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Early View

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Safety of prolonged treatment with bedaquiline in programmatic conditions

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INTRODUCTION

Tuberculosis (TB) remains a major global health problem that is further complicated by the emergence of antimicrobial resistance. TB strains resistant to key drugs, such as rifampicin-resistant (RR) TB or multidrug-resistant (MDR)-TB, substantially reduce the probability of treatment success. Strains with added resistances to second-line drugs, such as extensively drug resistant (XDR)-TB, further limit treatment options and probability of success. The most recent data suggest a global treatment success rate of 59% for RR/MDR-TB [1].

Bedaquiline is a drug with antituberculous bactericidal activity approved by the European Medicines Agency in 2013 for treatment of MDR-TB over a period of 24 weeks. It is now considered a first-line medicine for RR/MDR-TB treatment according to the World Health Organization (WHO) [2,3]. In 2020, the WHO allowed off-label prolonged use of bedaquiline, defined as longer than 24 weeks. This recommendation was based on analysis of data derived from the endTB observational study [4,5]. Prolonged use of bedaquiline is frequently considered by clinicians due to limited number of options available for treatment of patients with highly-resistant TB. However, evidence of the safety of prolonged bedaquiline use under programmatic conditions is limited [6].

The primary objective of our study was to evaluate the safety of prolonged use of bedaquiline, defined as use for more than 190 days, under programmatic conditions. The secondary objective was to compare incidence of serious adverse events (AEs) and bedaquiline-related AEs experienced among individuals treated with standard and prolonged treatment with bedaquiline.

MATERIAL AND METHODS

Study design and population

This was a prospective cohort study using data from a cohort event monitoring study combined with routine data of the programmatic management of drug-resistant TB, defined as all associated functions related to providing services in the country, based on the TB strategy to achieve the targets set for drug-resistant TB in the Global Plan to End TB [6,7]. The study protocol was approved by the Ethics Committee at the Republican Scientific Practical Centre on Pulmonology and Phthisiatry (RSPCPP) of Belarus. All new and previously treated patients with bacteriologically confirmed pulmonary RR-TB initiating treatment with bedaquiline at RSPCPP, a tertiary care hospital, between March 2015 and June 2016 were consecutively included in the study. Successfully treated patients were followed-up for 24 months for possible recurrence of TB. Patients receiving delamanid concurrently with bedaquiline were excluded from this study.

Definitions

WHO definitions for drug resistance, patient registration groups and treatment outcomes from 2013 were used [8]. Patients with RR-TB, whose isolates were resistant to either a fluoroquinolone or to any of the second-line injectables, but not to both, were defined as having pre-XDR-TB. An adverse event was defined as any untoward medical occurrence that may present in a patient during treatment with TB drugs, but which does not necessarily have a causal relationship with this treatment [9]. A serious event was one which either led to death or a life-threatening experience, hospitalization or prolongation of hospitalization, persistent significant disability or a congenital anomaly/birth defect [10]. Severity of the event was classified as mild (grade 1), moderate (grade 2) and severe (grades 3 and 4) according to the Common Terminology Criteria for Adverse Events, version 5 [10,11].

Study procedures

All bacteriological tests were performed at the Reference Laboratory of the National TB Centre in Minsk, Belarus, which was quality-assured by the Supranational Reference Laboratory in Milan, Italy [12]. Details of bacteriological tests are described at Supplementary Appendix 1.

Treatment regimens were individually tailored according to the drug susceptibility profile and contained bedaquiline, linezolid and clofazimine, unless contraindicated. If confirmed susceptible, the regimens had one second-line injectable and/or a fluoroquinolone added to the regimen. Terizidone, pyrazinamide, imipenem-cilastatin with amoxicillin clavulanate and/or ethionamide/protionamide were added to bring the total number of effective drugs (i.e., defined as drugs to which patient's isolates were not resistant to) in the treatment regimen to six.

The recommended standard duration of bedaquiline use is 24 weeks (168 days) [5]. However, this duration may vary due to events, such as missed or cancelled clinic visits. Based on a histogram of the duration of bedaquiline use, we grouped the patients to those, who received bedaquiline for <190 days as receiving standard treatment with bedaquiline and to patients, who received bedaquiline for ≥190 days as receiving prolonged treatment with bedaquiline (histogram presented at Supplementary Appendix 2).

The decision to prolong treatment with bedaquiline was based on the following criteria: remaining sputum culture-positive after ≥3 months of treatment, but not meeting the criteria for treatment failure; less than four effective drugs remaining in the treatment regimen if bedaquiline was discontinued; and/or individual risk factors for poor outcomes, such as body mass index (BMI) <18.5 kg/m^2, high pre-treatment sputum smear bacillary load defined semi-quantitatively as 2+ or 3+, HIV-positivity and extensive/advanced pulmonary disease [13]. Injectables were continued throughout the treatment, if tolerated. The overall treatment duration was at least 12 months after the culture conversion for a minimum total treatment duration of 18 months.

Treatment efficacy and safety monitoring was implemented through bacteriological, clinical and laboratory assessment. All assessments were performed at the start of treatment and monitored at least monthly during the treatment and semi-annually post treatment for 24 months (Supplementary Table 1). AEs were recorded and considered potentially bedaquiline treatment-related, if they occurred either during treatment or up to 5 months after bedaquiline was stopped, in view of the prolonged terminal elimination half-life of bedaquiline [14].

The Belarussian national electronic TB registry and national pharmacovigilance electronic database were used for data collection. Pharmacovigilance specialists checked the contents of the data for completeness, accuracy and judged on the severity of all reported AE, as well as performed causality assessment for serious AE.

Data Analysis

We compared individuals, who received standard treatment with bedaquiline, with those, who received prolonged treatment. We described each group based on demographic, clinical and treatment-related factors and calculated the number and incidence of all AEs, serious AEs and bedaquiline-related events for each group. We compared groups using two-sided tests: Kruskal-Wallis test for medians, Pearson's chi square test for proportions and Fisher exact test for rates. Uncertainty in incidence rates were calculated using exact Poisson confidence intervals. We calculated the proportion of patients experiencing QTcF >500 ms or an increase by >60 ms from baseline during treatment with bedaquiline.

We then conducted regression analyses to compare between patients, who completed standard treatment and those, who received prolonged treatment. We did this to minimize survivor bias that may occur from patients, who died early in treatment or stopped bedaquiline due to a bedaquiline-related AEs and therefore never had an opportunity to receive prolonged treatment. e We used generalized estimating equations with a Poisson distribution and log-link to estimate incidence rate ratios and their 95% confidence intervals (using robust standard errors). The analyses accounted for clustering at the individual

level and used an autoregressive correlation structure. The primary outcome was the incidence of serious AEs occurring within 5 months of bedaquiline cessation and the secondary outcome was the incidence of serious AEs occurring during receipt of bedaquiline up to day 189.

To construct multivariate models, we first performed univariate analysis on various predictors of our outcomes. The predictors were selected *a priori*, based on the literature, as well as on what we perceived would be known by the treating clinicians [15]. The predictors included: sex (male or female), age (per ten-year increase), use of second-line injectable drugs (yes or no), number of concomitant TB medications (per additional drug), smear-positivity at treatment initiation (yes or no), cavitation on chest x-ray at treatment start (yes or no), BMI (<18.5 or ≥ 18.5 kg/m^2), QT interval corrected by the Fridericia's correction formula (QTcF) (per 10 ms increase), alcohol use (defined as alcohol use led to problems in relationship, health, employment or finances within the past year; yes or no), diabetes mellitus (yes or no), and HIV co-infection (yes or no). Multivariate models were constructed including group allocation (i.e., standard vs. prolonged), age, sex and all predictors with $p < 0.2$ in univariate analysis. We also conducted a sensitivity analysis that included all predictors in multivariate models to see if conclusions might differ.

We conducted a secondary analysis in the prolonged bedaquiline group. We compared the incidence of serious AEs in the first 189 days of treatment vs. the incidence of serious AEs from day 190 up to 5 months after the stopping bedaquiline.

We did a *post hoc* analysis to compare the time to first instance of QTcF prolongation by >60 ms between the standard and prolonged treatment groups among those, who had both baseline and at least one QTcF measurement during the treatment. We considered the last QTcF measure as a censoring event. We used Cox proportional hazards model adjusted for the variables considered in our previous multivariate model to estimate the hazard ratio and 95% confidence interval for the incidence of QTcF prolongation by >60 ms between the groups.

All analyses were conducted with R software (The R Foundation, Vienna, Austria, version 4.0.0) using package geepack (version 1.3-1).

