Review of available evidence on the use of bedaquiline for the treatment of multidrug-resistant tuberculosis: Data analysis report

Prepared for:
The World Health Organization

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Summary

To review new evidence on the use of bedaquiline to inform changes in the World Health Organization (WHO) interim policy guidance on the use of bedaquiline for the treatment of multidrug-resistant tuberculosis (MDR-TB), a systematic review of the literature was conducted to identify cohorts of patients treated with bedaquiline for six months in addition to a recommended baseline regimen.

After a comprehensive and exhaustive search, five cohorts were identified: a phase II, single arm, open-label multicentre study conducted by the drug manufacturer – Janssen Therapeutics (n=205), a retrospective cohort of patients receiving bedaquiline under compassionate use in France (n=45), the South African Bedaquiline Clinical Access Programme (BCAP; n=195), and the compassionate use programmes in Georgia (n=30) and Armenia (n=62). Data from these cohorts were requested from the investigators, standardized and pooled to estimate treatment outcomes, safety and survival (n=537). Outcomes were estimated only for cohorts with sufficient follow-up. In addition to this, a large comparative dataset containing mortality data on 25095 patients with MDR-TB of which 1556 (6.2%) received bedaquiline was used to further explore survival. These data were drawn from the South African Electronic Drug-Resistant Tuberculosis Register and supplemented with vital statistics records.

These five cohorts differed considerably in baseline characteristics, with notable variability in prevalence of HIV, resistance profiles, constitution of optimised baseline regimens and duration on bedaquiline Overall, the average age was 36.4 years (standard deviation [SD]: 11.8). About sixty-four percent were males. One hundred and thirty-eight patients (25.7%) were living with HIV of which 120 (87%) were on antiretroviral therapy. The duration on bedaquiline was 6.37 months (SD:2.3).

Bedaquiline was found to be effective in the treatment of MDR-TB with 79.7% (95% CI 75.2-83.5; 317/391) of patients experiencing sputum culture conversion at 6 months. The cure and success (cure + completed) rates at the end of follow-up (18-24 months) were 63.8% (95% CI 57.8-69.4; 223/351) and 69.1% (95% CI 59.1 – 77.6; 234/351) respectively.

All patients recruited in these cohorts had safety data collected (537 cases). In addition to this, safety data from 28 additional cases from the drug manufacturer, multi-country study were used. These patients experienced a total of 2622 adverse events, with the most frequent being gastrointestinal (367/2622 events; 14.0%), metabolic (224/2622 events; 8.5%) and nervous system (224/2622 events; 8.5%). Twenty percent (118/565) of patients experienced a severe adverse event. Seven per cent of patients (42/565) experienced a total of 48 serious adverse events. The most frequent serious adverse events were respiratory (25%; 12/48), cardiac (16.7%; 8/48) and hepatic (14.6%7/48). Due to reported cardiotoxicity of bedaquiline, patients

were closely monitored for QT prolongation, using QTcF[1] measurement. A worst QTcF prolongation above 500 milliseconds occurred in 24 patients (4.7%; 24/511). About forty-seven percent of patients (238/511) had an increase in QTcF from baseline (to worst measurement) of 0-30 milliseconds; 33.7% (172/511) had an increase between 30 and 60 milliseconds and 14.8% (76/511) had an increase above 60 milliseconds. Data on the use of bedaquiline for more than 6 months are very limited and do not allow to draw any conclusions regarding the effect of bedaquiline on QT prolongation when used for more than 6 months.

Among patients with complete 18-24 months' follow-up data (excluding Georgia and Armenia, *n* = 351), the death rate was 10.6% (95% CI 3.80-20.0; 37/351). Additionally, 19 deaths were reported among cases with incomplete follow-up data. Mortality seemed to be higher among HIV-infected persons. Only 32% of deaths occurred within the first six months of treatment (18/56). Most deaths seemed to have occurred among MDR-TB patients with additional resistance to fluoroquinolones and/or injectable (3.0% MDR-TB; 16.3% MDR-TB_{+FQ}; 10.9% MDR-TB_{+INJ}; and 10.1% XDR-TB).

Survival of MDR-TB patients was further investigated in the larger South African dataset. The analysis was carried out after adjusting for key covariates[2]. This showed that MDR-TB patients who received bedaquiline were more likely to survive (adjusted odds ratio (aOR) 0.39; 95% CI 0.31-0.59; p<0.001; adjusted hazards ratio (aHR) 0.48; 95% CI 0.39-0.59) as compared to those who did not received bedaquiline. This effect was present across resistance profile categories and history of previous TB disease.

[1] Corrected QT interval using Fridericia's formula

[2] Gender, age, province, HIV and antiretroviral therapy status, TB site (pulmonary or extra pulmonary), TB history, year of treatment initiation, drug resistance pattern, diagnostic method and weeks of exposure to regimen

List of abbreviations

BCAP	Bedaquiline Compassionate Access Programme
BDQ	Bedaquiline
CENTRAL	Cochrane Central Register of Controlled Trials
CSV	Comma Separated Values
ECG	Electrocardiogram
EDRWeb	Electronic Drug-Resistant Tuberculosis Register
FLQ	Fluoroquinolone
GDG	Guidelines Development Group
HIV	Human Immunodeficiency Virus
MDR	Multidrug resistant
MDR-TB	Multidrug resistant tuberculosis with addition resistance to fluoroquinolones
$MDR\text{-}TB_{+INJ}$	Multidrug resistant tuberculosis with additional resistance to a second line injectable drugs
$MDR\text{-}TB_{+FLQ}$	Multidrug resistant tuberculosis with addition resistance to fluoroquinolones
PCR	Polymerase Chain Reaction
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RR-TB	Resistance to Rifampicin
SD	Standard deviation
TB	Tuberculosis
WHO	World Health Organization

Definition of treatment outcomes for drug-resistant patients[3]

Cured	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase
Treatment failure	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: •Lack of conversion by the end of the intensive phase; or •Bacteriological reversion in the continuation phase after conversion to negative; or •Evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs; or •Adverse drug reactions.
Died	A patient who dies for any reason during the course of treatment.
Lost to follow-up	A patient whose treatment was interrupted for two consecutive months or more.
Treatment success	The sum of Cured and Treatment completed.

[3] WHO. Companion handbook to the 2011 WHO guidelines for the programmatic management of drug-resistant tuberculosis. 2014. http://www.who.int/tb/publications/pmdt_companionhandbook/en/ (Last accessed 16 October 2016.

Background and Objectives:

The emergence of drug-resistant tuberculosis (TB) is a major threat to global TB care and control, and even more so when there is resistance to multiple drugs. [1] One of the new drugs available for the treatment of multi-drug resistant TB is bedaquiline. Bedaquiline was provided marketing authorisation by the United States Food and Drug Administration under a procedure of "accelerated approval" for the treatment of MDR-TB, in December 2012. [2] A review of the available evidence on the use of bedaquiline led to the issuance of an Interim Guidance for the use of bedaquiline in the treatment of MDR-TB in June 2013 by the World Health Organization (WHO). [3]So far, WHO estimates that the drug has been introduced and used in 46 countries worldwide, under various mechanisms of compassionate use, expanded access programme, donation programmes, import waiver and registered market access. [4]

As part of the process of reviewing new evidence for the interim Guidance document, this report was commissioned by the WHO to the Department of Clinical Epidemiology and Biostatistics at McMaster University, to answer specific questions relating to the safety, effectiveness and survival of patients with MDR-TB treated with bedaquiline.

Overall aim:

To support the WHO assessment of evidence on the use of bedaquiline as part of WHO-recommended MDR-TB treatment regimens to inform any potential update of the interim policy guidance.

Specific objectives:

1. To use data from a series of cohorts of MDR-TB patients receiving treatment with bedaquiline to assess the following performance indicators:
    a. Effectiveness - through the evaluation of treatment outcomes in cohorts of patients treated with bedaquiline in addition to (optimised) background regimen,
    b. Safety - through the evaluation of the type, frequency, severity and seriousness of adverse events related to the use of bedaquiline;
    c. Survival - through evaluation of the mortality rates when receiving bedaquiline (and related causes of death).

Research question

In MDR-TB patients, does the addition of bedaquiline to WHO-recommended second-line drug therapy safely improve patient outcome, as reflected by sputum culture conversion at the end of 6 months, cure at the end of treatment, and patient survival?

Table 1: Outline of research question

Population	Intervention	Comparator	Outcomes
MDR-TB patients including: 1. Newly diagnosed MDR-TB patients 2. Suspected MDR-TB patients treated empirically 3. HIV infected patients (with or without ART) *4.* Children	Addition of bedaquiline to background therapy during the first six (6) months of MDR-TB treatment	WHO recommended MDR-TB therapy without bedaquiline.	1. Safety: type, frequency and severity of adverse events related to the use of bedaquiline; 2. Effectiveness: evaluation of treatment outcomes in cohorts of patients treated with bedaquiline on top of optimised background regimen 3. Patient survival

Methods:

Study selection and appraisal

The following databases were searched from December 2015 to January 2016: Cochrane Central Register of Controlled Trials (CENTRAL), PubMed/MEDLINE® and Embase®. The drug manufacturer (Janssen Therapeutics) was contacted for unpublished data. Conference proceedings and reference lists were also searched as an additional technique to identify additional published studies that were not retrieved in the initial search.

Preliminary selected studies were screened and assessed for eligibility based on the following criteria: all studies conducted in individuals diagnosed with MDR-TB (pulmonary and extra-pulmonary) in which bedaquiline was added to an anti-tuberculosis regimen for at least 6 months, and in which drug-monitoring data were collected at least at baseline and at end of treatment. The following exclusion criteria were applied: (i) studies conducted in animals; (ii) pharmacokinetics/pharmacodynamics studies; (iii) studies of only-bedaquiline therapy; (iv) studies which did not provide information on background therapy; (v) studies that did not provide outcome information;(vi) case-reports or other observational studies with sample size ‹ 10; and (vii) qualitative reports. Screening and study selection were conducted in duplicate.

A total of 687 records were retrieved, of which 638 were excluded based on their titles, and an additional 48 after screening the abstracts (9 duplicates and 39 not meeting inclusion criteria). Forty-three (43) full-text articles were screened and five were selected for inclusion. The screening and selection process are described in Appendix 2.

Data sources

In total, five data sources were used for this analyses: The ”Médecins Sans Frontières” cohorts in Armenia and Georgia,[5] the South African Bedaquiline Compassionate Access Program (BCAP),[6] the French ‘MDR-TB cohort’, [7] the drug manufacturer study, [8, 9] and data from the South African Electronic Drug-Resistant Tuberculosis Register (EDRWeb). The EDRWEb data was not identified through a search, but was presented to the Guideline Development Group (GDG) by the South African representatives. These data sets are described in more detail below:

The MSF cohorts in Armenia and Georgia

"Médecins Sans Frontières" hosted two prospective cohorts in Armenia and Georgia, beginning in 2013 and 2014 respectively. They included MDR-TB patients with additional resistance to fluoroquinolones (MDR-TB_{+FQ}) or injectables (MDR-TB_{+INJ}) or both (XDR-TB). Access to bedaquiline was provided through compassionate use. BDQ was provided for 24 weeks as part of a regimen constructed according to WHO guidelines: at least four effective drugs including a fluoroquinolone and an injectable if possible. At the time of these analyses, 62 patients had been enrolled in Armenia and 30 in Georgia. The only publication from this work is a poster. Data were provided as comma separated value (CSV) files.

