week loading dose (400 mg once daily), and a 2-week loading dose (400 mg once daily) would be required. The cases where the optimal loading dose strategy differed from the typical patient are indicated in Table S2.

Example of clinical utility – patient case

The utility of the approach for re-introduction of BDQ after dose interruption was applied to a patient case treated for pulmonary MDR-TB in Sweden during 2021.

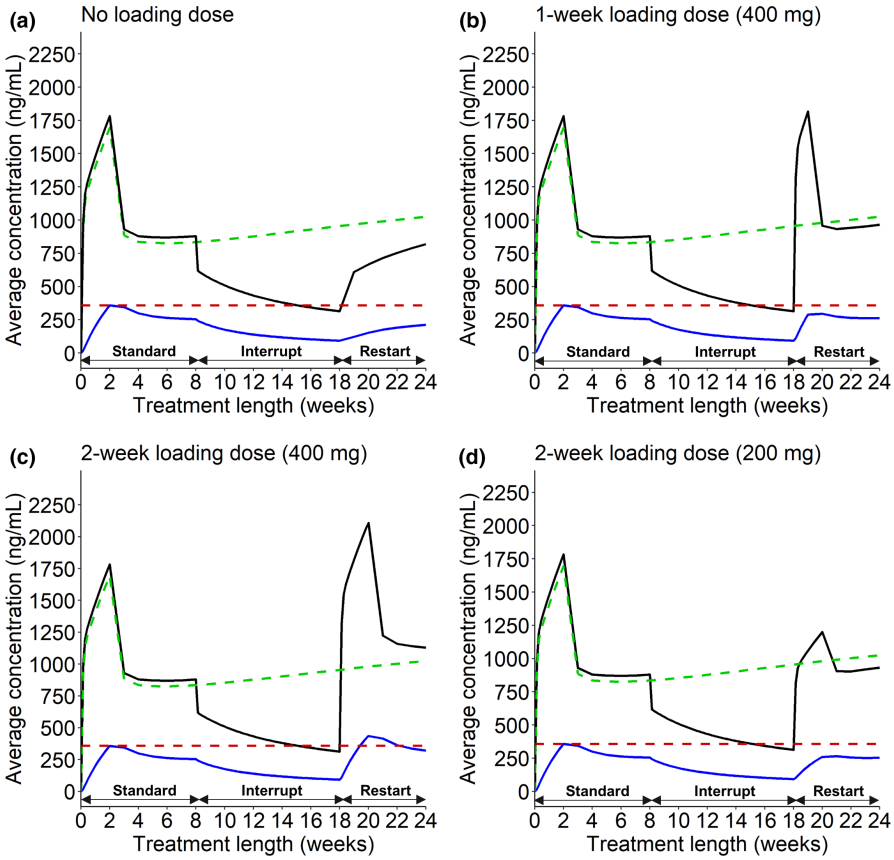

FIGURE 3 Model-based predictions of average daily (during weeks 0–2 and weeks 8–18) and weekly (remaining weeks) bedaquiline (BDQ; black solid line) and M2 metabolite (blue solid line) concentrations in the typical patient following a dose interruption at week 8 for a duration of 10 weeks. The green dashed line represents the time-varying efficacy target (average BDQ concentration) and the lower red dashed line is the safety target (maximal average M2 concentration in a scenario without dose interruption). (a) Scenario where no loading dose is administered. (b) Scenario where a 1-week loading dose of 400 mg once daily is administered. (c) Scenario where a 2-week loading dose of 400 mg once daily is administered. (d) Scenario where a 2-week loading dose of 200 mg once daily is administered. It becomes evident that a 2-week loading dose of 400 mg once daily is necessary to reach the efficacy target, but the safety target is then slightly exceeded

In the patient (60 years, 44 kg, Black race, 3.1 g/dl albumin plasma concentration), treatment had been interrupted for 8 weeks due to hepatotoxicity after 11 weeks of BDQ treatment. Simulations showed that a 1-week loading dose of 400 mg once daily was most appropriate from an efficacy and safety point of view (Figure 4). The individualized treatment was re-introduced for the patient after the 8-week long interruption and no safety issues were observed.