RESULTS

Sociodemographic data and disease characteristics

A total of 120 RR-TB patients were treated at the RSPCPP during March 2015 through June 2016. Out of them, 7 were excluded from the cohort: 5 because no bedaquiline was used and 2 because of getting delamanid in addition to bedaquiline. A total of 113 patients with pulmonary RR-TB were subjected to the analyses. Of these, 83 (73.5%) received standard treatment with bedaquiline and 30 (26.5%) received prolonged. The proportion of patients, who were smear-positive ($p<0.01$) at the start of treatment, was higher among the patients, who received prolonged treatment (Table 1). Other characteristics did not significantly differ between the treatment groups.

TABLE 1. Characteristics of patients on standard or prolonged treatment with bedaquiline.[1]

	Standard treatment with bedaquiline	Prolonged treatment with bedaquiline	Overall	p-value[4]
Number of patients	83	30	113	--
Patient characteristics				
Median (IQR) age	37 (29 to 47)	38 (31 to 51)	38 (30 to 47)	0.74
Male	60 (72.3%)	21 (70%)	81 (71.7%)	0.99
HIV infection	4 (4.8%)	0 (0%)	4 (3.5%)	0.52
Thyroid disease	3 (3.6%)	0 (0%)	3 (2.7%)	0.69
Alcohol abuse disorder	11 (13.3%)	6 (20%)	17 (15%)	0.56
Diabetes	6 (7.2%)	1 (3.3%)	7 (6.2%)	0.75
Median (IQR) baseline QTcF interval [2]	388 (360 to 407)	386 (362 to 416)	387 (360 to 410)	0.63
Microbiologic/radiologic findings				
AFB smear positive at baseline[3]	21 (25.3%)	23 (76.7%)	44 (38.9%)	<0.01
Cavitation on chest X-ray	50 (60.2%)	22 (73.3%)	72 (63.7%)	0.29
Previous treatment				
Never previously treated for TB	9 (10.8%)	1 (3.3%)	10 (8.8%)	0.39
Previously treated with first line drugs	12 (14.5%)	1 (3.3%)	13 (11.5%)	0.19
Previously treated with second line drugs	62 (74.7%)	28 (93.3%)	90 (79.6%)	0.06
DST				
DST performed for fluoroquinolones	78 (94%)	30 (100%)	108 (95.6%)	0.39
If DST performed, fluoroquinolone resistant	67 (85.9%)	27 (90%)	94 (87%)	0.80
DST performed for second line injectables	79 (95.2%)	30 (100%)	109 (96.5%)	0.52
If DST performed, second line injectable resistant	60 (75.9%)	22 (73.3%)	82 (75.2%)	0.97

AFB: acid-fast bacilli; DST: drug susceptibility test; HIV: human immunodeficiency virus; TB: tuberculosis.
[1]: reported as n (%) unless otherwise specified. [2]: missing for 5 patients (2 in the bedaquiline 6 months group and 3 in the bedaquiline more than 6 months group).[3]: missing for 1 patient (1 in the bedaquiline 6 months group). [4]: following tests were used to calculate p-value: for medians - Kruskal-Wallis Test; for proportions - Chi Square Test; for rates - Exact Fisher two-sided test.

Treatment

Characteristics of the treatment regimen and outcomes are reported in Table 2. The number of effective drugs included in the initial regimen was six in both groups. The median total treatment duration was 24.2 months among those, who received prolonged treatment with bedaquiline and 23.7 months among those, who received standard treatment (p<0.01). The median (IQR) duration of bedaquiline use among those receiving prolonged bedaquiline was 8.0 (7.3 to 9.2) months. The duration of receiving second-line injectables was also significantly longer among those receiving prolonged bedaquiline (median 13.8 months vs. 5.3 months; p=0.02). Treatment success was equivalent between groups (92.8% among standard duration vs. 96.7% among prolonged duration; p=0.92). There was no recurrent TB among successfully treated patients during the follow-up period of 24 months.

TABLE 2. Regimen received and treatment outcomes among patients on standard and prolonged treatment with bedaquiline.[1]

		Bedaquiline <190 days (N=83)		Bedaquiline ≥ 190 days (N=30)	p-value[4]
Regimen duration					
Median (IQR) total treatment duration, months		23.7 (20.7 to 24.0)		24.2 (23.8 to 24.9)	<0.01
Median (IQR) treatment duration with bedaquiline, months		5.5 (5.4 to 5.6)		8.0 (7.3 to 9.2)	<0.01
Median (IQR) treatment duration with linezolid, months[2]		23.5 (20.1 to 24.0)		24.1 (23.7 to 24.4)	<0.01
Median (IQR) treatment duration with injectables, months[3]		5.3 (5.3 to 21.2)		13.8 (10.7 to 24.2)	0.02
Treatment outcomes					
Number with treatment success		77 (92.8%)		29 (96.7%)	0.75
Number with failure		1 (1.2%)		0 (0%)	1
Number dying during treatment		3 (3.6%)		1 (3.3%)	1
Number lost to follow-up		2 (2.4%)		0 (0%)	0.96
Regimen Received	**Initial**	**Added During Treatment**	**Initial**	**Added During Treatment**	
Number of drugs in initial regimen; median (IQR)	6 (5 to 6)	--	6 (6 to 6)	--	0.80
Included moxifloxacin or levofloxacin or gatifloxacin	11 (13.3%)	43 (51.8%)	0 (0%)	15 (50%)	0.08
Included linezolid	83 (100%)	0 (0%)	29 (96.7%)	1 (3.3%)	0.59
Included clofazimine	80 (96.4%)	1 (1.2%)	27 (90%)	2 (6.7%)	0.39
Included terizidone	82 (98.8%)	0 (0%)	28 (93.3%)	2 (6.7%)	0.35
Included amikacin or capreomycin or kanamycin	32 (38.6%)	6 (7.2%)	14 (46.7%)	10 (33.3%)	0.58
Included pyrazinamide	54 (65.1%)	2 (2.4%)	23 (76.7%)	0 (0%)	0.35
Included imipenem/cilastatin with amoxicillin and clavulanic acid	42 (50.6%)	2 (2.4%)	16 (53.3%)	7 (23.3%)	0.97
Included ethionamide or prothionamide	8 (9.6%)	8 (9.6%)	2 (6.7%)	3 (10%)	0.91

[1]: reported as n (%) unless otherwise specified. [2]: all patients received linezolid during treatment. [3]: only if received injectables ever during treatment (n=35 Bedaquiline 6 months; n=20 Bedaquiline more than 6 months; n=55 Overall). [4]: following tests were used to calculate p-value: for medians - Kruskal-Wallis Test; for proportions - Chi Square Test; for rates - Exact Fisher two-sided test. For the regimen received, p-value only refers to initial regimen.

Safety profile

Any adverse event

The most common AEs observed among patients were elevated liver enzymes, eosinophilia, ECG abnormalities including prolongation of the QTcF, electrolyte disorders, hyperuricaemia, hyperglycaemia, and elevated creatinine and alkaline phosphatase. Details of the AEs recorded during the treatment are presented in Table 3, while the complete list of events and their classification as per system organ class and category is presented in Supplementary Appendix 3.

More than 90% of patients in both groups experienced at least one AE during treatment with a total 2,030 events registered. There was no statistically significant difference in total incidence of any AE during treatment among patients who received the prolonged treatment with bedaquiline, compared to those who received standard treatment (80.9 vs. 80.1 per 100 person months of treatment; p=0.83). However, when comparing those AEs that occurred within five months of cessation of bedaquiline, significantly more events occurred in the standard bedaquiline group than in the prolonged group (128.0 vs. 114.2 per 100 person months of treatment, respectively; p=0.04). The cumulative incidence of any AE appeared similar between the groups during treatment (Figure 1A).

The incidence of any bedaquiline-related AE within 5 months of stopping bedaquiline was significantly higher among patients, who received standard treatment versus those, who received prolonged treatment with bedaquiline (3.0 vs. 1.0 per 100 person months, respectively; p=0.01). QTcF prolongation was the most common bedaquiline-related AE in both groups. This accounted for 72% of events in the standard treatment group (median time to event 102 days, IQR 35 to 142 days) and 100% of the events in the prolonged treatment group (median time to event 112 days, IQR 109 to 135 days). A total of six persons stopped bedaquiline due to a bedaquiline-related AE in the standard group, while no patients stopped bedaquiline due to a bedaquiline-related-event in the prolonged group.