The South African BCAP

The BCAP cohort started in March 2013, and included patients with pulmonary MDR-TB: MDR-TB_{+FQ}, MDR-TB_{+INJ} and XDR-TB. Patients received BDQ 400mg once daily for 2 weeks, then 200mg thrice a week for 24 weeks in addition to their baseline regimen. Access to bedaquiline was through compassionate use. At the time of this analyses, 195 patients had been recruited of which 101 had been followed up for 18 months or more. Interim analyses from this cohort were published for the first 91 patients. [6] Data were provided as Microsoft excel sheets.

The French cohort

In France, 45 patients were enrolled since January 2011. They had MDR-TB, MDR-TB_{+FQ}, MDR-TB^{+INJ} or XDR. Patients with both pulmonary and extra pulmonary TB were included. Patients received BDQ 400mg once daily for 2 weeks, then 200mg thrice a week in addition to their baseline regimen. Access to bedaquiline was through an expanded access programme. At the time of this analyses all 45 patients had been followed up for 18 months or more. Interim analyses for the first 35 patients have been published. [7]Data were provided as Microsoft excel sheets.

The drug manufacturer

The pharmaceutical company conducted a phase II single arm open label trial of bedaquiline in 31 sites spread over 11 countries (China, Estonia, Republic of Korea, Latvia, Peru, Philippines, Russian Federation, South Africa, Thailand, Turkey, Ukraine). Only patients with sputum smear positive pulmonary MDR-TB, MDR-$_{TB+FQ}$, MDR-TB_{+INJ} or XDR were included. Patients received 400mg of BDQ once daily for the first two weeks and 200 mg thrice weekly for weeks 3 through 24. They enrolled 233 patients of which 205 were followed up for 18 months or more. Data from this study have been published.[8] Data were made available on a secure remote platform. [10]

The South African EDRWeb

The EDRWEb is a web-based software used in the surveillance and management of drug resistant TB in South Africa (https://edrweb.net/). It is used in 22 drug resistant TB units in all the 9 provinces of South Africa. We received data on 25177 patients. Eighty-two cases belonged in the BCAP cohort and were excluded. Of the remaining 25095, 1556 (6.2%) had received bedaquiline and the others had not. The only outcome of interest in this dataset was mortality. Mortality data were supplemented by information from vital statistics registries. There are no publications from this database. Data were provided as Microsoft excel sheets.

Data management

For the relevant studies, the investigators were contacted with requests to share individual patient data. The investigators were given a copy of the study protocol and invited to sign a data-sharing agreement. Data were shared with the McMaster team by email, remote secure access or cloud sharing platforms. The shared files were saved on a secure server at the Biostatistics Unit of St Joseph's Healthcare Hamilton. The files were cleaned and

merged when appropriate and possible. Data custodians were contacted for issues related to missing data and interpretation of variables. For consistency, data were cleaned and outcomes pulled in the same manner across studies. As such minor discrepancies, may appear between the numbers in this report and the estimates from the individual studies. Attempts have been made to resolve these discrepancies. Any persisting discrepancies are minor and do not affect the conclusions drawn from this report.

Analysis

Baseline characteristics and other outcomes were described as counts (percentage) for categorical data and means (standard deviation) for continuous data. Outcomes were merged using random effects meta-analysis of proportions. Statistical heterogeneity was assessed using the I^2 statistic. Due to variations in completeness and availability of data, different numbers were used for each analysis. The number of patients available for each analysis is outlined in detail in appendix 1. The analysis of the survival data from South Africa was conducted in three steps: First, a descriptive analysis of the cohort, by use of bedaquiline; second, a replication of the results using cox regression and covariate adjustment using propensity scores, and third a logistic regression analysis adjusting for the same covariates used to create the propensity scores.

Modifications to initial analytical plan

Several changes to the initial analytical plan[4] were made due to availability of data, limitations in data quality and recommendations from the WHO Guideline Development Group (GDG).

Changes to control group:

We initially planned to conduct comparative analyses using two cohorts of patients with MDR-TB who did not receive bedaquiline. [11, 12] Given that we were unable to secure individual patient level data to create similar comparison groups, the GDG deemed this to be an inadequate control group. In addition, we were later made aware of the availability of individual patient and comparative control data on mortality from South Africa.

Changes to participant inclusion criteria:

To ensure that all the patients had similar follow-up times, we decided to exclude the cohorts in which less than 50% of the participants had not been followed up for 18 months or more. This led to the exclusion of the Armenia and Georgian cohorts from the analyses of treatment outcome.

[4] The analytical plan can be found here: http://yoda.yale.edu/sites/default/files/bdq_protocol_10.02.2016.pdf

Baseline characteristics, baseline regimens and antiretroviral therapy:

Baseline characteristics:

The baseline characteristics of the participants in the included cohorts are summarised in table 2. Noteworthy are the higher proportions of males in the French and Armenian cohorts, the longer duration on bedaquiline in the French cohort, with close to 71% using it for more than 6 months; higher prevalence of HIV in the South African cohort, and more severe resistance profiles in the South African, French, Armenian and Georgian cohorts. Overall, the average age was 36.4 years (standard deviation [SD]: 11.8). About sixty-four percent were males. The duration on bedaquiline was 6.37 months (SD:2.3). One hundred and thirty-eight (25.7%) were living with HIV of which 120 (22.3%) were on antiretroviral therapy. Almost all had pulmonary TB (341/342; 99.7%). Their resistance profiles were as follows: MDR-TB (191; 35.5%), MDR-TB$_{+FQ}$ (148; 27.5%); MDR-TB$_{+INJ}$ (55; 10.2%), XDR-TB (191; 35.5%). The baseline information of the patients in the South Africa EDRWeb database are reported in detail in the 'Survival" section (table 23).

Table 2: Baseline characteristics of participants in the included studies

	Country/ data source					
Variable	**South Africa (n=195)**	**France (n=45)**	**Drug manufacturer (n=205)**	**Armenia (n=62)**	**Georgia (n=30)**	**Total (n=537)**
Age (years): mean (SD)	35.8 (11.2)	37.4 (12.1)	34.9 (12.2)	41.6 (12.6)	38.7 (11.9)	36.4 (11.8)
Gender						
Male: n (%)	98 (50.3)	36 (80.0)	132 (64.4)	55 (88.7)	21 (70.0)	342 (63.7)
Female: n (%)	97 (49.7)	9 (20.0)	73 (35.6)	7 (11.3)	9 (30.0)	195 (36.3)
Duration on BDQ (months): mean (SD)	5.8 (1.2)	12.3 (7.0)	5.9 (1.1)	5.6 (1.6)	6.0 (1.3)	6.37 (2.3)
Duration on BDQ >6months: n (%)[1]	4 (2.1)*	32 (71.1)	0.0 (0.0)	6 (9.6) *	4 (13.3) *	46 (8.5)
Duration on treatment (months): mean (SD)	14.9 (6.7)	19.4 (4.7)	21.8 (7.6)	17.2 (8.4)	9.2 (3.6)	17.8 (7.0)
Received full treatment (18-20 months): n (%)	101 (51.8)	45 (100.0)	205 (100.0)	29 (46.7)	7 (23.3)	207 (38.5)
HIV status (positive): n (%)[2]	123 (63.1)	2 (4.4)	8 (4.0)	4 (6.5)	1 (3.3)	138 (25.7)
On antiretroviral therapy: n (%)	110 (56.4)	2 (4.4)	8 (4.0)	0 (0.0)	0 (0.0)	120 (22.3)
Type of TB						
Pulmonary	NR	44 (97.8)	205 (100.0)	62 (100.0)	30 (100.0)	341 (99.7)
Extra-pulmonary	NR	8 (17.8)	0 (0.0)	0 (0.0)	0 (0.0)	8 (2.3)
History of previous TB treatment	NR	34 (75.6)	193 (94.1)	24 (38.7)	20 (66.7)	271 (79.2)
History of previous second line TB treatment	NR	27 (60.0)	177 (86.3)	62 (100.0)	29 (96.7)	295 (86.3)
Cavities (yes): n (%)	NR	39 (86.7)[3]	135 (65.8)	55 (88.7)	24 (80.0)	253 (73.9)
Resistance profile: n (%)[4]						
MDR-TB	0 (0)	7 (15.6)	93 (45.4)	0 (0.0)	0 (0.0)	100 (18.6)
MDR-TB$_{+FQ}$	73 (37.4)	8 (17.8)	31 (15.1)	30 (48.4)	5 (16.7)	147(27.3)
MDR-TB$_{+ INJ}$	29 (14.9)	6 (13.3)	13 (6.3)	7 (11.3)	0 (0.0)	55 (10.2)
XDR-TB	77 (39.5)	24 (53.3)	37 (18.0)	25 (40.3)	25 (83.3)	188 (35.0)

**Different approaches to computing duration on bedaquiline and incomplete data on interruptions led to certain patients appearing to have received bedaquiline for more than 6 months; [1] Missing data: SA=15; [2]Missing data: SA=13; Drug manufacturer=7; Georgia=8; Armenia =1; [3] Missing data: France=1; [4]Missing data: SA=16; Drug manufacturer =31; Armenia=1; Georgia=8. SD=Standard deviation; BDQ=Bedaquiline; HIV=human immunodeficiency virus; TB=tuberculosis; MDR=multidrug resistant; FQ=fluoroquinolone; INJ=Injectable; XDR=extensively drug resistant*

Baseline regimens:

The composition of the baseline regimens was different across studies, with a high use of aminoglycosides in the French, and drug manufacturer cohorts, high use of fluoroquinolones in the South African and drug manufacturer cohorts, and a low use of macrolides overall. Other miscellaneous anti-tuberculosis drugs were highly used in all cohorts. For ***Armenia and Georgia***, the baseline regimen was constructed according WHO recommendations (at least four effective drugs including a fluoroquinolone and injectable if possible, with clofazimine, linezolid and imipenem-cilastatin included when needed. In ***South Africa***, the baseline regimens included at least three effective second line drugs (a combination of some or all of the following: linezolid, clofazimine, pyrazinamide, ethambutol, high dose isoniazid, p-aminosalicylic acid, capreomycin, kanamycin, levofloxacin, ethionamide or terizidone, as per the South African National Tuberculosis Control Programme guidelines and according to availability). Levofloxacin was preferred over moxifloxacin, to mitigate QT effects. In ***France***, the baseline regimen was tailored to drug susceptibility results. In the ***drug manufacturer*** study, baseline regimen was selected in accordance with local treatment guidelines. Typically, the intensive phase (4-6 months) would include an injectable aminoglycoside with 3 or 4 other drugs, including a fluoroquinolone and then followed by a continuation phase without an aminoglycoside and without pyrazinamide. The proportions who used each drug are outlined in table 3.