DISCUSSION

We hereby propose an optimized strategy for BDQ reintroduction after treatment interruption, which is important because patients may interrupt dosing due to lack of access to the drug, severe adverse events, or treatment adherence issues. In this work, we developed an easy-to-use clinical decision support tool, which takes efficacy

TABLE 3 Loading dose strategy recommendations for a typical patient without access to individual bedaquiline concentrations

Interruption at week	Length of interruption, weeks	Required loading dose
1	1–2	1-week 400 mg o.d.
1	>2	2-week 400 mg o.d.[a]
2	1–6	2-week 200 mg o.d.
2	>6	2-week 400 mg o.d.[a]
3–31	1–6	2-week 200 mg o.d.
3–31	7	1-week 400 mg o.d.
3–31	>7	2-week 400 mg o.d.[a]
32–72	1–7	2-week 200 mg o.d.
32–72	8	1-week 400 mg o.d.[a]
32–72	>8	2-week 400 mg o.d.[a]

[a]Loading dose needed for efficacy, but safety target might be exceeded, depending on the occurrence and length of interruption.

and safety into account. The simulations showed that a reduced loading dose strategy (2-week 200 mg once daily) was sufficient in most interruption scenarios (interruption at treatment weeks 3–72 for 1–6 weeks). This model-based approach has been applied in clinical use, where BDQ was safely re-introduced in a patient with pulmonary MDR-TB following the dosing strategy suggested by our simulations.

Optimal re-introduction of BDQ after dose interruption is important to avoid excessive or subtherapeutic drug exposure. Due to the severity of the adverse events, mainly the risk of fatal ventricular arrhythmias, it is of utmost importance to keep M2 metabolite exposures low, especially because BDQ is commonly administered in combination with drugs that are also known to cause QTc-prolongation (e.g., fluoroquinolones and clofazimine). In addition, sufficient BDQ exposures are needed to avoid resistance development as well as to ensure cure.

An efficacy target commonly utilized is a C_{avg} of 600 ng/ml.[27,28] This is based on a mouse study[4] and has not sufficiently been validated in clinical trials. For the purpose of this study, we therefore based the efficacy and safety target on the exposure in the typical patient during standard treatment without any dose interruption, because the standard BDQ dosing has been shown to be efficacious and safe in the majority of patients.[3] The efficacy and safety targets thus corresponded to BDQ and M2 exposures reached in the clinic. The efficacy target was based on BDQ exposure, because an exposure-response relationship between BDQ exposure and antimycobacterial activity has previously been demonstrated.[12,29] The M2 metabolite is four to six times less active[3,9,30] and was therefore not incorporated in the efficacy target. Because the BDQ C_{avg} is much higher during the loading dose phase and then drastically decreases during the maintenance phase, the efficacy was evaluated 3 weeks after BDQ re-introduction, thus avoiding overestimation of BDQ exposure. To avoid