Serious adverse events

Serious AEs are described in Table 4; the complete list of registered serious events occurring up to 5 months after bedaquiline cessation (n=63) are provided in Supplementary Table 2. We did not observe a significant difference in the incidence of serious AEs between the standard and prolonged bedaquiline groups during treatment (2.8 vs. 3.6 per 100 person months; p=0.30). This was consistent, when limiting analysis to the first 190 days of treatment (7.5 vs. 5.4 per 100 person months of treatment; p=0.07). There was no significant difference between the groups in serious AEs for up to five-months after bedaquiline cessation (5.4 vs. 4.4 per 100 person months; p=0.48).

Among patients, who experienced a serious AE within 5 months of stopping bedaquiline, the median time to the first serious AE was 91 days in the standard treatment group and 112 days in the prolonged treatment group. The most common serious AEs among these persons in the standard treatment group were liver enzyme elevation (35.5%), eosinophilia (17.8%) and hypokalaemia (13.3%). In the prolonged treatment group, they were QTcF prolongation (27.8%) and hypokalaemia (22.2%). The cumulative incidence of serious AEs was lower in the prolonged group early in treatment, but surpassed the standard group in approximately one year.

The incidence of serious bedaquiline-related AEs did not differ between the standard and prolonged treatment groups (0.7 vs. 0.2 per 100 person months; p=0.22). The QTcF prolongation was the most common serious bedaquiline-related AE in both groups. One patient stopped bedaquiline due to a serious bedaquiline-related AE in the standard duration group.

QTcF changes throughout the treatment

Among the 108 patients with the baseline QTcF interval measurements available, the average (±SD) estimate was 385.7 ± 33.9 ms (Table 5). After one month of treatment with bedaquiline, the QTcF intervals had increased by an average of 17.6 ± 24.4 ms and appeared to continually increase throughout the treatment to reach a maximum of 61.9±49.1 ms on the ninth month of treatment. While the QTcF prolongations of 60 ms above the baseline were common, only one patient developed a prolongation of the QTcF interval up to more than 500 ms during the treatment. Monthly QTcF intervals were largely similar between standard and prolonged treatment groups (Supplement Appendix 3). When the prolonged and standard treatments were compared using Cox proportional hazard models, there was no significant difference for the rate of QTcF prolongation by >60 ms above the baseline between the standard group (10 events per 100 person months) and the prolonged group (14.8 events per 100 person months), with an adjusted hazard ratio of 1.16 (95% CI 0.56 to 2.42).

Deaths

Four deaths occurred among the 113 patients, one in the prolonged group and three in the standard group. The death in the prolonged group occurred in a 31-year-old female due to sudden death from a pulmonary thromboembolism and cardiac failure 350 days after initiating treatment. The patient had received 223 days of bedaquiline treatment, hence, the event was deemed unlikely to be related to bedaquiline.

Two deaths in the standard group were deemed unlikely related to bedaquiline. A 50-year-old female received bedaquiline for 47 days and on day 112 of treatment, she died due to a pre-existing neoplasm. A 42-year-old male received bedaquiline for 175 days, but died on day 799 of treatment due to respiratory failure owing to progression of tuberculosis.

One death in the standard group was deemed possibly related to bedaquiline. A 41-year-old male receiving a regimen of bedaquiline, pyrazinamide, linezolid, clofazimine, terizidone, imipenem-cilastatin and amoxicillin-clavulanate died 42 days after initiating treatment due to acute cardiopulmonary failure. The patient had ankylosing spondylitis and a history of alcohol abuse. The patient’s QTcF measurement taken on the day of treatment initiation was 428 ms; the last QTcF measurement was performed 15 days before his death and the result was 441 ms.

TABLE 3. All adverse events registered during the treatment course among patients on standard and prolonged treatment with bedaquiline.

	Bedaquiline <190 days	Bedaquiline ≥ 190 days	Overall	P-value[1] between standard and prolonged
Number of patients	83	30	113	--
Total treatment duration (months)	1807.8	722.7	2530.5	--
Total treatment with bedaquiline (months)	440.3	257.2	697.5	--
Total treatment up to 5 months after bedaquiline cessation (months)				
All adverse events				
Patients experiencing any adverse event	81 (97.6%)	28 (93.3%)	109 (96.4%)	--
Events during treatment total	1448	585	2033	--
Incidence per 100 person months (95% CI)	80.1 (76.0 to 84.3)	80.9 (74.5 to 87.8)	80.3 (76.9 to 83.9)	0.83
Adverse events during periods of treatment				
Events with bedaquiline up to day 190 of treatment	783	280	1063	--
Incidence per 100 person months (95% CI)	177.8 (165.6 to 190.7)	150.1 (133.1 to 168.8)	169.6 (159.5 to 180.1)	0.01
Events with bedaquiline from day 190 to cessation	N/A	62	62	--
Incidence per 100 person months (95% CI)	N/A	87.8 (67.3 to 112.6)	87.8 (67.3 to 112.6)	--
Events after stopping bedaquiline up to 5 months after bedaquiline cessation	288	120	408	--
Incidence per 100 person months (95% CI)	81.5 (67.5 to 97.4)	72.7 (64.5 to 81.6)	75.1 (68.0 to 81.6)	0.31
Events more than 5 months after stopping bedaquiline, to end of treatment	377	123	500	--
Incidence per 100 person months (95% CI)	38.8 (35.0 to 42.9)	38.7 (32.1 to 46.1)	38.8 (35.4 to 42.3)	0.97
All events during bedaquiline	783	342	1125	--
Incidence per 100 person months (95% CI)	177.8 (165.6 to 190.7)	133.0 (119.2 to 147.8)	161.3 (152.0 to 171.0)	<0.001
All events up to 5 months after stopping bedaquiline	1071	462	1533	--
Incidence per 100 person months (95% CI)	128.0 (1120.5 to 135.9)	114.2 (104.0 to 125.1)	123.5 (117.4 to 129.9)	0.04
Bedaquiline-related adverse events				
Patients with at least one bedaquiline-related adverse event	12	3	15	--
Number of bedaquiline-related adverse events up to 5 months after bedaquiline cessation	25	4	29	--
Incidence per 100 person months (95% CI)	3.0 (1.9 to 4.4)	1.0 (0.3 to 2.5)	2.3 (1.6 to 3.4)	0.01
Category of adverse events				--
QTcF prolongation	18 (72%)	4 (100%)	22 (75.7%)	--
Liver enzyme elevation	3 (12%)	0 (0%)	3 (10.3%)	--
Hyperuricemia	1 (4%)	0 (0%)	1 (3.4%)	--
Pancreatitis	1 (4%)	0 (0%)	1 (3.4%)	--
Anxiety	1 (4%)	0 (0%)	1 (3.4%)	--
Cardiac Failure	1 (4%)	0 (0%)	1 (3.4%)	
Patients stopping treatment due to bedaquiline related adverse event	6	0	6	--
Median (IQR) months to bedaquiline cessation	5.5 (5.1 to 5.5)	N/A	5.5 (5.1 to 5.5)	--

[1]: exact Fisher two-sided test was used to calculate p-value.

TABLE 4. Serious adverse events registered during the treatment course among patients on standard and prolonged treatment with bedaquiline.

	Bedaquiline <190 days	Bedaquiline ≥ 190 days	Overall	P-value[1] between standard and prolonged
Number of patients	83	30	113	--
Total treatment duration (months)	1807.8	722.7	2530.5	--
Total treatment with bedaquiline (months)	440.3	257.2	697.5	--
Total treatment up to 5 months after bedaquiline cessation (months)	836.5	404.4	1240.9	--
Serious adverse events				
Patients experiencing any serious adverse event	32 (38.6%)	16 (53.3%)	48 (42.5%)	--
Events during treatment total	50	26	76	--
Incidence per 100 person months (95% CI)	2.8 (2.1 to 3.6)	3.6 (2.4 to 5.3)	3.0 (2.4 to 3.8)	0.30
Serious adverse events during periods of treatment				
Events with bedaquiline up to day 190 of treatment	37	10	47	--
Incidence per 100 person months (95% CI)	7.5 (5.5 to 10.0)	5.4 (2.6 to 9.9)	8.4 (5.9 to 11.6)	0.07
Events with bedaquiline from day 190 to cessation	N/A	0	0	--
Incidence per 100 person months (95% CI)	N/A	0 (0 to 5.2)	0 (0 to 5.2)	--
Events after stopping bedaquiline up to 5 months after bedaquiline cessation	8	8	16	--
Incidence per 100 person months (95% CI)	2.0 (0.9 to 4.0)	5.4 (2.3 to 10.7)	2.9 (1.7 to 4.8)	0.10
Events more than 5 months after stopping bedaquiline, to end of treatment	5	8	13	--
Incidence per 100 person months (95% CI)	0.5 (0.2 to 1.2)	2.5 (1.1 to 5.0)	1.0 (0.5 to 1.7)	0.03
All events up to 5 months after stopping bedaquiline	45	18	63	--
Incidence per 100 person months (95% CI)	5.4 (3.9 to 7.2)	4.4 (2.6 to 7.0)	5.1 (3.9 to 6.5)	0.48
Bedaquiline-related serious adverse events				
Patients with at least one bedaquiline-related serious adverse event	5	1	6	--
Number of bedaquiline-related serious adverse events up to 5 months after bedaquiline cessation	6[2]	1	7	--
Incidence per 100 person months (95% CI)	0.7 (0.3 to 1.6)	0.2 (0.1 to 1.4)	0.6 (0.2 to 1.2)	0.22
Category of Serious Adverse Events				--
QTcF prolongation	2 (33.3%)	1 (100%)	3 (42.8%)	--
Liver enzyme elevation	1 (16.7%)	0 (0%)	1 (14.3%)	--
Pancreatitis	1 (16.7%)	0 (0%)	1 (14.3%)	--
Hyperuricemia	1 (16.7%)	0 (0%)	1 (14.3%)	--
Cardiac Failure	1 (16.7%)	0 (0%)	1 (14.3%)	--
Patients stopping treatment due to bedaquiline-related serious adverse event	1	0	1	--
Months to bedaquiline cessation	1.4	N/A	N/A	--