Table 3: Composition of optimised baseline regimen in the included studies

	Country/ data source				
Drug	**South Africa (n=195)**	**France (n=45)**	**Drug manufacturer (n=205)**	**Armenia (n=62)**	**Georgia (n=30)**
Aminoglycosides	**56 (28.7)**	**45 (100.0)**	**152 (74.1)**	**17 (27.4)**	**1 (3.3)**
Amikacin sulfate	1 (0.5)	32 (71.1)	47 (22.9)	1 (1.6)	*0 (0.0)*
Kanamycin	55 (28.2)	0 (0.0)	103 (50.2)	16 (25.8)	1 (3.3)
Streptomycin	0 (0.0)	45 (100.0)	3 (1.5)	*0 (0.0)*	*0 (0.0)*
Fluoroquinolones	**158 (81.0)**	**26 (57.7)**	**180 (87.8)**	**28 (45.2)**	**7 (23.3)**
Ciprofloxacin	0 (0.0)	0 (0.0)	7 (3.4)	*0 (0.0)*	*0 (0.0)*
Gatifloxacin	0 (0.0)	0 (0.0)	1 (0.5)	*0 (0.0)*	*0 (0.0)*
Levofloxacin	158 (81.0)	8 (17.8)	66 (32.2)	28 (45.2)	7 (23.3)
Moxifloxacin	0 (0.0)	24 (53.3)	1 (0.5)	*0 (0.0)*	*0 (0.0)*
Ofloxacin	0 (0.0)	0 (0.0)	101 (49.3)	*0 (0.0)*	*0 (0.0)*
Sparfloxacin	0 (0.0)	0 (0.0)	5 (2.4)	0 (0.0)	0 (0.0)
Macrolide	**19 (9.7)**	**0 (0.0)**	**22 (10.7)**	**0 (0.0)**	**0 (0.0)**
Azithromycin	9 (4.6)	0 (0.0)	16 (7.8)	0 (0.0)	0 (0.0)
Clarithromycin	10 (5.1)	0 (0.0)	6 (2.9)	*0 (0.0)*	*0 (0.0)*
Miscellaneous anti-TB drugs	**170 (87.2)**	**45 (100.0)**	**205 (100.0)**	**62 (100.0)**	**30 (100.0)**
Ethambutol	*103 (52.8)*	*20 (44.4)*	*109 (53.2)*	*3 (4.8)*	*0 (0.0)*
Isoniazid	*34 (17.4)*	*0 (0.0)*	*30 (14.6)*	*0 (0.0)*	*0 (0.0)*
Pyrazinamide	*159 (81.5)*	*0 (0.0)*	*152 (74.1)*	*7 (11.3)*	*5 (16.7)*
Rifampicin	*1 (0.5)*	*19 (42.2)*	*1 (0.5)*	*0 (0.0)*	*0 (0.0)*
Amoxicilin Clavunate	5 (2.6)	0 (0.0)	20 (9.8)	50 (80.6)	29 (96.7)
Capreomycin	38 (19.5)	3 (6.7)	45 (22.0)	22 (35.5)	11 (36.7)
Clofazimine	151 (77.4)	20 (44.4)	13 (6.3)	51 (82.3)	24 (80.0)
Cycloserine	0 (0.0)	32 (71.1)	53 (25.9)	45 (72.6)	13 (43.3)
Dapsone	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Ethionamide	99 (50.8)	11 (24.4)	84 (41.0)	*0 (0.0)*	*0 (0.0)*
Imipenem	3 (1.5)	28 (62.2)	1 (0.5)	0 (0.0)	0 (0.0)
Imipenem-Cilastatin	0 (0.0)	0 (0.0)	0 (0.0)	44 (71.0)	27 (90.0)
Linezolid	121 (62.1)	43 (95.6)	12 (5.9)	62 (100.0)	30 (100.0)

Para-aminosalicylic acid	157 (80.5)	40 (88.9)	97 (47.3)	31 (50.0)	12 (40.0)
Meropenem	1 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*	*0 (0.0)*
Meropenem/Amoxicilin Clavunate	0 (0.0)	2 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)
Para-aminosalicylic acid salt	0 (0.0)	0 (0.0)	0 (0.0)	*0 (0.0)*	1 (3.3)
Prothionamide	0 (0.0)	0 (0.0)	76 (37.1)	10 (16.1)	1 (3.3)
Terizidone	161 (82.6)	0 (0.0)	60 (29.3)	*0 (0.0)*	*0 (0.0)*
Thioacetazone	0 (0.0)	0 (0.0)	3 (1.5)	*0 (0.0)*	*0 (0.0)*

Composition of antiretroviral therapy

In the South African cohort, the most used antiretroviral drugs were lamivudine, nevirapine and tenofovir. In the French and drug manufacturer cohorts they were lamivudine, efavirenz and tenofovir. These results are summarised in table 5. None of the patients in the Armenian and Georgian cohorts were receiving antiretroviral therapy.

Table 4: Composition of antiretroviral therapy in the included studies

	Country/ data source[1]		
Antiretroviral drug	**South Africa (n=110)**	**France (n=2)**	**Drug manufacturer (n=8)**
Lamivudine	93 (47.7)	2 (4.4)	8 (100.0)
Abacavir	7 (3.6)	1 (2.2)	0 (0.0)
Zidovudine	21 (10.8)	0 (0.0)	2 (25.0)
Stavudine	27 (13.8)	0 (0.0)	0 (0.0)
Efavirenz	7 (3.6)	2 (4.4)	8 (100.0)[1]
Emtricitabine	15 (7.7)	1 (2.2)	0 (0.0)
Lopinavir/ritonavir	27 (14.3)	0 (0.0)	0 (0.0)
Nevirapine	74 (37.9)	0 (0.0)	1 (12.5)
Tenofovir	56 (28.7)	1 (2.2)	6 (75%)

[1] None of the patients from Georgia or Armenia where on antiretroviral therapy; [2]In the Drug manufacturer cohort, EFV was used only after BDQ was stopped

SUMMARY OF COHORT DATA:

The baseline characteristics of the participants differed greatly with important differences noted in the completeness of follow-up in the cohorts, the duration on bedaquiline, the proportion of participants who were HIV positive, the types of antiretroviral therapy used, the presence of cavities, resistance profile and constitution of baseline regimen. These differences were in part due to the inclusion criteria of the cohorts, the country-specific guidelines for the use of baseline regimens and antiretroviral therapy and the purpose of the cohorts: programmes of care versus research.

Effectiveness

Culture conversion at six months

Effectiveness was calculated as the proportion of participants who had sputum culture conversion at the end of the initial six months of bedaquiline treatment. A total of 391 patients had received treatment for 6 months and had sputum collected at 6 months. The effectiveness of bedaquiline was 79.7% (95% CI 75.2 to 83.5). There was minimal heterogeneity in this analysis (I^2=38.7%). These results are illustrated in figure 1.

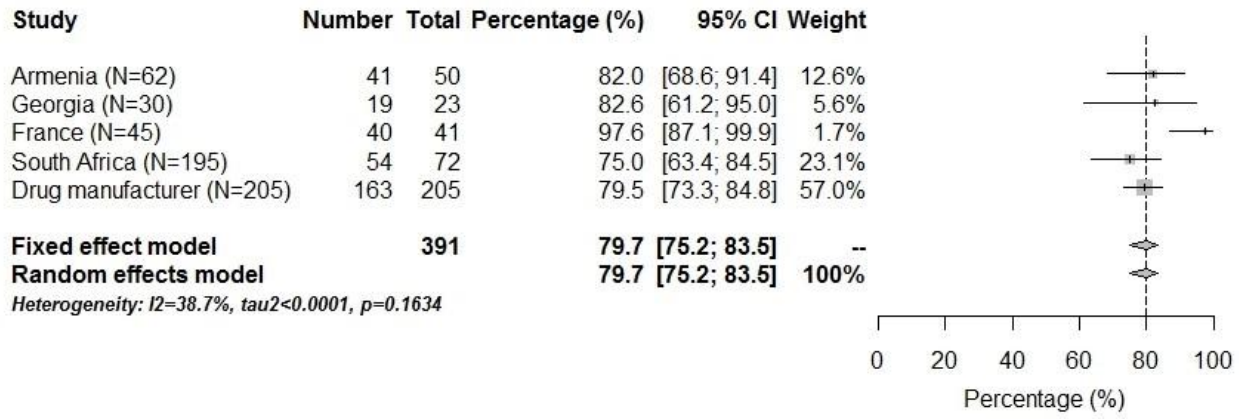

Figure 1: Effectiveness of BDQ at 6 months (random effects meta-analysis of proportions)

Treatment outcomes: Cure, death, lost to follow-up, treatment complete, treatment failure and treatment success

Treatment outcomes (cure, death, lost to follow-up, treatment complete and treatment failure) were estimated for patient who had at least 18-20 months of follow-up data available. For this analysis, the Armenian and Georgian cohorts were excluded because they had very few (less than 50%) of their participants who had complete follow-up data and therefore all outcomes could not be adequately estimated. The treatment outcomes for the French, South African and drug manufacturer cohorts are summarised in table 5.

Table 5: Treatment outcomes for included studies

Outcome	South Africa n (%)	France n (%)	Drug manufacturer n (%)
Cured	64 (63.4)	34 (75.5)	125(61.0)
Death	20 (19.8)	3 (6.7)	14 (6.8)
Lost to follow up	10 (9.9)	5 (11.1)	31 (15.1)
Treatment complete	6 (5.9)	2(4.4)	3 (1.5)
Treatment failure	1 (1.0)	1 (2.2)	32(15.6) *
Total	101	45	205
*Treatment success***	70 (69.3)	36 (80.0)	128 (62.4)

**The drug manufacturer used a missing equals failure approach; **treatment success=cured + treatment complete*

These outcomes were pooled using a random effects meta-analysis of proportions. The results of these meta-analyses are summarised in table 6. The forest plots for these analyses are displayed below (figures 2-7).