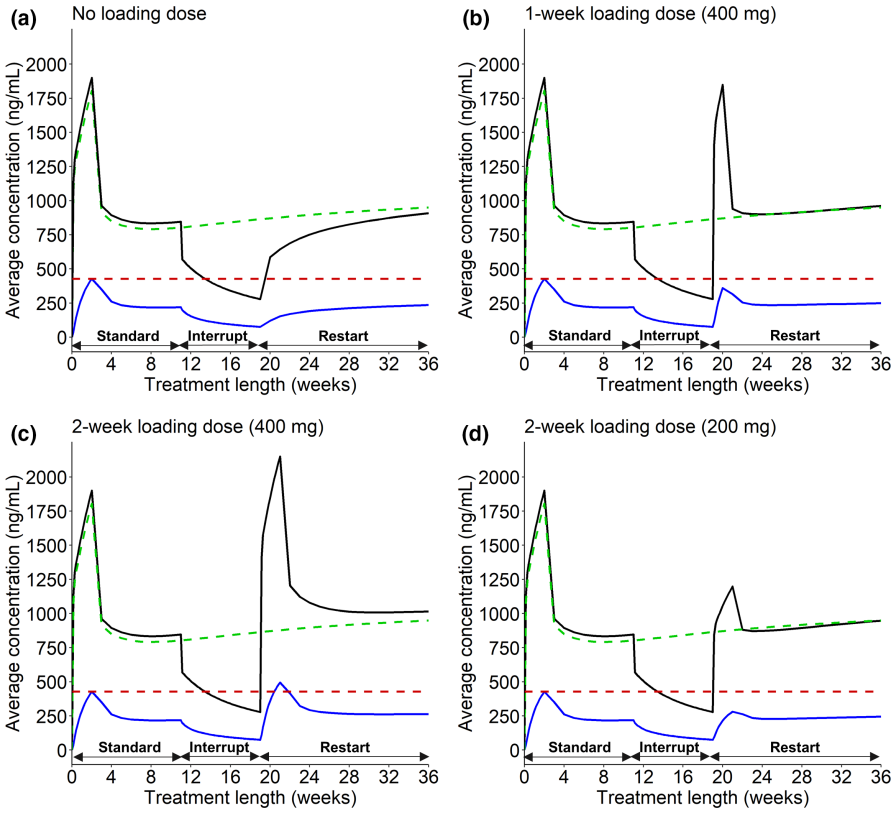

FIGURE 4 Patient case. Model-based predictions of average daily (during weeks 0–2 and weeks 11–19) and weekly (remaining weeks) bedaquiline (BDQ; black solid line) and M2 metabolite (blue solid line) concentrations in a real patient (60 years, 44 kg, Black race, 3.1 g/dl albumin plasma concentration) following a dose interruption at week 11 for a duration of 8 weeks. The green dashed line represents the time-varying efficacy target (average BDQ concentration) and the lower red dashed line is the safety target (maximal average M2 concentration in a scenario without dose interruption). (a) Scenario where no loading dose is administered. (b) Scenario where a 1-week loading dose of 400 mg once daily is administered. (c) Scenario where a 2-week loading dose of 400 mg once daily is administered. (d) Scenario where a 2-week loading dose of 200 mg once daily is administered. It becomes evident that a 1-week loading dose of 400 mg once daily is appropriate to meet both the efficacy and the safety target

a higher loading dose associated with an increased risk of toxicity in case of a negligible decrease in drug exposure, we defined the efficacy target to be 95.0% of the BDQ exposure. The M2 metabolite, however, has been associated with severe toxicity, mainly QTc-prolongation[3,8,19] and hepatotoxicity,[8] and was thus chosen as the safety target. As a limit, the maximal average M2 metabolite exposure during standard treatment was not to be exceeded at any timepoint after BDQ re-introduction, because M2 metabolite concentration is thought to have a direct effect on QTc-prolongation without any time delay.[9]

This simulation-based study suggests that dose interruptions occurring between treatment weeks 3 and 72 (interruption length: 1 to 6 weeks) require a 2-week loading dose (200 mg once daily) in the typical patient (Figure 1 and Tables 2, 3). In cases where treatment was interrupted for longer than 8 weeks, a 2-week loading dose of 400 mg once daily was needed to reach the efficacy target (Figure 3 and Tables 2, 3). However, the risk for QTc-prolongation might be increased as the safety limit is exceeded (see Table 2 and Figure 3). In some scenarios, either a 1-week (400 mg once daily) or 2-week (200 mg once daily) loading dose was appropriate regarding efficacy and safety (see Table 2). For the final dosing recommendations (Table 3), the dosing strategy leading to both efficacious and safe exposures in the majority of scenarios was selected in order to keep the final recommendations as easy-to-use as possible.