[1]: exact Fisher two-sided test was used to calculate p-value. [2]: Patient experienced two serious adverse events: the first was hyperuricaemia 21 days into treatment and the second was aspartate aminotransferase elevation 147 days into treatment.

TABLE 5. Change in mean QTcF interval by month of treatment.[1]

Month	Number of patients with measure	Average (SD) maximum QTcF measure	Average (SD) change in QTcF from baseline	Average (SD) change in QTcF from previous month	Number of patients (%) with QTcF that is >60ms from baseline
Baseline	108	385.7 (33.9)	-	-	-
1	105	402.5 (33.1)	17.6 (24.4)	17.6 (24.4)	6 (5.7%)
2	77	414.6 (28.7)	26.5 (33.9)	10.1 (32.4)	12 (15.6%)
3	94	416.1 (32.1)	28.5 (36.9)	3.2 (30.1)	21 (22.3%)
4	86	420.8 (33.4)	34.2 (37.4)	8.2 (33.4)	22 (25.6%)
5	89	422.7 (29)	33.8 (38.5)	1.0 (33.6)	21 (23.6%)
6	61	426 (29.6)	40.2 (40.7)	4.2 (27.0)	14 (23%)
7	24	418.5 (34.6)	34.1 (57.4)	-15 (36.8)	8 (33.3%)
8	12	411.2 (32.6)	24.8 (42.5)	1 (24.0)	3 (25%)
9	10	434.1 (28.4)	61.9 (49.1)	11.7 (31.9)	5 (50%)
10	4	442 (15.6)	58.8 (35.4)	9.5 (9.0)	1 (25%)

[1]: only 1 patient included in months 11 and beyond. ECG measures done on the same day were averaged to arrive at an estimate.

Regression Analyses

The regression analyses included 30 patients in the prolonged treatment group and 75 patients in the standard treatment group (Table 6). Multivariate regression analyses showed that the persons, who received prolonged treatment with bedaquiline versus those, who received standard treatment, did not experience significantly different incidence in serious AEs either within the first 190 days of exposure to bedaquiline (IRR 0.73, 95% CI: 0.33 to 1.61) or up to five-months after the cessation of bedaquiline (incidence rate ratio [IRR] 0.82, 95% CI: 0.42 to 1.61) . Other factors associated with AEs for both primary and secondary outcomes are reported in Supplementary Table 3 and 4. In our secondary analysis, we did not observe any significant difference in the incidence of serious AEs between the first 190 days of treatment and treatment after this time-point (IRR 0.75, 95% CI 0.30 to 1.88) among persons receiving prolonged bedaquiline treatment (Supplementary Table 5).

TABLE 6. Primary and Secondary Multivariate Analyses.

Outcome	Events / person-months	Events / person-months	Multivariate IRR (95% CI)
Serious adverse events	**Standard treatment with bedaquiline[1]**	**Prolonged treatment with bedaquiline**	
Up to 5 months after bedaquiline cessation	38 / 767	18 / 405	0.82 (0.42 to 1.61)
Within the first 190 days of treatment	33 / 410	10 / 187	0.73 (0.33 to 1.61)
Serious adverse events	**Within the first 190 days of treatment***	**From day 190 until 5 months after bedaquiline cessation**	
Among persons receiving prolonged treatment	10 / 187	8 / 212	0.75 (0.30 to 1.88)

[1]: reference group

DISCUSSION

Our prospective study shows that the prolonged use of bedaquiline appears to be safe under programmatic conditions with rigorous oversight and pharmacovigilance. Multivariate statistical methods allowed us to control for concomitant anti-TB medication and to compare events associated with standard and/or prolonged use of bedaquiline. There was no significant difference identified in incidence of overall and bedaquiline-related serious events during treatment among the patients, who received prolonged treatment with bedaquiline compared to those, who received standard one. These findings concur with similar conclusions from retrospective studies using spontaneously reported cases [13,16]. Considering the fact that the terminal half-life of bedaquiline has been estimated to be 5.5 months, we also identified that the incidence of serious events was not different, when analysed within the five months after bedaquiline was stopped [17].

Bedaquiline was deemed to be related to <10% of all serious AEs registered in our study. However, bedaquline was responsible for approximately half of all serious QTcF interval prolongations and one death occurred in the standard group due to sudden death. In both groups, QTcF prolongation was the most common bedaquiline-related AE overall and bedaquiline-related serious event in particular. While increases in QTcF interval up to 20 ms have been commonly described, a continual increase throughout the treatment that surpassed 60 ms above the baseline by the 9th month of treatment has not been reported previously [24]. Although in the present study, the risk of QTcF prolongation was not significantly higher in those patients, who received bedaquiline for prolonged period, the finding of continual increase in QTcF may still be a particular concern right now, when the number of patients, who receive standard RR-TB regimens of a duration of 9 to 12 months with inclusion of bedaquiline throughout the whole course of the treatment [4]. Cardiotoxic effects of the currently recommended RR-TB treatments are potentially impacted by the concomitant use of fluoroquinolones and clofazimine [13, 23-29]. Moreover, there is a long list of auxiliary medicines that are associated with the QTcF interval prolongation [30]. The higher number of QTcF prolonging anti-TB medicines used in the standard bedaquiline treatment group causing additive cardiotoxic action can explain more frequent non-serios QTcF prolongation observed in this group of patients. Our current finding further emphasizes the need for performing ECG on a regular basis for strict monitoring of QTcF interval. This also supports requirement for ECG monitoring for programmes that use bedaquiline during prolonged period to ensure accessibility of cardioversion to manage torsades de pointes and cardiac arrest (3). Hence, management of patients with prolonged QTcF interval requiring life-saving anti-TB treatment need multidisciplinary approach including meticulous revision of medicines used for concomitant diseases, as well as consultations with the specialist in cardiology about the need in temporary or permanent pacemaker to prevent deadly arrhythmias. According to available literature, alcohol abuse observed in our study population may also contribute to cardiotoxicity, necessitating joint intervention with services on addictive behaviours [31-35]. According to CTCAE 5.0, which is currently recommended scale for grading AEs and is used for reporting within this study, QTc interval prolongation more than 60 ms compared to baseline is defined as grade 3 AE. At the same time, earlier studies reporting QTc interval prolongation use older version of grading scale CTCAE 4.0, where prolongation more than 60 ms compared to baseline without Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia was not considered as AE at all [13, 15]. This potentially cause underreporting of severe QTc prolongation.

The finding that the majority of patients in both groups of our study experienced at least one AE coincides with well-documented toxicity of long-term anti-TB treatment [15, 18, 19]. The most common serious AEs not necessarily related to bedaquiline were liver enzyme elevation, eosinophilia and hypokalaemia. In contrast to what was observed within the period of bedaquiline treatment, the number of total non-serious AEs within five months after cessation of bedaquiline was significantly higher in the standard bedaquiline group. This can be explained by earlier replacement of bedaquiline

and longer use of other anti-TB medicines with worse safety profile, such as thiamide, second-line injectables, PAS, pyrazinamide or carbapenems, in the regimen [15, 19-23].

We found that second-line injectables were strongly associated with serious AEs throughout treatment. Extreme toxicity of injectables already triggered initiatives on fully oral RR-TB treatment, while there is still a lack of anti-TB medicines that could be used instead in highly resistant cases, urging further developments in the field [5, 36-38].