Table 6: Meta-analysis of treatment outcomes

Outcome	n= 351	%* (95%CI)	I^2
Cure	223	63.8 (57.8-69.4)	39.5%
Treatment complete	11	3.3 (0.7-7.3)	58.7%
Treatment failure	34	5.2 (0.0-16.3)	92.2%
Death	37	10.6 (3.8-20.0)	81.7%
Lost to follow-up	46	12.8 (9.2-16.8)	0%
Treatment success	234	69.3 (59.7 – 78.2)	64.9%

**Random effects meta-analysis of proportions for 3 studies.*

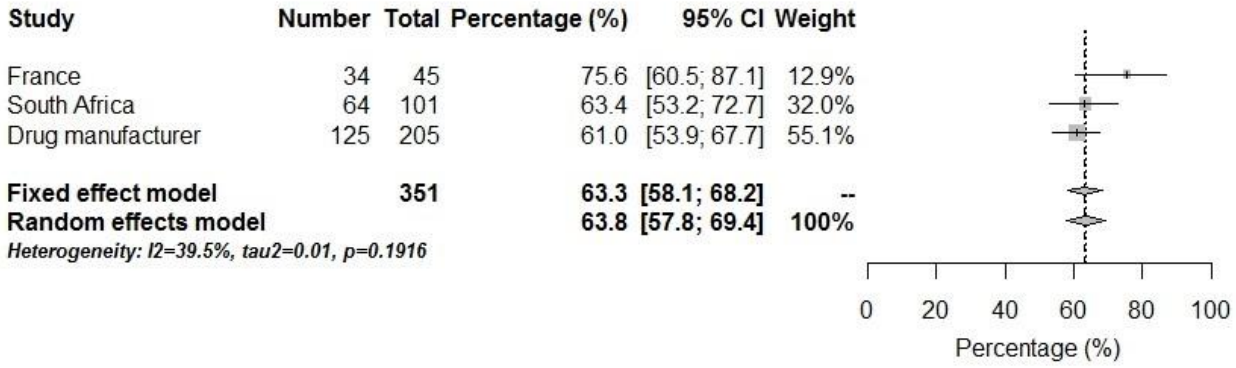

Figure 2: Forest plot for meta-analysis of cure rates

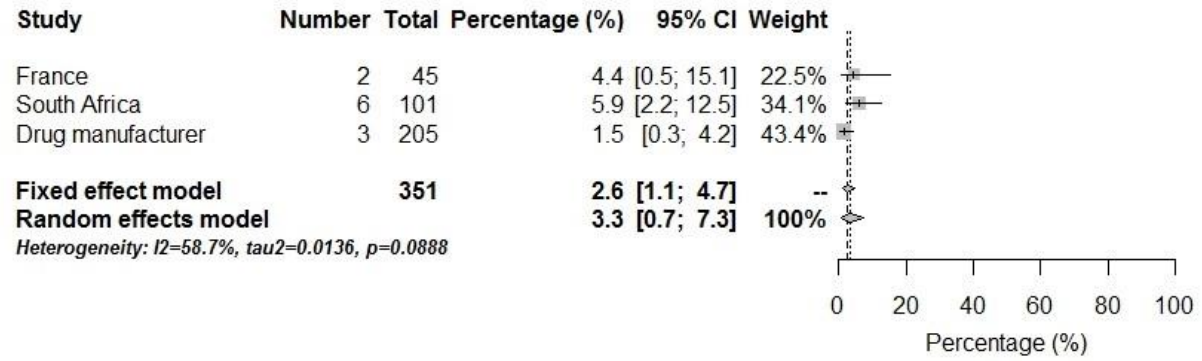

Figure 3: Forest plot for meta-analysis of treatment completion rates

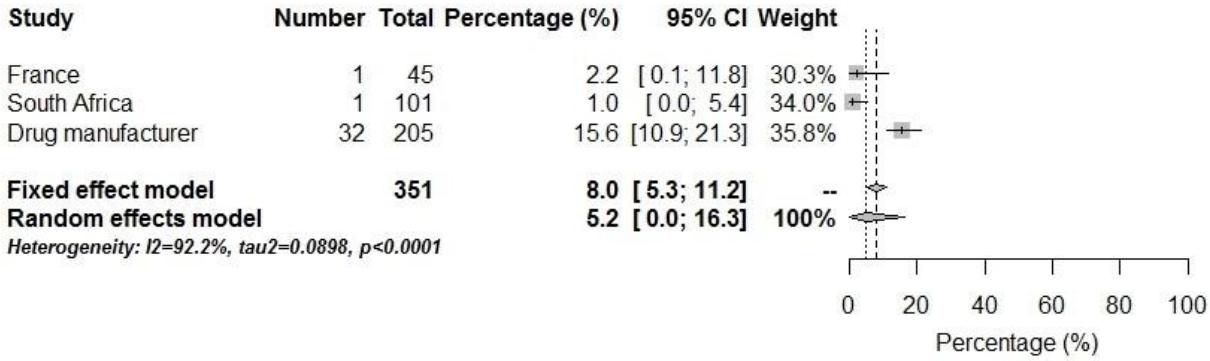

Figure 4: Forest plot for meta-analysis of treatment failure rates

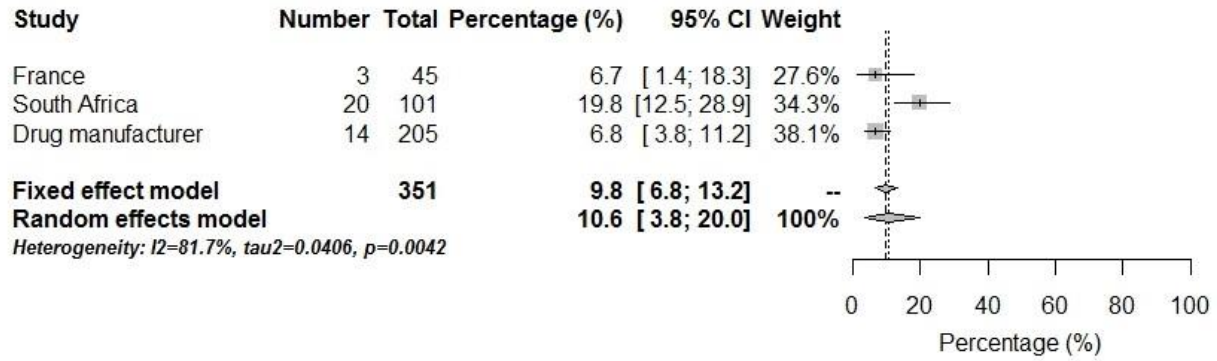

Figure 5: Forest plot for meta-analysis of death rates

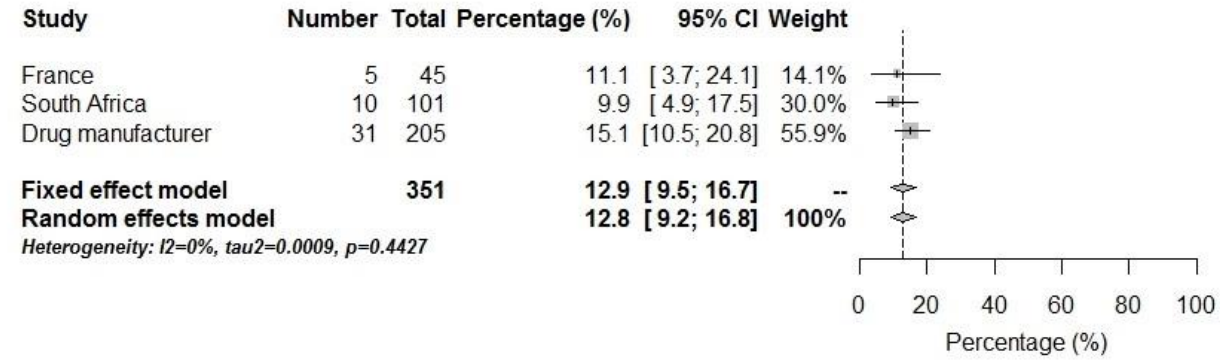

Figure 6: Forest plot for meta-analysis of lost-to-follow-up rates

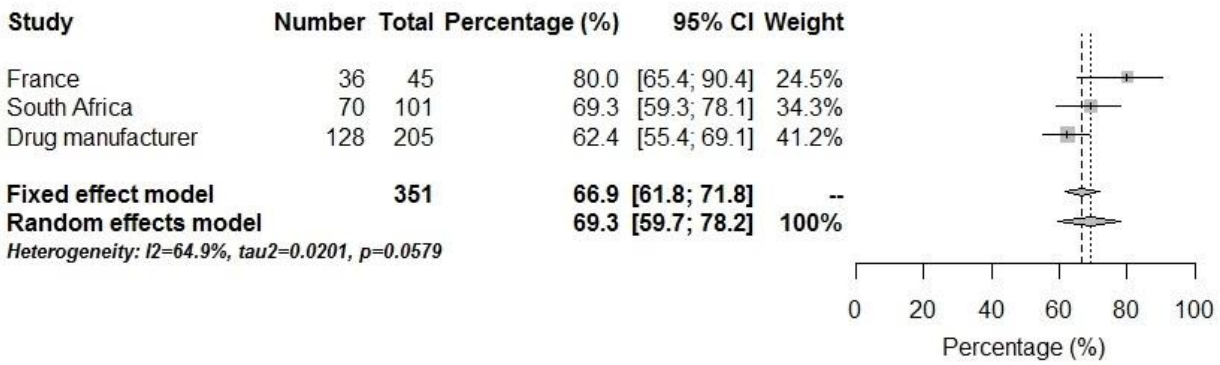

Figure 7: Forest plot of meta-analysis of success rates

SUMMARY OF EFFECTIVENESS AND TREATMENT OUTCOME DATA

The use of bedaquiline led to a 79.7 % culture conversion rate at 6 months. At the end of follow-up (18-24 months) the cure rate was 63.8%. The death rate was 10.6%. Overall treatment success rate was 69.3%.

Safety

Overview of safety data:

Definition of terms:

Adverse event: Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.[5]

Severity refers to the intensity of a specific event, often categorised as mild, moderate or severe. For safety outcomes, severity was considered as reported by the authors (severe adverse event or grades 3 and 4).

Serious adverse event: An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.[5]

Data were grouped according to system based on available information, for example: gastrointestinal adverse events include events reported by authors as gastrointestinal or all related to the gastrointestinal system such as nausea, vomiting, diarrhoea etc.; hepatic adverse events were considered as reported by the authors or including liver enzyme elevation and clinical reports; cardiovascular adverse events included events reported by authors as cardiovascular or other clinical and ECG reports. The same approach was adopted for all reported systems. Safety data includes all patients who received bedaquiline irrespective of duration. Safety data were reported to various degrees of completeness and consistency, but were interpreted and grouped into meaningful categories. Classification of adverse events by severity was not reported in the Armenian and Georgian cohorts. Adverse events reported as life threatening and fatal were considered as serious.

[5]Code of Federal Regulation, title 21, Volume 5 (revised 01 April 2016) CITE: 21CFR312.32. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=312.32

Any adverse event

The number of adverse events experienced is reported in table 7. The most frequent adverse events experienced were gastrointestinal (14%), followed by metabolic disorders (8.5%) and nervous system disorders (8.5%)

Table 7: Distribution of all adverse events by system affected and study

System	South Africa	France	Drug manufacturer	Armenia	Georgia	Total
Gastrointestinal symptoms	22 (8.6)	37 (20.7)	251 (12.9)	46 (22.4)	11 (28.2)	367 (14.0)
Metabolisms and nutrition disorders	36 (14.1)	3 (1.7)	185 (9.5)	0 (0)	0 (0)	224 (8.5)
Musculoskeletal and connective tissue disorders, arthralgia	19 (7.4)	7 (3.9)	147 (7.6)	5 (2.4)	0 (0)	178 (6.8)
Nervous system disorders (dizziness, headache)	34 (13.3)	42 (23.5)	111 (5.7)	34 (16.6)	3 (7.7)	224 (8.5)
Skin and subcutaneous tissue disorders	17 (6.6)	8 (4.5)	90 (4.6)	5 (2.4)	0 (0)	120 (4.6)
Respiratory, thoracic and mediastinal disorders	3 (1.2)	2 (1.1)	125 (6.4)	5 (2.4)	2 (5.1)	137 (5.2)
Ear and labyrinth disorders, Eye	23 (9.0)	10 (5.6)	90 (4.6)	10 (4.9)	1 (2.6)	134 (5.1)
Psychiatric disorders	9 (3.5)	12 (6.7)	60 (3.1)	0 (0)	0 (0)	81 (3.1)
Blood and lymphatic system disorders	20 (7.8)	12 (6.7)	65 (3.3)	0 (0)	1 (2.6)	98 (1.9)
Cardiac disorders (including ECG changes and QT prolongation)	5 (2.0)	8 (4.5)	31 (1.6)	4 (2.0)	1 (2.6)	49 (1.9)
Laboratory signs of hepatitis	2 (0.8)	20 (11.2)	24 (1.2)	35 (17.1)	7 (17.9)	88 (3.4)
Laboratory signs of pancreatitis	2 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.1)
Renal failure	9 (3.5)	7 (3.9)	14 (0.7)	5 (2.4)	3 (7.7)	38 (1.4)
Other*	55 (21.5)	11 (6.1)	750 (38.6)	56 (27.3)	10 (25.6)	882 (33.6)
Total	256 (100)	179 (100)	1943 (100)	205 (100)	39 (100)	2622 (100)

**Other includes congenital, familial and genetic, general disorders and admin site conditions, injury, poisoning and procedural complications, investigations, neoplasms and events reported as 'other'.*

The number of patients who experienced at least one adverse event is reported in table 8. Overall, 520/565 patients (92.0%) experienced at least one adverse event.