Simulations for different patient subpopulations showed that these conclusions are applicable to the majority of patient covariates. There were few cases in which the most optimal dosing strategy was different compared with the one for the typical patient. Differences for specific subpopulations and scenarios compared to the typical individual are marked in Table S2. However, one should also note that in all cases where the optimal dosing strategy for a patient subpopulation was different compared to the typical patient, the differences in exposure were minor. For example, whereas for simulated patients with high bodyweight (79 kg at start of treatment), a 1-week loading dose of 400 mg after an 8-week interruption at 52 weeks resulted in 94.6% of the BDQ C_{avg} without interruption (i.e., not reaching the efficacy target), in the typical patient with a bodyweight of 57 kg, 95.4% of the BDQ C_{avg} was reached (i.e., meeting the efficacy target). It can therefore be concluded that the proposed dosing recommendations derived on the typical patient level (Table 3) could be seen as one dose fits all recommendations and thus be applied to all patient subpopulations.

The results from the simulations should be regarded a decision support to the treating physician. Additional considerations may apply when the physician makes the decision on how BDQ should be introduced, such as disease severity or risk of adverse events. If QTc-prolongation was the reason for treatment interruption, a lower than usual M2 exposure might have to be targeted. In this case, the treating physician should consider a more conservative re-introduction strategy. Table 2 presents the M2 exposures for multiple interruption scenarios following different loading dose strategies, which can be used as guidance. In general, a 2-week (200 mg once daily) loading strategy led to the lowest M2 concentrations compared to the other loading strategies, and might thus be preferred for patients with a history of QTc-prolongation. A thorough review of concomitant QTc-prolonging drugs is also needed.

The derived dosing recommendations in this study are based on a one dose fits all approach. This approach does not take BDQ and M2 metabolite measured plasma concentrations (i.e., variability in PK parameters) into account, which is beneficial from a practical point of view, because most settings do not have the facilities to quantify BDQ and M2 metabolite concentrations. However, if individual plasma BDQ and M2 metabolite concentrations are available, the dosing recommendation should be refined on an individual level using Bayesian forecasting. The presented model-based approach could easily be extended to account for individual drug exposure, and a Bayesian forecast can be done by pharmacometrically trained pharmacists using the targets defined in this work.

The PopPK model used for simulation[9] was built on data from the two phase IIb studies C208 (ClinicalTrials.gov number NCT00449644) and C209 (ClinicalTrials.gov number NCT00910871). These studies were conducted at various study sites across different continents and included patients living with and without HIV co-infection and patients with Black, White, Hispanic, and Asian race. However, the covariate effects and variability in BDQ and M2 metabolite exposure might be different in different study populations, especially in a nonclinical trial setting. Validating the model-derived dosing recommendations in a real-world setting is thus of importance. Although the here proposed one dose fits all approach is easily implemented in all settings, considering individual observed BDQ and M2 metabolite plasma concentrations using Bayesian forecasting would provide more accurate dose predictions on an individual patient level. Investigating the role of model-informed precision dosing for optimized BDQ re-introduction in future work would therefore be of interest. In addition, this work utilizes nonvalidated efficacy and safety targets. Because there is a lack of sufficiently clinically validated targets for BDQ, the efficacy and safety targets for this study were based on the exposure in a patient receiving standard BDQ treatment. This approach assumes that the licensed dosing regimen[3] is appropriate from a safety and efficacy perspective. There is a need to investigate safety and efficacy in the clinic further and to establish targets.

In conclusion, we here propose an optimized strategy for BDQ re-introduction after treatment interruption which is easy to use and provides guidance to clinicians for safe and efficacious BDQ dosing.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

L.K., Y.A.S., L.D.F., and U.S.H. wrote the manuscript. U.S.H. and L.K. designed the research. L.K., Y.A.S., L.D.F., and U.S.H. performed the research. L.K. analyzed the data.

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