This was not a randomized study, the results may have been biased by the fact that the decision to continue to prolonged use of bedaquiline might have been affected by better tolerability of bedaquiline by the respective patients and better survival during the first 190 days of treatment, as compared to the case in those patients, who did not continue with bedaquline However, efforts were made to mitigate this bias with the statistical analysis, as were groups similar for the majority of other parameters.

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CONCLUSION

In conclusion, this study demonstrated that prolonged use of bedaquiline under programmatic conditions with pharmacovigilance appears to be safe. Clinicians should carefully monitor QTcF interval throughout treatment with bedaquiline due to the risk of QTcF prolongation. Further studies are needed to establish strategies to manage prolonged QTcF interval during prolonged treatment with bedaquiline.

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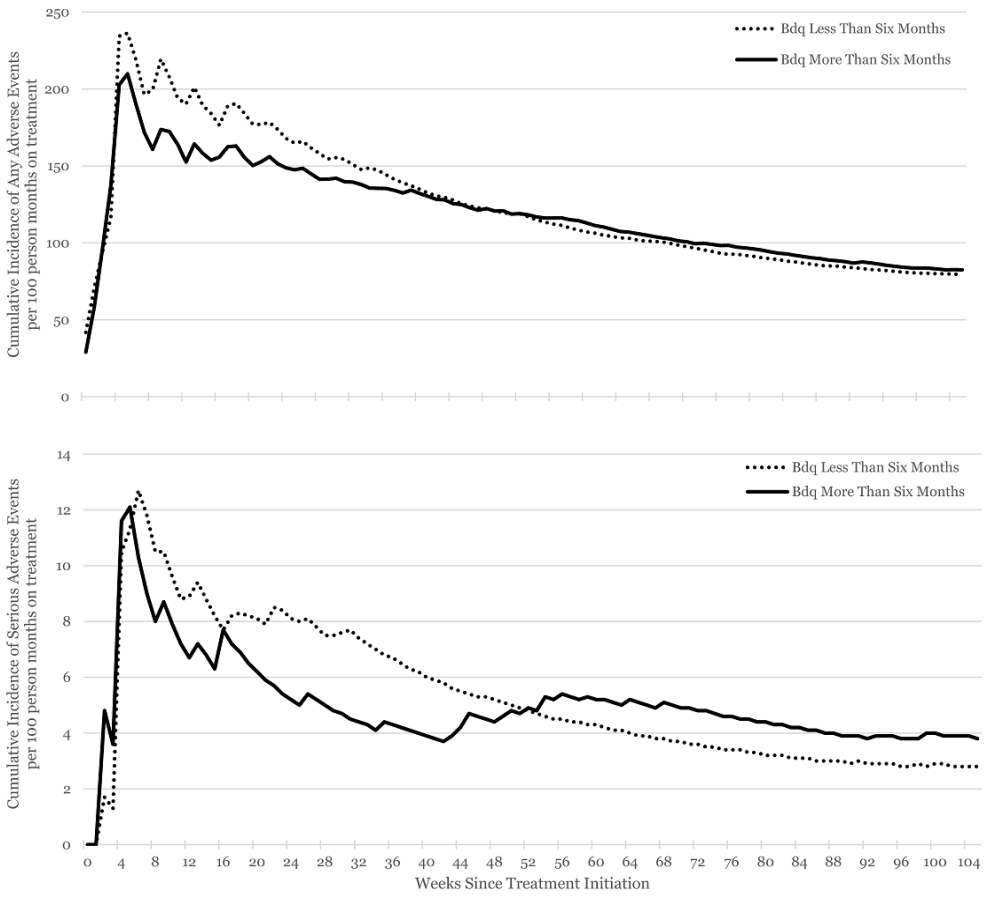

Patients on Treatment

Bedaquiline Less Than Six Months	83	83	82	82	82	80	80	80	80	79	79	79	79	79	78	78	78	77	77	77	75	71	66	61	56	51	40
Bedaquiline More Than Six Months	30	30	30	30	30	30	30	30	30	30	30	30	30	29	29	29	29	28	28	28	28	28	28	28	27	27	23

Patients on Bedaquiline

Bedaquiline Less Than Six Months	83	83	81	79	79	79	73	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Bedaquiline More Than Six Months	30	30	30	30	30	30	30	30	26	14	11	3	2	2	2	1	1	1	1	1	0	0	0	0	0	0	0

Figure 1. Cumulative rates of any (top panel) and serious (bottom panel) adverse events during treatment, stratified by the duration of bedaquiline exposure.

Supplementary material

This material has been provided by the authors to give readers additional information about their work.

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Supplementary material

Safety of prolonged treatment with bedaquiline in programmatic conditions

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Contents

Supplementary Table 1. Bacteriological, clinical and laboratory assessment schedule of the patients.

Measure to be monitored	**Time point(s)**
Vital signs	At baseline, monthly during treatment and semi-annually during follow-up period
Weight	At baseline, monthly during treatment and semi-annually during follow-up period
Brief peripheral neuropathy screen	At baseline and monthly during treatment
Visual acuity and colorblindness screen	At baseline and monthly during treatment
Smear and culture	At baseline, monthly during treatment and semi-annually during follow-up period
LPA (Hain GenoType MTBDRsl)	At baseline and if susceptibility sustained, then in case of smear- or culture-positivity after 3rd month of treatment
Culture-based second-line DST	At baseline and if smear- or culture-positive after 3rd month of treatment
Full blood count (hemoglobin, white blood cells and platelets)	At baseline and monthly during treatment
Liver function tests (AST, ALT, ALP, bilirubin)	At baseline and monthly during treatment
Serum creatinine	At baseline and monthly during treatment
Serum potassium, calcium, magnesium	At baseline and monthly during treatment
Glucose	At baseline and monthly during treatment
Hepatitis Bs antigen	At baseline
Hepatitis C antibody	At baseline
HIV testing	At baseline
ECG	At baseline, 2nd week and monthly thereafter during treatment. QT interval correction was calculated according to Fridericia formula (QTcF)
Chest X-Ray	At baseline, quarterly during treatment and semi-annually during follow-up period

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DST: drug susceptibility test; ECG: electrocardiogram; HIV: human immunodeficiency virus; LPA: line probe assay.

Supplementary Table 2. List of registered serious events within 5 months of Bedaquiline stop.