Table 8: Number of patients with at least one adverse event

Country/study	Number with at least one adverse event n (%)
France (n=45)	45 (100.0)
South Africa (n=195)	164 (84.1)
Drug manufacturer (n=233) *	219 (93.9)
Armenia (n=62)	62 (100.0)
Georgia (n=30)	30 (100.0)
Total (n=565)	520 (92.0)

**Includes some patients (n=28) who were later found to be ineligible or withdrew consent*

The number of patients who experienced at least one severe or one serious adverse event are summarised in table 9. A total of 118 patients (20.8%) experienced a severe adverse event, while 42 (7.4%) experienced a serious adverse event.

Table 9: Number of patients who experienced at least one severe or at least one serious adverse event

Country/study	Any Severe Adverse Event n (%)	Any Serious Adverse event n (%)
France (n=45)	28 (62.2)	7 (15.6)
South Africa (n=195)	32 (16.4)	6 (3.1)
Drug manufacturer (n=233) *	50 (21.5)	15 (6.4)
Armenia (n=62)	5 (8.1)	11 (17.7)
Georgia (n=30)	3 (10.0)	3 (10.0)
Total (n=565)	118(20.8)	42 (7.4)

**Includes some patients (n=28) who were later found to be ineligible or withdrew consent*

All serious adverse events

When all cohorts were put together, the systems most frequently affected by serious adverse events were respiratory (25.0%), cardiac (16.7%) and laboratory signs of hepatitis (14.6%).

Table 10: Distribution of number of serious adverse events by system in all studies

System	Total n (%)
Gastrointestinal symptoms	1 (2.1)
Metabolisms and nutrition disorders	2 (4.2)
Musculoskeletal and connective tissue disorders, arthralgia	0 (0.0)
Nervous system disorders (dizziness, headache)	4 (8.3)
Skin and subcutaneous tissue disorders	0 (0.0)
Respiratory, thoracic and mediastinal disorders	12 (25.0)
Ear and labyrinth disorders, Eye	0 (0.0)
Psychiatric disorders	2 (4.2)
Blood and lymphatic system disorders	0 (0.0)
Cardiac disorders (including ECG changes and QT prolongation)	8 (16.7)
Laboratory signs of hepatitis	7 (14.6)
Laboratory signs of pancreatitis	0 (0.0)
Renal failure	2 (4.2)
Other*	10 (20.8)
Total	48 (100.0)

***Includes some deaths*

Adverse events by resistance profile

Severe adverse events by resistance profile are illustrated in table 11. Individual patient level data on resistance profile was not available from the drug manufacturer cohort. Patients with MDR-TB (42.8%) and XDR-TB (30.5%) had the highest proportions of severe adverse events.

Table 11: Severe adverse event by resistance category

Resistance profile[1]	SA n=195		France n =45		Armenia n=62		Georgia n=30		Total n (%)	
	n (%)	NRC*	n (%)	NRC*	n (%)	NRC*	n (%)	NRC*	n (%)	NRC*
MDR-TB	0 (0.0)	0	3 (42.9)	7	0 (0.0)	0	0 (0.0)	0	3 (42.8)	7
MDR-TB$_{+FQ}$	8 (10.8)	74	3 (37.5)	8	1 (3.3)	30	1 (20.0)	5	11 (11.1)	117
MDR-TB$_{+ INJ}$	1 (3.4)	29	3 (50.0)	6	1 (14.3)	7	0 (0.0)	0	5 (11.9)	42
XDR-TB	23 (28.8)	80	19 (79.2)	24	3 (12.0)	25	2 (8.0)	25	47 (30.5)	154
Total	32 (17.5)	183	28 (62.2)	45	5 (8.1)	62	3 (10.0)	30	66 (20.6)	320

**Number in resistance category; [1] Missing data on resistance profile: South Africa=16*

Serious adverse events by resistance profile are illustrated in table 12. Serious adverse events were highest in the MDR-TB (14.3%) and XDR-TB groups (9.3%).

Table 12: Serious adverse event by resistance profile

Resistance profile[1]	SA n=195		France n=45		Armenia n=62		Georgia n=30		Total n (%)	
	n (%)	NRC*	n (%)	NRC*	n (%)	NRC*	n (%)	NRC*	n (%)	NRC*
MDR-TB	0 (0.0)	0	1 (14.3)	7	0 (0.0)	0	0 (0.0)	0	1 (14.3)	7
MDR-TB$_{+FQ}$	3 (4.1)	73	0 (0.0)	8	5 (16.6)	30	1 (20.0)	5	9 (7.7)	116
MDR-TB$_{+INJ}$	0 (0.0)	29	0 (0.0)	6	1 (14.3)	7	0 (0.0)	0	1 (2.3)	42
XDR-TB	1 (1.3)	77	6 (25.0)	24	5 (20.0)	25	2 (8.0)	25	14 (9.3)	151
Total	4 (2.2)	179	7 (15.6)	45	11 (17.7)	62	3 (10.0)	30	25 (7.9)	316

**Number in resistance category; [1] Missing data on resistance profile: South Africa=16*

Additional safety data reported in the appendix include:

- Appendix 3: Severe adverse events by system for France, South Africa and the drug manufacturer
- Appendix 4: Serious adverse events by system for France, South Africa and the drug manufacturer
- Appendix 5: All severe adverse events by system for Armenia and Georgia

SUMMARY OF SAFETY DATA

On bedaquiline-containing treatment, 20.8% of patients experienced a severe adverse event and 7.4% experienced a serious adverse event. The systems most frequently affected by adverse events are gastrointestinal, metabolic and nervous. The systems most affected by serious adverse events are respiratory, cardiac and hepatic.

QTc prolongation

QTc prolongation was estimated using the Fredericia correction. [13] Change in QTcF was assessed in three ways. First, we noted the worst instances of QTcF and categorised them (≤ 450, >450-480, >480-500 and >500milliseconds). Second, we measured the differences between baseline or reference measures and categorised them (0-30, >30-60 and >60). Thirdly, in order to capture the sustained effect of bedaquiline on QTcF, we used average values. QTcF at the end of follow-up was estimated as the average of all measures during treatment for MDR-TB. Increase from baseline was estimated as the difference between average measures during treatment and baseline measures (or the first available measure). This approach was adopted to make the most use of the data given the different follow-up times and durations of follow-up.

Worst QTcF measurement

The worst QTcF measurements recorded are outlined in table 13. About 70% patients had a worst measurement ≤ 450 ms; 20.5% had a worst measurement between 450 and 480ms; 5.1% had a worst measurement between 480 and 500ms; and 4.7% had a worst measurement above 500ms.

Table 13: Distribution of worst QTcF measurements

Worst QTcF measurement (ms)	France n=45	South Africa n=141	Armenia n=62	Georgia n=30	Drug manufacturer n=233	Total n (%)
≤450	14 (31.1)	105 (74.5)	34 (54.8)	13 (43.3)	190 (81.5)	356 (69.7)
>450-480	16 (35.6)	24 (17.0)	15 (24.2)	14 (46.7)	36 (15.5)	105 (20.5)
>480-500	7 (15.6)	6 (4.3)	6 (9.7)	2 (6.7)	5 (2.1)	26 (5.1)
>500	8 (17.8)	6 (4.3)	7 (11.3)	1 (3.3)	2 (0.9)	24 (4.7)
Total	45 (100.0)	141 (100.0)	62 (100.0)	30 (100.0)	233 (100.0)	511 (100.0)

QTcF increase from baseline

Table 14 illustrates QTcF increases from baseline. About forty-seven percent patients had an increase of 0-30 milliseconds; 33.7% had an increase >30-60ms and 14.8% had an increase >60ms.

Table 14: Increase in QTcF from baseline to worst measurement

QTcF increase from baseline to worst measurement (ms)	France n=45	South Africa n=141	Armenia n=62	Georgia n=30	Drug manufacturer n=233	Total n (%)
0-30	17 (37.8)	68 (48.2)	17 (27.4)	9 (30.0)	127 (54.5)	238 (46.6)
>30-60	6 (13.3)	46 (32.6)	15 (24.2)	9 (30.0)	96 (41.2)	172 (33.7)
>60	8 (17.8)	26 (18.4)	24 (38.7)	8 (26.7)	10 (4.3)	76 (14.8)
Missing	14 (31.1)	1 (0.7)	6 (9.7)	4 (13.3)	0 (0.0)	25 (4.9)
Total	45 (100.0)	141 (100.0)	62 (100.0)	30 (100.0)	233 (100.0)	511 (100.0)

QTcF prolongation by duration on bedaquiline

Only the French cohort had patients who used bedaquiline for more than 6 months. Tables 15 and 16 show the crude average QTcF length and the average increase in QTcF from baseline respectively, by duration on bedaquiline. The effect of bedaquiline on QT prolongation when used for more than six months appears uncertain.

Table 15: Crude average QTcF prolongation by duration on bedaquiline

QTcF length (ms)	France (n=45)		Total
	BDQ 0-6mo: n (%)	BDQ >6mo: n (%)	n (%)
≤450	7 (53.8)	23 (71.9)	30 (66.7)
>450-480	6 (46.2)	9 (28.1)	15 (33.3)
>480-500	0 (0.0)	0 (0.0)	0 (0.0)
>500	0 (0.0)	0 (0.0)	0 (0.0)
Total	13 (100.0)	32 (100.0)	45 (100.0)

Table 16: Average increase in QTcF from baseline by duration on bedaquiline

QTc increase from baseline (ms)	France (n=31)		Total
	BDQ 0-6mo: n (%)	BDQ >6mo: n (%)	n (%)
0-30	7 (70)	17 (81.0)	24 (77.4)
>30-60	2 (20)	4 (19.0)	6 (19.4)
>60	1 (10)	0 (0.0)	1 (3.2)
***Total**	10 (100.0)	21 (100.0)	31 (100.0)

**Missing data: France=14*

SUMMARY OF QTc DATA

Worst QTcF measurements above 500ms occurred in 4.7% of the participants. About 15% had an increase of more than 60ms from baseline. The effect of bedaquiline on QT prolongation in patients who take bedaquiline for more than 6 months is uncertain.