Patient ID	Age	Sex	Event	Time of event from treatment start (days)	Time event ended if resolved) from treatment start (days)	Received Standard or Prolonged Bedaquiline	Event possibly bedaquiline-related?	Grade of the event	Patient hospitalized?	Event outcome
1	27	F	Pancreatitis	49	84	Standard	Yes	3	No	Resolved
2	40	M	Hyperuricaemia	21	55	Standard	Yes	3	No	Resolved
2	40	M	Liver enzyme elevation [AST]	147	231	Standard	Yes	3	No	Resolved
3	34	F	QTc prolongation	182	271	Prolonged	No	3	No	Resolved
3	34	F	QTc prolongation	308	U	Prolonged	No	3	No	Resolved
4	18	F	Hypokalaemia	63	151	Standard	No	3	No	Resolved
5	31	M	Liver enzyme elevation [GGT]	126	N/A	Standard	No	3	No	Not resolved
5	31	M	Liver enzyme elevation [ALT]	126	323	Standard	No	3	No	Resolved
5	31	M	Liver enzyme elevation [ALT]	140	152	Standard	No	4	Yes	Resolved
5	31	M	Liver enzyme elevation [AST]	154	323	Standard	No	3	No	Resolved
6	16	M	Hypomagnesaemia	98	227	Standard	No	3	No	Resolved
7	50	F	Neoplasm	28	N/A	Standard	No	4	No	Not resolved
8	25	F	Hypokalaemia	98	N/A	Prolonged	No	4	No	Not resolved
9	30	M	Seizure	35	U	Standard	No	4	No	Resolved
9	30	M	Liver enzyme elevation [AST]	217	359	Standard	No	3	No	Resolved
10	53	M	Eosinophilia	119	210	Standard	No	3	No	Resolved
11	23	F	Psychomotor agitation	14	U	Prolonged	No	3	Yes	Unknown
12	33	F	QTcF prolongation	210	327	Standard	Yes	3	No	Resolved
12	33	F	Hypokalaemia	217	237	Standard	No	4	No	Resolved
13	52	M	QTcF prolongation	112	161	Prolonged	Yes	3	No	Resolved
14	27	F	Eosinophilia	35	272	Standard	No	3	No	Resolved
15	31	M	Hypokalaemia	35	181	Standard	No	3	No	Resolved
15	31	M	Eosinophilia	35	212	Standard	No	3	No	Resolved
16	42	M	Liver enzyme elevation [AST]	182	270	Standard	No	3	No	Resolved
17	34	F	Blood enzyme elevation	35	97	Standard	No	3	No	Resolved
17	34	F	Liver enzyme elevation [GGT]	35	97	Standard	No	3	No	Resolved
17	34	F	Liver enzyme elevation [AST]	35	65	Standard	No	3	No	Resolved
18	44	M	Hypocalcaemia	308	N/A	Prolonged	No	4	No	Not resolved
19	58	M	Liver enzyme elevation [GGT]	63	306	Standard	No	3	No	Resolved
20	39	M	Liver enzyme elevation [GGT]	252	N/A	Prolonged	No	3	No	Not resolved
21	18	M	Liver enzyme elevation [GGT]	91	114	Standard	No	3	No	Resolved
21	18	M	Eosinophilia	91	176	Standard	No	3	No	Resolved
22	27	M	Eosinophilia	168	252	Standard	No	3	No	Resolved
23	40	M	Liver enzyme elevation [GGT]	28	N/A	Standard	No	3	No	Not resolved
24	56	M	Liver enzyme elevation [GGT]	119	U	Standard	No	3	No	Resolved
25	31	F	QTcF prolongation	343	N/A	Prolonged	No	4	No	Died
25	31	F	Thrombosis	350	N/A	Prolonged	No	5	No	Died
26	55	M	Liver enzyme elevation [GGT]	224	U	Standard	No	3	No	Resolved
27	34	M	Hypomagnesaemia	140	U	Standard	No	3	No	Resolved
28	28	F	Eosinophilia	182	299	Standard	No	4	No	Resolved
29	44	M	Hypokalaemia	175	203	Standard	No	3	No	Resolved
30	50	M	Hypocalcaemia	322	471	Prolonged	No	3	No	Resolved
30	50	M	Hypokalaemia	322	623	Prolonged	No	3	No	Resolved
31	49	M	Eosinophilia	91	246	Standard	No	3	No	Resolved
31	49	M	Liver enzyme elevation [AST]	126	N/A	Standard	No	3	No	Not resolved
31	49	M	Liver enzyme elevation [ALT]	154	246	Standard	No	3	No	Resolved
31	49	M	Hypomagnesaemia	154	N/A	Standard	No	3	No	Not resolved
31	49	M	Liver enzyme elevation [GGT]	154	N/A	Standard	No	3	No	Not resolved
32	29	M	Hypokalaemia	210	240	Standard	No	3	No	Resolved
33	19	F	QTcF prolongation	35	U	Standard	Yes	4	No	Resolved
33	19	F	Hypomagnesaemia	35	273	Standard	No	3	Yes	Resolved
33	19	F	Hypokalaemia	35	U	Standard	No	4	No	Resolved
34	51	M	Liver enzyme elevation [AST]	63	91	Prolonged	No	3	No	Resolved
35	20	F	Eosinophilia	91	217	Standard	No	3	No	Resolved
36	29	F	Liver enzyme elevation [GGT]	42	101	Standard	No	3	No	Resolved
37	53	M	QTcF prolongation	364	371	Prolonged	No	3	Yes	Resolved
38	30	F	Eosinophilia	28	383	Prolonged	No	3	No	Resolved

38	30	F	Hypokalaemia	112	175	Prolonged	No	3	No	Resolved
39	40	F	Hyperglycaemia	42	N/A	Prolonged	No	3	No	Not resolved
40	31	M	Hypomagnesaemia	35	339	Prolonged	No	3	No	Resolved
40	31	M	Hypokalaemia	35	339	Prolonged	No	3	No	Resolved
41	41	M	Cardiac Failure	42	N/A	Standard	Yes	5	Yes	Died
41	41	M	Respiratory Failure	42	N/A	Standard	No	5	Yes	Died

F: female; M: male; QTcF: QT interval corrected using Fredericia formula; U: unknown; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase

Supplementary Table 3. Comparison of serious adverse events that occurred within five-months of cessation of bedaquiline between patients of standard and prolonged bedaquiline group.

Variable	Events / person-months	Univariate IRR (95% CI)	Univariate p-value	Multivariate IRR (95% CI)
Bedaquiline duration[1]				
Less than 6 months	38 / 767	1.0 (Reference)		1.0 (Reference)
More than 6 months	18 / 405	0.90 (0.48 to 1.72)	0.75	0.82 (0.42 to 1.61)
Sex				
Female	21 / 316	1.0 (Reference)		1.0 (Reference)
Male	35 / 857	0.62 (0.33 to 1.16)	0.14	0.73 (0.35 to 1.53)
Age				
Per 10-year increase		0.78 (0.58 to 1.06)	0.11	0.88 (0.64 to 1.20)
Concomitant anti-TB medicines				
Per additional concomitant anti-TB medicine		0.96 (0.76 to 1.21)	0.74	--
Injectable received				
No	24 / 772	1.0 (Reference)		1.0 (Reference)
Yes	32 / 401	2.55 (1.31 to 4.96)	0.01	2.42 (1.14 to 5.13)
BMI				
BMI $\geq$ 18.5 kg/m^2	43 / 929	1.0 (Reference)		
BMI < 18.5 kg/m^2	13 / 243	1.16 (0.59 to 2.25)	0.67	--
Baseline ECG[2]				
Per 10 ms increase		0.95 (0.88 to 1.04)	0.26	--
Alcohol				
No alcohol abuse	49 / 995	1.0 (Reference)		
Alcohol abuse	7 / 177	0.80 (0.34 to 1.89)	0.61	--
Diabetes				
No diabetes	52 / 1098	1.0 (Reference)		
Has diabetes	4 / 74	1.14 (0.28 to 4.60)	0.86	--
HIV				
No HIV	55 / 1140	1.0 (Reference)		
Has HIV	1 / 32	0.65 (0.12 to 3.45)	0.61	--
Surgery				
No MDR surgery	49 / 992	1.0 (Reference)		
Had MDR surgery	7 / 181	0.78 (0.36 to 1.71)	0.54	--
Baseline Sputum smear[3]				
Smear negative	44 / 950	1.0 (Reference)		
Smear positive	10 / 212	1.02 (0.49 to 2.15)	0.95	--
Chest X-Ray findings				
No cavitation	19 / 404	1.0 (Reference)		
Cavitation	37 / 768	1.03 (0.53 to 1.97)	0.94	--

BMI: body mass index; ECG: electrocardiography; HIV: human immunodeficiency virus; IRR: incidence rate ratio; MDR: multidrug-resistant tuberculosis; TB: tuberculosis.

Estimates generated using generalized estimating equations with a Poisson distribution and log-link to estimate incidence rate ratios and their 95% confidence intervals (using robust standard errors).

[1]: Person-months reflective of follow-up time, not the duration of bedaquiline receipt. [2]: only 100 patients. [3]: only 104 patients. Note: no difference in findings if all predictors included in multivariate model.

Supplementary Table 4. Comparison of serious adverse events up to the first 190 days of treatment with bedaquiline between patients of standard and prolonged bedaquiline group (N=105).

Variable	Events / person-months	Univariate IRR (95% CI)	Univariate p-value	Multivariate IRR (95% CI)
Bedaquiline duration				
Less than 6 months	33 / 410	1.0 (Reference)		1.0 (Reference)
More than 6 months	10 / 187	0.67 (0.30 to 1.50)	0.33	0.73 (0.33 to 1.61)
Sex				
Female	17 / 163	1.0 (Reference)		1.0 (Reference)
Male	26 / 434	0.57 (0.26 to 1.25)	0.16	0.80 (0.35 to 1.83)
Age				
Per 10-year increase		0.69 (0.46 to 1.03)	0.07	0.76 (0.52 to 1.11)
Concomitant anti-TB Medicines				
Per additional concomitant anti-TB medicine		0.76 (0.56 to 1.02)	0.07	0.97 (0.68 to 1.40)
Injectable received				
No	13 / 344	1.0 (Reference)		1.0 (Reference)
Yes	30 / 253	3.14 (1.42 to 6.97)	<0.01	2.81 (1.23 to 6.43)
BMI				
BMI ≥ 18.5 kg/m^2	35 / 477	1.0 (Reference)		
BMI < 18.5 kg/m^2	8 / 120	0.91 (0.38 to 2.16)	0.83	--
Baseline ECG[1]				
Per 10ms increase		0.96 (0.87 to 1.06)	0.41	--
Alcohol				
No alcohol abuse	39 / 507	1.0 (Reference)		
Alcohol abuse	4 / 90	0.58 (0.18 to 1.86)	0.36	--
Diabetes				
No diabetes	39 / 557	1.0 (Reference)		
Has diabetes	4 / 39	1.45 (0.35 to 6.02)	0.61	--
HIV				
No HIV	42 / 579	1.0 (Reference)		
Has HIV	1 / 18	0.79 (0.14 to 4.42)	0.79	--
Surgery				
No MDR surgery	41 / 504	1.0 (Reference)		1.0 (Reference)
Had MDR surgery	2 / 93	0.27 (0.07 to 1.04)	0.06	0.26 (0.08 to 0.88)
Baseline Sputum Smear[2]				
Smear negative	36 / 491	1.0 (Reference)		
Smear positive	5 / 101	0.68 (0.21 to 2.16)	0.51	--
Chest X-Ray findings				
No cavitation	15 / 208	1.0 (Reference)		
Cavitation	28 / 389	1.00 (0.45 to 2.19)	0.99	--

BMI: body mass index; ECG: electrocardiography; HIV: human immunodeficiency virus; IRR: incidence rate ratio; MDR: multidrug-resistant tuberculosis; TB: tuberculosis.

Estimates generated using generalized estimating equations with a Poisson distribution and log-link to estimate incidence rate ratios and their 95% confidence intervals (using robust standard errors).

[1]: only 100 patients. [2]: only 104 patients. Note: no difference in findings if all predictors included in multivariate model.

Supplementary Table 5. Comparison of serious adverse events that occurred in the first 189 days vs. beyond 189 days up to 5 months after bedaquiline stop in the prolonged bedaquiline group (N=30).

Variable	Events / person-months	Univariate IRR (95% CI)	Univariate p-value	Multivariate IRR (95% CI)
Time period of bedaquiline receipt[1]				
First 189 days of treatment	10 / 187	1.0 (Reference)		1.0 (Reference)
From Day 190 to up to 5 months after stop	8 / 212	0.71 (0.26 to 1.99)	0.52	0.75 (0.30 to 1.88)
Sex				
Female	9 / 113	1.0 (Reference)		1.0 (Reference)
Male	9 / 285	0.40 (0.15 to 1.06)	0.07	0.13 (0.03 to 0.64)
Age				
Per 10-year increase		0.89 (0.57 to 1.38)	0.59	1.63 (0.82 to 3.39)
Concomitant anti-TB medicines				
Per additional concomitant anti-TB medicine		0.84 (0.55 to 1.29)	0.42	--
Injectable received				
No	10 / 229	1.0 (Reference)		
Yes	8 / 169	1.08 (0.39 to 3.02)	0.88	--
BMI				
BMI $\geq$ 18.5 kg/m^2	8 / 265	1.0 (Reference)		1.0 (Reference)
BMI < 18.5 kg/m^2	10 / 133	2.50 (0.95 to 6.59)	0.06	3.04 (0.97 to 9.50)
Baseline ECG[2]				
Per 10 ms increase		1.05 (0.91 to 1.22)	0.48	--
Alcohol				
No alcohol abuse	13 / 321	1.0 (Reference)		
Alcohol abuse	5 / 77	1.59 (0.62 to 4.07)	0.34	--
Diabetes				
No diabetes	17 / 386	1.0 (Reference)		
Has diabetes	1 / 12	1.92 (0.47 to 7.88)	0.36	--
HIV				
No HIV	18 / 398	1.0 (Reference)		
Has HIV	0 / 0	--	--	--
Surgery				
No MDR surgery	14 / 322	1.0 (Reference)		
Had MDR surgery	4 / 76	1.22 (0.36 to 4.19)	0.75	--
Baseline sputum smear				
Smear negative	10 / 272	1.0 (Reference)		
Smear positive	8 / 126	1.72 (0.61 to 4.83)	0.31	--
Chest X-Ray findings				
No cavitation	8 / 107	1.0 (Reference)		1.0 (Reference)
Cavitation	10 / 291	0.46 (0.17 to 1.25)	0.13	0.31 (0.13 to 0.76)

BMI: body mass index; ECG: electrocardiography; HIV: human immunodeficiency virus; IRR: incidence rate ratio; MDR: multidrug-resistant tuberculosis; TB: tuberculosis.

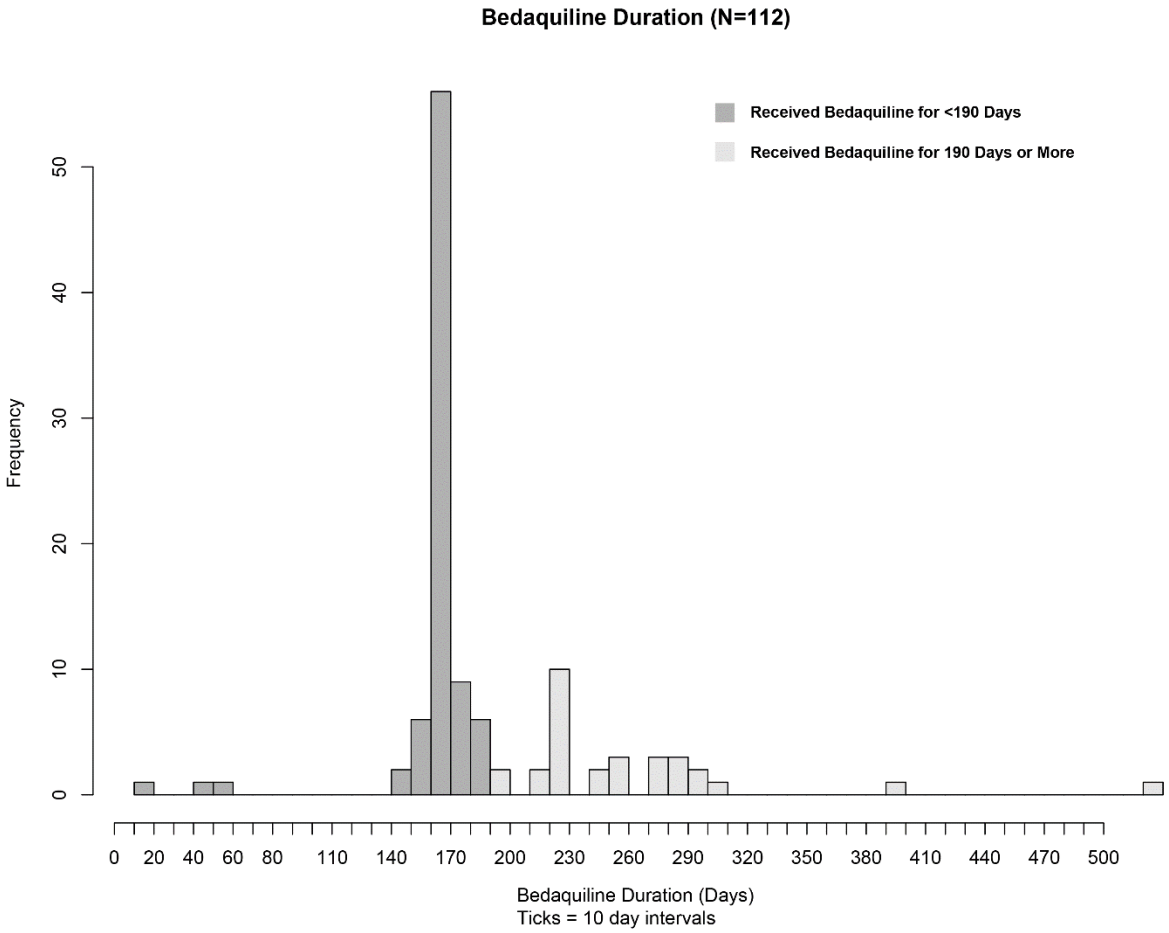
Estimates generated using generalized estimating equations with a Poisson distribution and log-link to estimate incidence rate ratios and their 95% confidence intervals (using robust standard errors).

[1]Person-months reflective of follow-up time, not the duration of bedaquiline receipt. [2]: only 27 patients. Note: no difference in findings if all predictors included in multivariate model.

Supplementary Appendix 1. Bacteriological tests used during the study.

All cultures were done using BACTEC broth media using a fluorometric BACTEC MGIT960 system (Becton Dickinson, Sparks, MD, USA). The full drug susceptibility testing (DST) was performed as an indirect test by the proportion method rifampicin (1.0 µg/mL), isoniazid (0.1 µg/mL), streptomycin (1.0 µg/mL), ethambutol (5.0 µg/mL), pyrazinamide (100.0 µg/mL), levofloxacin (1,5 µg/mL), moxifloxacin (0,5 µg/mL), kanamycin (30.0 µg/mL), capreomycin (40.0 µg/mL), amikacin (1.0 µg/mL) and prothionamine (40.0 µg/mL). DST to linezolid, clofazimine and bedaquiline was not available at the time of the study. Genotypic DST was obtained with commercially available assays: Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA), GenoType MTBDRplus and GenoType MTBDRsl (Hain Lifescience, Nehren, Germany). If resistance was identified to rifampicin, the respective isolate was tested against the rest of the first- and second-line anti-TB drugs.