Survival

Survival data is reported for the five pooled cohorts and then separately for the EDRWEb dataset.

Timing of deaths

More than half of the reported deaths occurred between 6 and 26 months (57.1%), and a third within the first six months (32.1%). Only the Drug manufacturer study followed up patients beyond 26 months and reported 2 deaths between 26 and 30 months and 4 deaths after 30 months.

Table 17: Timing of deaths

Timing of deaths	South Africa n (%)	France n (%)	Drug manufacturer n (%)	Armenia n (%)	Georgia n (%)	Total n (%)
0-6 month	9 (32.1)	1 (33.3)	3 (18.7)	3 (50.0)	2 (50.0)	18 (32.1)
6-26 months	18 (57.1)	2 (66.7)	7 (43.8)	3(50.0)	2 (50.0)	32 (57.1)
26-30 months	NA	NA	2 (12.5)	NA	NA	2 (3.6)
30+ months	NA	NA	4 (25.0)	NA	NA	4 (7.1)
Total	27 (100.0)	3 (100.0)	16 (100.0)	6 (100.0)	4 (100.0)	56 (100.0)

**NA=Not applicable*

Distribution of deaths among patients with HIV

The distribution of deaths among the patients with HIV, without HIV and with HIV status unknown is shown for all the cohorts. Overall, 13.0% of the patients with a known HIV-positive status died, compared to 8.8% of those with a known HIV-negative status (RR 1.4; 95% CI 0.86-2.50; p=0.187) and 9.0% among those with HIV status unknown. These results are summarised in table 18.

Table 18: Distribution of deaths among patients with HIV

Study (n)	Number HIV positive	Deaths among HIV positive n (%)	Number HIV negative	Deaths among HIV negative n (%)	Number with HIV unknown	Deaths among HIV unknown n (%)
Drug manufacturer (233)	8	1 (12.5)	225	15 (6.7)	0	0 (0.0)
South Africa (195)	123	17 (13.8)	59	8 (13.6)	13	2 (15.4)
France (45)	2	0 (0.0)	43	3 (6.9)	0	0 (0.0)
Armenia (62)	4	0 (0.0)	57	6 (10.5)	1	0 (0.0)
Georgia (30)	1	0 (0.0)	21	4 (19.0)	8	0 (0.0)
Total	**138**	**18 (13.0)**	**405**	**36 (8.8)**	**22**	**2 (9.0)**

Distribution of deaths by resistance profile

The distribution of deaths by resistance profile is shown in table 19. Among those with MDR-TB 3.0% died, compared to 16.3% in those with MDR-TB_{+FQ}, 10.9% in those with MDR-TB_{+INJ} and 10.1% in those with XDR-TB.

Table 19: Distribution of deaths by resistance profile

Study (N)	MDR Deaths n (%)	Number MDR	MDR-TB_{+FQ} Deaths n (%)	Number MDR-TB_{+FQ}	MDR-TB_{+INJ} Deaths n (%)	Number MDR-TB_{+INJ}	XDR Deaths n (%)	Number XDR
Drug manufacturer[1](233)	2 (2.2)	93	6 (19.4)	31	3 (23.1)	13	5 (13.5)	37
South Africa[2] (195)	0 (0.0)	0	14 (18.9)	73	2 (6.9)	29	7 (11.3)	77
France (45)	1 (14.3)	7	0 (0.0)	8	0 (0.0)	6	2 (8.3)	24
Armenia (62)	0 (0.0)	0	3 (10.0)	30	1 (14.3)	7	2 (8.0)	25
Georgia (30)	0 (0.0)	0	1 (20.0)	5	0 (0.0)	0	3 (12.0)	25
Total*	**3 (3.0)**	**100**	**24 (16.3)**	**147**	**6 (10.9)**	**55**	**19 (10.1)**	**188**

[1] 31 patients with missing resistance profile data; [2]16 patients with missing resistance profile data;
**4 patients from South Africa died with missing resistance profile data*

Listing of all deaths

The affected organ (system), age, gender, HIV status, resistance profile, and circumstance of death are reported for the 56 deaths in table 20. Almost all deaths were related to the respiratory (22/56; 39.2%) or cardiovascular system (4/56; 7.1%). The other systems affected were the central nervous system (1/56; 1.7%), the urinary system (1/56; 1.7%). There were 3 culture reversions (5.3%), 3 infections (5.3%), 1 sudden death (1.7%) and 1 death due to trauma (1.7%) and 1 suicide (1.7%). The causes and circumstances of death were not reported in 19 cases (33.9%). Overall, 18 deaths (32.1%) were due to exacerbation of TB.

Table 20: List of all deaths (n= 56)

#	System	Age	Gender	HIV status	Resistance profile	Details
Georgia						
1	NA	51	Male	*NR	MDR-TB_{+INJ}	Suicide
2	Respiratory	53	Male	NR	MDR-TB_{+INJ}	Respiratory failure due to TB
3	Cardiac	52	Female	NR	MDR-TB_{+INJ}	Cardiopulmonary failure
4	Respiratory	32	Female	NR	MDR-TB_{+INJ}	Respiratory failure due to TB
Armenia						
1	Respiratory	49	Male	NR	MDR-TB_{+FQ}	Respiratory insufficiency due to severe tuberculosis and late stage cor-pulmonale
2	Respiratory	45	Male	NR	MDR-TB_{+FQ}	Severe tuberculosis, stage II-III pulmonary-heart insufficiency (cor-pulmonale)

3	Respiratory	37	Male	NR	NR	Acute respiratory insufficiency (hospitalized)
4	Respiratory	29	Male	NR	XDR	Death due to extensive tuberculosis
5	Cardiac	42	Male	NR	MDR-TB$_{+FQ}$	Sudden death due to myocardial infarction (autopsy report available)
6	Respiratory	50	Male	NR	XDR	Death due to extensive tuberculosis
France						
1	Respiratory	61	Male	No	MDR-TB	Dissemination of a pharyngolaryngeal cancer.
2	Neuro/Psychiatric	62	Male	No	XDR	Since month 15 of treatment, the patient developed peripheral neuropathy, difficulty to swallow, myoclonia, and psychiatric disorders. He died one month later with no clear diagnosis.
3	Infection	37	Male	No	XDR	Septic shock due to candida catheter infection at month 21
Drug manufacturer						
1	Respiratory	59	Male	No	XDR	Tuberculosis
2	Respiratory	22	Female	Yes	XDR	Respiratory failure
3	Respiratory	52	Female	No	XDR	Tuberculosis
4	Cardiac	57	Female	No	MDR-TB$_{+FQ}$	Cardiac failure**
5	Respiratory	37	Male	No	MDR-TB$_{+FQ}$	TB-related illness
6	Respiratory	19	Male	No	MDR-TB$_{+INJ}$	Tuberculosis
7	Renal	63	Female	No	MDR-TB$_{+FQ}$	Renal impairment
8	Respiratory	34	Male	No	MDR-TB	Tuberculosis
9	Respiratory	27	Female	No	XDR	TB-related illness
10	Respiratory	32	Female	Yes	MDR-TB	Tuberculosis
11	Respiratory	59	Male	No	XDR	Pneumonia
12	Cardiac	46	Male	No	MDR-TB$_{+FQ}$	Hypertension
13	Respiratory	32	Male	No	MDR-TB$_{+FQ}$	TB-related illness: hemoptysis
14	Respiratory	31	Male	No	MDR-TB$_{+INJ}$	Lung infection
15	Respiratory	20	Male	No	MDR-TB$_{+INJ}$	TB-related illness
16	Respiratory	56	Male	No	MDR-TB	Haemoptysis
South Africa						
1	NR	36	Male	Negative	XDR	NR
2	NR	25	Male	Negative	MDR-TB$_{+INJ}$	Sudden death at home
3	NR	32	Male	Positive	MDR-TB$_{+FQ}$	NR
4	NR	48	Male	Positive	MDR-TB$_{+FQ}$	NR
5	NR	26	Male	Positive	MDR-TB$_{+FQ}$	NR

6	NR	43	Male	Positive	MDR-TB$_{+FQ}$	NR
7	NR	28	Female	Positive	XDR	Unclear, relapsed culture
8	NR	32	Female	Positive	MDR-TB$_{+FQ}$	Pulmonary emboli
9	NR	45	Female	Positive	XDR	NR
10	NR	30	Female	Positive	XDR	Neurogenic sepsis
11	NR	59	Male	Negative	XDR	Gastroenteritis
12	NR	NR	Male	NR	NR	Culture reversion
13	NR	NR	Female	Positive	MDR-TB$_{+FQ}$	NR
14	NR	NR	Female	Positive	MDR-TB$_{+FQ}$	NR
15	NR	NR	Male	NR	NR	NR
16	NR	NR	Male	Negative	MDR-TB$_{+FQ}$	NR
17	NR	24	Female	Negative	MDR-TB$_{+FQ}$	Culture reversion
18	NR	24	Male	Negative	MDR-TB$_{+FQ}$	Trauma
19	NR	41	Male	Negative	XDR	NR
20	NR	51	Male	Positive	MDR-TB$_{+FQ}$	NR
21	NR	42	Male	Positive	XDR	NR
22	NR	55	Male	Positive	MDR-TB$_{+FQ}$	NR
23	NR	35	Male	Positive	MDR-TB$_{+FQ}$	NR
24	NR	50	Female	Positive	MDR-TB$_{+FQ}$	NR
25	NR	52	Female	Positive	XDR	NR
26	NR	39	Female	Negative	MDR-TB$_{+INJ}$	NR
27	NR	49	Female	Positive	XDR	NR

*NR=Not reported; **Excerpt of notes from Drug manufacturer report: "A clinically significant abnormality in ECG parameters had been observed the day before: QTcB was 461 ms; QTcF was within normal limits (418 ms).*

Comparative Survival

Comparative data on mortality were analysed from the South African Electronic Drug-Resistant Tuberculosis Register (EDRWeb). The file contained mortality data on 25,177 patients with MDR-TB. Eighty-two (82) of these patients belonged to the BCAP cohort and were excluded from the analysis leaving 25,095. These patients were placed on treatment between 2014 and 2016. An excerpt of the indications for treatment with bedaquiline in the South African National TB Programme are outlined below: [14]

- Patients ≥18 years of age; and
- Laboratory-confirmed RR-TB (at least resistance to RIF) by culture-based phenotypic drug sensitivity testing or genotypic line probe assay or PCR testing (Xpert MTB/RIF) from pulmonary and/or extrapulmonary sites; and
- No history or family history of QT prolongation; and
- Baseline QTcF< 450 msec;

and any one of the following three conditions:

a. Drug resistance in addition to RR-TB: XDR TB; or preXDR TB (resistant to either fluoroquinolone or second line injectable drug); or both inhA and katG mutations;
b. Documented / recorded intolerance to 2nd line anti-TB treatment at baseline (prior to treatment initiation) or during RR-TB treatment, e.g. hearing loss, renal dysfunction

c. History of, or surgical candidate for pneumonectomy or lobectomy

Patients who meet the above criteria, regardless of HIV infection status or concomitant treatment with ARVs can be considered eligible for the 6 months of BDQ treatment.