Supplementary Appendix 2.



Histogram of the duration of bedaquiline use by the patients. Based on a histogram of the duration of bedaquiline use, we grouped the patients to those, who received bedaquiline for <190 days (referred to as receiving standard treatment with bedaquiline) and to patients, who received bedaquiline for ≥190 days (referred to as receiving prolonged treatment with bedaquiline).

Supplement Appendix 3.
List of registered events classified as per system organ class.

System.Organ.Class	Total events
Investigations	879
Metabolism and nurtrition disorders	417
Blood and lymphatic system disorders	201
Cardiac Disorders	188
Hepatobiliary disorders	69
Gastrointestinal Disorders	59
Ear and labirynth disorders	39
Nervous system disorders	31
Skin and subcutaneous system disorders	30
Infections and Infestations	29
Psychiatric disorders	23
Musculoskeletal and connective tissue disorders	19
General disorders and administration site conditions	14
Renal and urinary disorders	9
Respiratory, thoracic and mediastinal disorders	9
Eye disorders	7
Endocrine disorders	4
Vascular disorders	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1

List of registered events classified as per category.

Category	Total events
Hepatobiliary investigations	353
Cardiac and vascular investigations	203
Renal and urinary tract investigations and urinalyses	192
Glucose metabolism disorders	142
Cardiac arrhythmias	139
White blood cell disorders	120
Bone, calcium, magnesium and phosphorus metabolism disorders	111
Enzyme investigations	107
Purine and pyrimidine metabolism disorders	93
Hepatic and hepatobiliary disorders	69
Electrolyte and fluid balance conditions	65
Anaemias (non-haemolytic) and marrow depression	44
Gastrointestinal signs and symptoms	41
Platelet disorders	36
Epidermal and dermal conditions	28
Gastrointestinal investigations	27
Hearing disorders	22
Cardiac disorder signs and symptoms	19
Fungal infectious disorders	14
Coronary artery disorders	13
Myocardial disorders	13
Rash	11

Joint disorders	11
Anxiety disorders and symptoms	9
Sleep disorders and disturbances	9
General system disorders	8
Inner ear and cranial nerve disorders	8
Gastrointestinal motility and defaecation conditions	7
Muscle disorders	7
Neurological disorders	7
Body temperature conditions	6
Middle ear infections and inflammations	6
Protein and amino acid metabolism disorders	6
Seizures	6
Peripheral neuropathies	5
Respiratory disorders	5
Vertigo	5
Gastrointestinal inflammatory conditions	4
Sleep disorders	4
Viral infectious disorders	4
Aural disorders	3
Nephropathies	3
Upper respiratory tract disorders	3
Urinary tract signs and symptoms	3
Vision disorders	3
Depressed mood disorders and disturbances	2
Diabetic complications	2
Eye disorders	2
Headaches	2
Mood disorders and disturbances	2
Movement disorders	2
Ocular infections, irritations and inflammations	2
Thyroid gland disorders	2
Tongue conditions	2
Adjustment disorders	1
Angioedema and urticaria	1
Bronchial disorders	1
Embolism and thrombosis	1
Exocrine pancreas condition	1
Gastrointestinal atonic and hypomotility disorders	1
Gastrointestinal conditions	1
Gastrointestinal ulceration and perforation	1
Haematopoietic neoplasm	1
Musculoskeletal and connective tissue disorders	1
Oral soft tissue conditions	1
Pericardial disorders	1
Renal and urinary tract neoplasm benign	1
Renal disorders	1
Skin and subcutaneous tissue disorders	1
Urinary Tract Neoplasms	1

Urolithiases	1
Vascular haemorrhagic disorders	1

List of registered events.

Event	Total Events
Aspartate aminotransferase increased	165
Eosinophilia	115
Alanine aminotransferase increased	113
Electrocardiogram abnormal	99
Hyperuricaemia	93
Electrocardiogram QT prolonged	89
Hyperglycaemia	85
Gamma-glutamyl transferase increased	75
Blood alkaline phosphatase increased	67
Blood creatinine increased	67
Hyperbilirubinaemia	66
Blood urea increased	65
Glomerular filtration rate decreased	60
Hypomagnesaemia	60
Hypoglycaemia	57
Hypocalcaemia	46
Anaemia	44
Hypokalaemia	41
Blood Lactate Dehydrogenase Increased	37
Sinus tachycardia	28
Amylase increased	26
Thrombocytopenia	26
Bradycardia	25
Hyperkalaemia	24
Tachycardia	22
Nausea	18
Sinus bradycardia	16
Haemoptysis	13
Pruritus	12
Rash	12
Arrhythmia supraventricular	11
Arthralgia	11
Supraventricular extrasystoles	11
Chest pain	10
Thrombocytosis	10
Vomiting	10
Upper respiratory tract infection	9
Abdominal pain	8
Atrial hypertrophy	8
Insomnia	8
Oral candidiasis	8
Tinnitus	8

Arrhythmia	7
Cochlear nerve deafness	7
Diarrhoea	7
Fatigue	7
Hearing decreased	7
Ventricular hypertrophy	7
Fever	6
Hypoalbuminaemia	6
Anxiety	5
Dyspepsia	5
Dyspnoea	5
Leukopenia	5
Seizure	5
Ventricular extrasystoles	5
Vertigo	5
Bundle branch block right	4
Cochlear nerve damage	4
Hypercalcemia	4
Muscle pain	4
Palpitation	4
Sleep disorders	4
Vaginal candidiasis	4
Blood pressure increased	3
Cramps legs	3
Ear pain	3
Gastritis	3
Hearing impaired	3
Hepatitis toxic	3
Hypoaesthesia	3
Influenza	3
Nephropathy toxic	3
Otitis media	3
Panic reaction	3
Right ventricular hypertrophy	3
Bundle branch block left	2
Eczema	2
Electrocardiogram QT interval abnormal	2
Epistaxis	2
Eustachitis	2
Headache	2
Myocardial infarction	2
Myopia	2
Neuritis	2
Polyneuropathy	2
Retinal disorder	2
Sinoatrial block	2
Syncope	2
Tachyarrhythmia	2

Taste bitter	2
Abnormal dreams	1
Accommodation disorder	1
Adjustment disorders	1
Albuminuria	1
Aspergillosis	1
Atrial conduction time prolongation	1
Atrioventricular block	1
Back pain	1
Bad mood	1
Blood creatine phosphokinase increased	1
Blood pressure decreased	1
Candidiasis	1
Cardiac hypertrophy	1
Cardiomyopathy	1
Chest discomfort	1
Chills	1
Chronic obstructive airways disease exacerbated	1
Conjunctivitis	1
Depression	1
Dermatitis Allergic	1
Diabetic neuropathy	1
Diabetic retinopathy	1
Dizziness	1
Duodenal ulcer	1
Duodenitis	1
Electrocardiogram QRS complex prolonged	1
Eyelid oedema	1
Fear	1
Gastroesophageal reflux	1
FALSE	1
Haematoma	1
Haematuria	1
Herpes zoster	1
Hyperaemia eye	1
Hypermagnesaemia	1
Hypothyroidism	1
Kidney stone	1
Lactate Blood Increase	1
LDH Increased Serum	1
Lipase increased	1
Loss of consciousness	1
Lymphatic system neoplasm	1
Mood disorder	1
Myocardial ischaemia	1
Nasal septum ulceration	1
Negative thoughts	1
Neuralgia	1

Neuropathy peripheral	1
Nodal arrhythmia	1
Oesophageal disorder	1
Otitis media chronic	1
Pancreatitis chronic	1
Papular rash	1
Partial Loss of Consciousness	1
Pericardial disease	1
Pneumonia	1
Psychomotor agitation	1
Renal cyst	1
Renal failure chronic	1
Renal pain	1
Skin ulceration	1
Stomatitis	1
Sudden hearing loss	1
Thrombosis	1
Thyroid Stimulating Hormone Increased	1
Tremor	1
Urinary Bladder Sarcoma	1
Urticaria	1
Ventricular tachycardia	1

Average QTcF measurement resultss by month of patients grouped by the length of bedaquiline treatment

Month	Standard (ms)	Prolonged (ms)
Baseline	384	388
Month 1	400	410
Month 2	411	431
Month 3	415	420
Month 4	419	427
Month 5	420	432
Month 6	420	435
Month 7	--	418
Month 8	--	411
Month 9	--	434
Month 10	--	442