Characteristics of participants in EDRWEB dataset by treatment group

Table 21 summarises the key differences between the patients who received bedaquiline and those who didn't. Statistically significant differences are indicated with an asterix (*). In brief, patients who received bedaquiline were more likely to be male, to have a history of TB, to be HIV positive and on antiretroviral therapy, and to have more severe resistance profiles. More of the patients on bedaquiline started treatment in 2015, while almost half of those who did not receive bedaquiline started treatment in 2014.

Table 21:Demographic and clinical characteristics of the participants in the EDRWeb database

Variables	Bedaquiline N=1556 (6.2%)	No bedaquiline 23539 (93.8%)	Total 25095 (100.0)
Age: mean (SD)	37.1 (11.5)	36.3 (12.6)	36.38 (12.58)
Gender: n (%)*			
Male	915 (58.8)	10518 (44.7)	11159 (44.5)
Female	641 (41.2)	13021 (55.3)	13936 (55.5)
Site of TB[1]: n (%)			
Pulmonary	1377 (88.5)	20959 (89.0)	22336 (89.0)
Extra pulmonary	20 (1.3)	344 (1.5)	364 (1.5)
History of TB: n (%)*	958 (61.6)	10543 (44.8)	11501 (45.8)
HIV status: n (%)			
Negative	404 (26.0)	6338 (26.9)	6742 (26.9)
Positive	1082 (69.5)	15952 (67.8)	17034 (67.9)
Unknown	70(4.5)	1249 (5.3)	1319 (5.3)
HIV and ART status: n (%)*			
HIV unknown	70 (4.5)	1249(5.3)	1319 (5.3)
HIV negative	404(26.0)	6338 (26.9)	6742 (26.9)
HIV positive	61 (3.9)	2549 (10.8)	2610 (10.4)
HIV positive on ART	1021 (65.6)	13403 (56.9)	14424 (57.5)
Drug resistance pattern: n (%)*			
RR or MDR-TB	919 (59.1)	21955 (93.3)	22874 (91.1)
MDR-TB $_{(FLQ\ or\ INJ)}$	253 (16.3)	776 (3.3)	1029 (4.1)
XDR-TB	384 (24.7)	808 (3.4)	1192 (4.7)
Deaths*	119 (7.6)	4288 (18.2)	4407 (17.6)
Duration on treatment (months): mean (SD)	7.2 (4.4)	9.7 (7.4)	9.6 (7.3)
Year of initiation of treatment: n (%)*			
2014	153 (9.8)	11717 (49.8)	11870 (47.3)
2015	1307 (84.0)	10956 (46.5)	12263 (48.9)
2016	96 (6.2)	866 (3.7)	962 (3.8)

[1]*Missing data: Bedaquiline=159; No bedaquiline=2236; SD=standard deviation; TB=tuberculosis; HIV=human immunodeficiency virus; ART=antiretroviral therapy; MDR=multidrug resistant; XDR=extensively drug resistant; * P<0.05 (Chi-squared test);*

Verification and adjusted analyses

Given the time-dependent nature of the primary outcome of interest (death), a survival analysis using cox regression was conducted using propensity score adjustment for this South African cohort. Propensity scores in the dataset were constructed using the following variables: Gender, age, province, HIV and antiretroviral therapy status, site of TB (pulmonary or extra pulmonary), history of TB, year of treatment initiation, drug resistance pattern, diagnostic method and weeks of exposure to regimen. The propensity scores were divided into quintiles to create comparable groups of patients with similar characteristics other than their exposure to bedaquiline. The first analysis included all the patients in the data set(1a), and subsequent analyses excluded the 82 patients who belonged in the BCAP cohort (1b). We were able to replicate the analyses reported by the South African team at the Guidelines Development Meeting for all the patients and secondly by resistance status (1a, 1e-g). In addition, we investigated the adjusted effect of bedaquiline by history of TB (1c, 1d) and by HIV status (1h-1j). Finally, as an alternative approach, we ran a logistic regression model for mortality, adjusting for the same covariates used in the propensity score adjustment (2a-i). All the results are consistent with a beneficial effect of bedaquiline. The adjusted hazard ratios, adjusted odds ratios, 95% confidence intervals and p-values are summarised in table 22.

Table 22: Summary of cox regression and logistic regression analysis

	Sample (population)	**N (25177)**	**Effect (95% CI)**	**P**
Analysis: 1. Cox regression * (adjusted hazard ratios reported)				
a.	All patients	22072	0.50 (0.41-0.61)	<0.001
b.	Without the BCAP patients (N=82)	21992	0.48 (0.39-0.59)	<0.001
	History of TB treatment			
c.	No history of TB treatment	11817	0.48 (0.34-0.68)	<0.001
d.	History of TB treatment	10175	0.46 (0.36-0.61)	<0.001
	Resistance profile			
e.	MDR patients	19898	0.51 (0.39-0.67)	<0.001
f.	MDR-TB $_{(FLQ\ or\ INJ)}$ patients	958	0.35 (0.20 -0.61)	<0.001
g.	XDR patients	1136	0.21 (0.14- 0.32)	<0.001
	HIV and ART status			
h.	HIV negative patients	6062	0.83 (0.56-1.22)	0.346
i.	HIV positive not on ART	2284	0.24 (0.06-0.96)	0.044
j.	HIV positive on ART	12531	0.86 (0.75-0.97)	0.020
Analysis: 2. Logistic regression (adjusted odds ratios reported)**				
a.	Without the BCAP patients (N=82)	21095	0.39 (0.31 -0.51)	<0.001
	History of TB treatment			
b.	No history of TB treatment	11098	0.42 (0.28-0.62)	<0.001
c.	History of TB treatment	9779	0.38 (0.28-0.53)	<0.001
	Resistance profile			
d.	MDR patients	118846	0.51 (0.37-0.68)	<0.001
e.	MDR-TB $_{(FLQ\ or\ INJ)}$ patients	932	0.49 (0.25-0.97)	0.040
f.	XDR patients	1099	0.34 (0.19-0.58)	<0.001
	HIV and ART status			
g.	HIV negative patients	6062	0.67 (0.43-1.06)	0.090
h.	HIV positive not on ART	2284	0.11 (0.02-0.48)	0.004
i.	HIV positive on ART	12531	0.35 (0.26-0.47)	<0.001

**With propensity score adjustment; **Adjusted for age, gender, HIV status, type of TB, history of TB, type of drug resistance, year of treatment, duration of treatment, province and type of resistance confirmation*

These results are illustrated in figure 8.

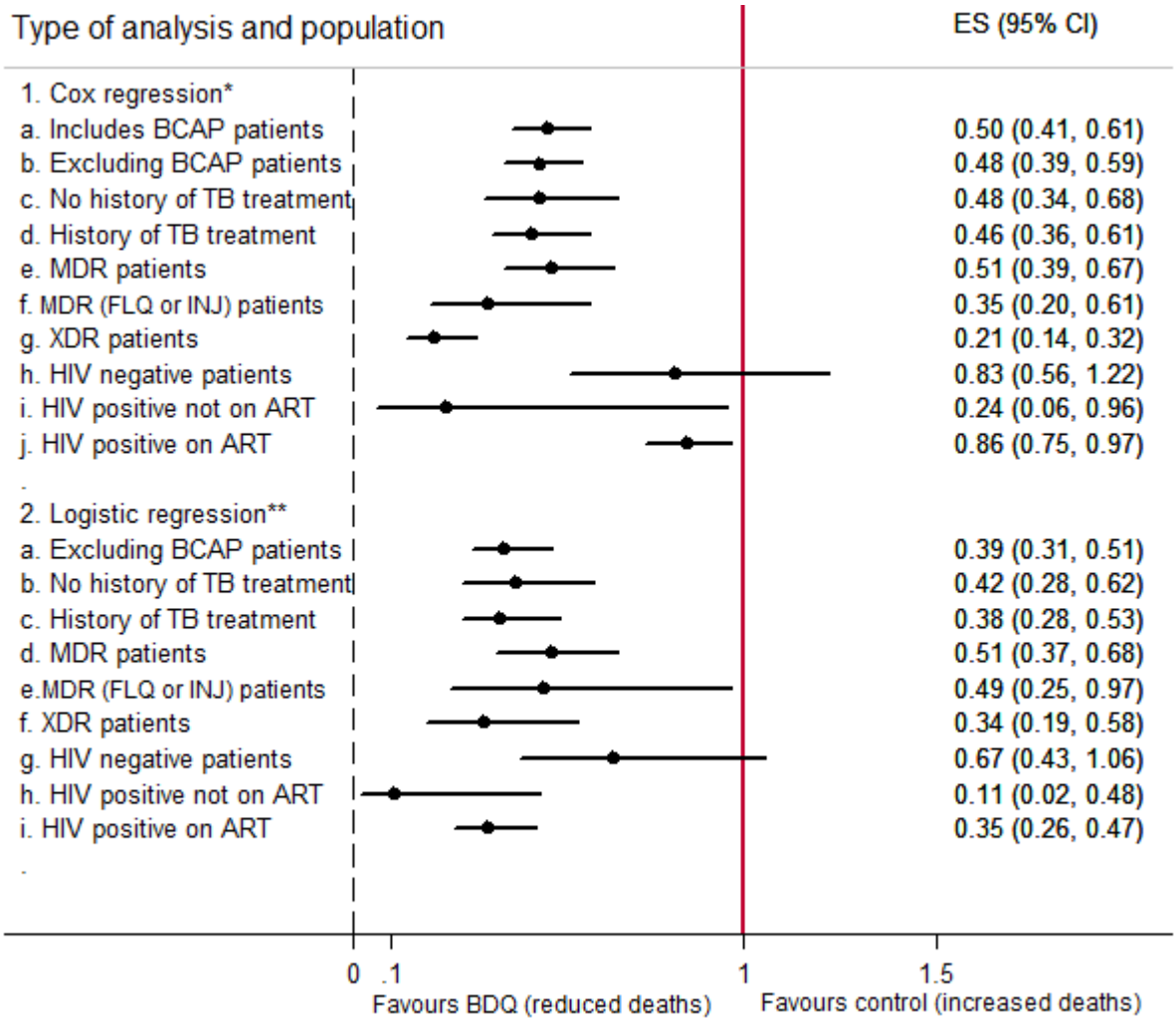

Figure 8: Summary of adjusted Cox and Logistic regression for mortality in patients who received bedaquiline

Adolescents

Data on adolescents aged 12-17 were examined separately. No major differences were found in mortality rates. The dataset included 669 adolescents of which 39 (5.6%) received bedaquiline and 630 (94.4%) did not. There were 47 deaths among those who did not receive bedaquiline and no deaths among those who did.

SUMMARY OF SURVIVAL DATA:

Fifty-six deaths were reported in the five cohorts, of which the majority (50/56; 89%) occurred within 6 and 26 months of treatment, with a two-fold increase in deaths among patients co-infected with HIV. The death rate was higher in the patients with worse resistance profile (MDR-TB$_{+FLQ}$, MDR-TB$_{+INJ}$, and XDR-TB) compared to MDR-TB. When compared to patients who did not receive bedaquiline adjusted analyses indicates a 50-60% reduction in mortality in the large South African cohort. Reductions in mortality were present irrespective of resistance profile groups or history of TB.

Limitations and strengths

Limitations

The two main limitations to this analysis are the quality of the data and the heterogeneity of cohorts. Outcomes, especially adverse events were not reported with the same completeness in all data-sets. Therefore, some studies contributed more information than others. Some outcomes of interest where either not collected or reported with large amounts of missing data. One cohort did not report the type of TB (extra-pulmonary/pulmonary). One cohort did not report on history of TB treatment. Large amounts of resistance profile data were missing. QT prolongation from baseline could not be computed accurately for patients who did not have a baseline measure. The differential follow-up times and dates of follow-up made it impossible to synchronise QTc final and worst measures. One cohort reported almost no data on the circumstances of death.

In addition to the differences in data quality and completeness, the studies were very heterogeneous by nature of geographical location, ethnicity and design. The baseline characteristics also differed across study, with different length of follow-up, treatment with bedaquiline, prevalence of HIV, baseline regimens and ART. These differences often led to statistical heterogeneity and wide confidence intervals.

These findings are also limited by the absence of comparative individual patient data for treatment effectiveness and safety precluding the possibility of estimating relative measures for these outcomes or robust adjusted analyses.

Strengths

The strengths of this analysis lie in the exhaustive search and collection of data; the use of individual patient level data and the application of random effects models to incorporate the heterogeneity in the cohorts. The heterogeneity of these cohorts may imply a broader generalisability of the findings in this analysis.

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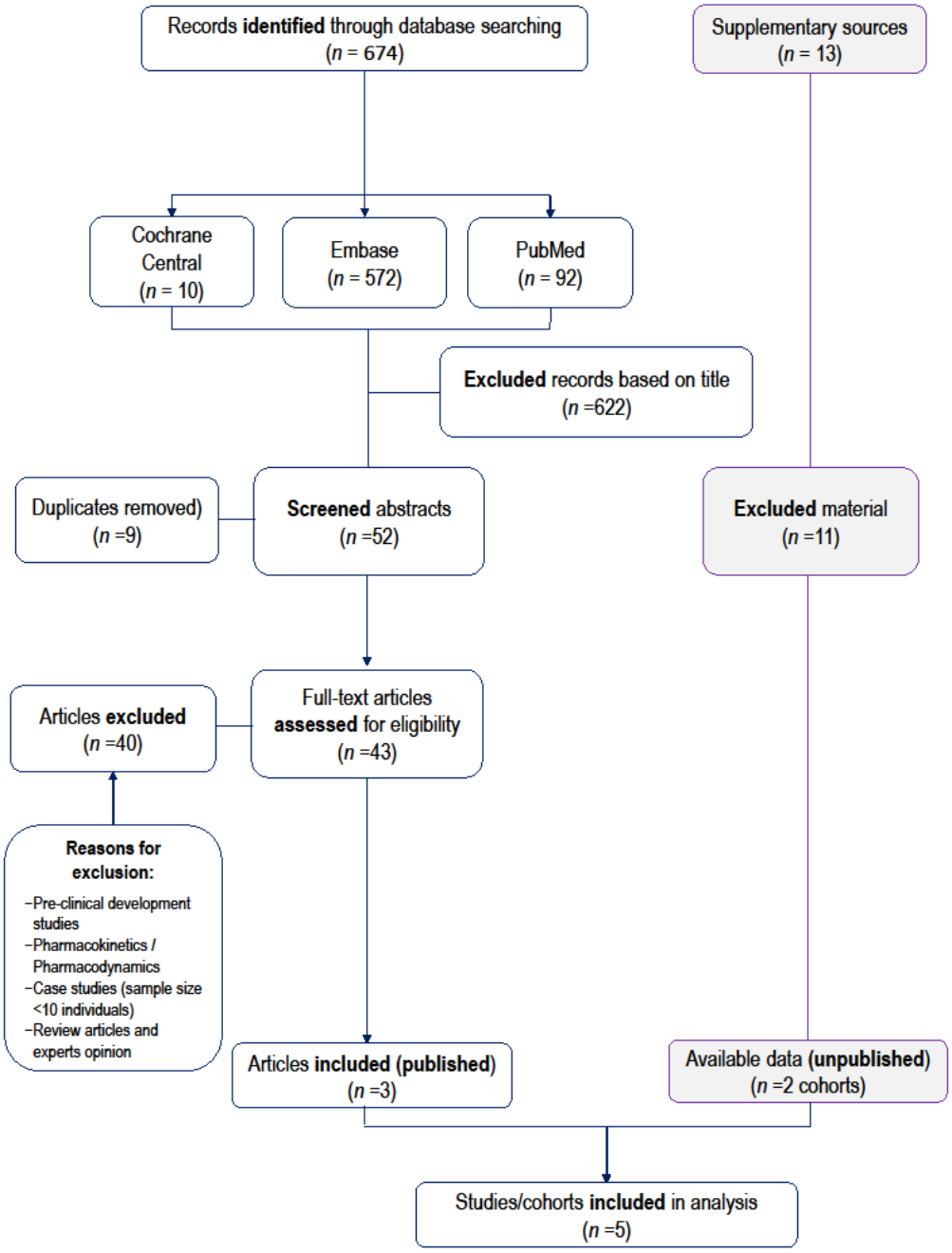
Appendix

Appendix 1: Flow diagram of study screening and selection



Appendix 2: Description of samples used for the various analyses

Analysis	Source	Total	Description
Description of baseline characteristics	South Africa=195 France=45 Drug manufacturer =205 Armenia =62 Georgia=30	537	Total sample with baseline characteristics available
Composition of OBR regimen	South Africa=195 France=45 Drug manufacturer =205 Armenia =60 Georgia=30	535	Data missing from 2 patients from Armenia
Composition of antiretroviral therapy	South Africa=110 France=2 Drug manufacturer =8	120	Data available only for HIV infected patients on antiretroviral therapy
Effectiveness (sputum culture conversion at 6 months)	South Africa =72 France=41 Janssen=205 Armenia =50 Georgia = 23	391	Data on patients who had a culture done at 6 months
Treatment outcomes (cure, death, lost to follow-up, treatment complete, treatment failure)	South Africa =101 France=45 Drug manufacturer = 205	351	Data on cohorts of patients with complete follow up (18 months and more) and available outcome data.
Safety (adverse events)	South Africa=195 France=45 Drug manufacturer =233 Armenia =62 Georgia=30	565	This analysis includes additional data from 28 patients from the drug manufacturer's cohort who received bedaquiline, but where later found to be ineligible or withdrew.
Safety (QT prolongation)	South Africa=141 France=45 Drug manufacturer =233 Armenia =62 Georgia=30	511	Data available only for 141 patients from south Africa who received complete follow-up.
Deaths	South Africa = 27 France =3 Drug manufacturer =16 Armenia=6 Georgia=4	56	

Appendix 3: Distribution of adverse events by system affected for France, South Africa and Drug manufacturer

System	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Gastrointestinal symptoms	219 (16.6)	45 (7.5)	13 (4.1)	277 (12.4)
Metabolisms and nutrition disorders	87 (6.6)	90 (14.9)	46 (14.6)	223 (10.0)
Musculoskeletal and connective tissue disorders, arthralgia	97 (7.4)	62 (10.3)	7 (2.2)	166 (7.4)
Nervous system disorders (dizziness, headache)	94 (7.1)	39 (6.5)	25 (7.9)	158(7.1)
Skin and subcutaneous tissue disorders	87 (6.6)	15 (2.5)	5 (1.6)	107 (4.8)
Respiratory, thoracic and mediastinal disorders	77 (5.9)	29(4.8)	22 (7.0)	128 (5.7)
Ear and labyrinth disorders, Eye	86 (6.5)	29 (4.8)	13 (4.1)	128 (5.7)
Psychiatric disorders	41 (3.1)	22 (3.6)	8 (2.5)	71 (3.2)
Blood and lymphatic system disorders	35 (2.7)	29 (4.8)	21 (6.6)	85 (3.8)
Cardiac disorders (including ECG changes and QT prolongation)	18 (1.4)	13 (2.2)	12 (3.8)	43 (1.9)
Laboratory signs of hepatitis	8 (0.6)	9 (1.5)	12 (3.8)	29 (1.3)
Laboratory signs of pancreatitis	2(0.2)	0 (0.0)	0 (0.0)	2 (0.1)
Renal failure	14 (1.1)	7 (1.2)	4 (1.3)	25 (1.1)
Other**	451 (34.3)	214 (35.5)	128 (40.5)	793 (35.5)
Total	1316 (100.0)	603 (100.0)	316 (100.0)	2235 (100.0)

**Includes only data from SA and Drug manufacturer. France contributed only severity data; **Other includes congenital, familial and genetic, general disorders and admin site conditions, injury, poisoning and procedural complications, investigations, neoplasms and events reported as 'other'.*

Appendix 4: Distribution of serious adverse events by system for France, South Africa and Drug manufacturer

System	Life-threatening N (%)	Fatal N (%)	Total N (%)
Gastrointestinal symptoms	0 (0.0)	0 (0.0)	0 (0.0)
Metabolisms and nutrition disorders	1 (7.1)	0 (0.0)	1 (3.3)
Musculoskeletal and connective tissue disorders, arthralgia	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders (dizziness, headache)	2 (14.3)	1 (8.3)	3 (10.0)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	3 (21.4)	2 (16.7)	5 (16.7)
Ear and labyrinth disorders, Eye	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	1 (7.1)	0 (0.0)	1 (3.3)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorders (including ECG changes and QT prolongation)	2 (14.3)	1 (8.3)	3 (10.0)
Laboratory signs of hepatitis	1 (7.1)	0 (0.0)	1 (3.3)
Laboratory signs of pancreatitis	0 (0.0)	0 (0.0)	(0.0)
Renal failure	1 (7.1)	1 (8.3)	2 (6.7)
Other*	3 (21.4)	7 (58.3)	10 (33.3)
Total	14 (100.0)	12 (100.0)	26 (100.0)

***Other** *includes congenital, familial and genetic, general disorders and admin site conditions, injury, poisoning and procedural complications, investigations, neoplasms, events reported as 'other', and some deaths.*

Appendix 5: Distribution of serious adverse events by system affected for Armenia and Georgia

System	Total n (%)
Gastrointestinal symptoms	1 (4.5)
Metabolisms and nutrition disorders	1 (4.5)
Musculoskeletal and connective tissue disorders, arthralgia	0 (0.0)
Nervous system disorders (dizziness, headache)	1 (4.5)
Skin and subcutaneous tissue disorders	0 (0.0)
Respiratory, thoracic and mediastinal disorders	7 (31.8)
Ear and labyrinth disorders, Eye	0 (0.0)
Psychiatric disorders	1 (4.5)
Blood and lymphatic system disorders	0 (0.0)
Cardiac disorders (including ECG changes and QT prolongation)	5 (22.7)
Laboratory signs of hepatitis	6 (27.3)
Laboratory signs of pancreatitis	0 (0.0)
Renal failure	0(0.0)
Total	22(100.0)