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Effectiveness and safety of bedaquiline-containing regimens in the treatment of multidrug and extensively drug-resistant tuberculosis: a multicentre study.

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Summary (200/200 words)

Large studies on bedaquiline used to treat multidrug-resistant (MDR-) and extensively drug-resistant tuberculosis (XDR-TB) are lacking. The study aim is to evaluate safety and effectiveness of bedaquiline-containing regimens in a large retrospective, observational study conducted in 25 centres and 15 countries in all continents.

428 culture-confirmed MDR-TB cases were analysed (61.5% males; 22.1% HIV-positive, 45.6% XDR-TB). MDR-TB cases were admitted to hospital for 179 days (92-280) and exposed to bedaquiline for 168 days (86-180). Treatment regimens included, among others, linezolid, moxifloxacin, clofazimine and carbapenems (82.0%, 58.4%, 52,6%, 15.3% of cases, respectively).

Sputum smear and culture conversion rates in MDR-TB cases were 63.6 and 30.1% at 30 days, 81.1 and 56.7% at 60 days; 85.5 and 80.5% at 90 days and 88.7% and 91.2%, respectively at the end of treatment. The median (IQR) time to smear and culture conversion was 34 (30-60) and 60 (33-90) days.

Out of 247 culture-confirmed MDR-TB cases completing treatment, 71.3% achieved success (62.4% cured; 8.9% completed treatment), 13.4% died, 7.3% defaulted, 7.7% failed.

Bedaquiline was interrupted due to adverse events in 5.8% of cases. A single case died having electrocardiographic abnormalities probably non-bedaquiline related.

Bedaquiline-containing regimens achieved high conversion and success rates under different non-experimental conditions.

Introduction

A total of 480,000 cases of multidrug-resistant tuberculosis (MDR-TB) and 100,000 of rifampicin-resistant (RR)-TB eligible for MDR-TB treatment were estimated by the World Health Organization (WHO) to have occurred in 2015, with 250,000 deaths [1]. Over half of the estimated MDR-TB cases occurred in India, China, Russian Federation, and the other Former Soviet Union countries, as well as in South Africa [1]. Globally, about 10% of the MDR-TB strains meet the criteria defining XDR-TB (resistance to any fluoroquinolone and at least one second-line injectable drug) [1,2].

Treatment for MDR-/XDR-TB is long, expensive, and characterised by a high rate of adverse events [3-15]. The main difficulty is the identification of at least four active drugs to design an effective regimen [3,5,7,10,11].
The previous stepwise approach based on the hierarchical use of first- and second-line anti-TB drugs classified into five groups has been recently modified by WHO. The new classification includes 4 groups of drugs (A: fluoroquinolones; B: second-line injectable agents; C: other core second-line agents and D: add-on agents, subdivided into the sub-groups D1, D2 and D3) [5].

Two newly available drugs, delamanid, [12-14] and bedaquiline [15-22], together with some re-purposed drugs (linezolid [7,23-26], carbapenems [27-31] and clofazimine [32-34] among others [35,36]) are presently pivotal in ongoing scientific discussions.
The information available today on bedaquiline is still limited to phase 2 studies and small individual cohorts treated under clinical trials conditions, the largest study not exceeding 233 patients [15-21,37].
In particular, at this present time, no study of size informs us on the effectiveness, safety, and tolerability of bedaquiline, in different continents and programmatic conditions.

Given the concerns around the adverse events of bedaquiline (particularly QT-prolongation, potentially at highest risk when added to fluoroquinolones – moxifloxacin, levofloxacin, oflofloxacin, clofazimine, delamanid and methadone amongst others), additional evidence on its safety, apart from that provided by the registration trials, is urgently needed [38-40].

Recently, TB reference centres belonging to the International Bedaquiline Study Group (IBSG, a network merging the centres belonging to the International Carbapenems Study Group-ICSG [29-

31] and the ERS/ALAT (European Respiratory Society/ Asociación Latinoamericana de Tórax) and Brazilian Society collaborative projects [41,42] coordinated by the ERS TB Collaborating Centre) conducted an observational study on the therapeutic contribution of bedaquiline within a background regimen (as per WHO guidelines) when treating MDR- and XDR-TB cases.

The aim of the present study is to evaluate the safety, tolerability and effectiveness of bedaquiline within background regimens in a large multi-centre cohort of MDR- and XDR-TB patients treated under different conditions (programmatic, expanded access, but not recruited for experimental studies).

Material and Methods

The methodological approach adopted for this study is similar to that described in previous ICSG studies [29-31]. Twenty-five MDR-TB reference centres located in 15 countries in Africa, Asia, Western and Eastern Europe, Oceania and Southern America (Argentina, Australia/Victoria State, Belarus, Belgium, Greece, India, Italy, Netherlands, Peru, Portugal, Russian Federation/Arkhangelsk and Moscow Oblasts, South Africa, Spain, Sweden, and United Kingdom) retrospectively collected data on RR- and culture-confirmed MDR-TB patients aged ≥15 years (Figure 1 and Electronic Annex 1).

An MDR-TB case was defined as an individual with TB disease caused by *M. tuberculosis* strains phenotypically resistant to at least isoniazid and rifampicin. RR-TB cases were those diagnosed through Xpert MTB/RIF® (Cepheid, Sunnyvale USA) complemented by line probe assays. XDR-TB cases were those whose disease was due to MDR *M. tuberculosis* strains with additional resistance to any fluoroquinolone and one of the second-line injectable drugs (i.e., amikacin, capreomycin, and kanamycin) [1,5].

Patients starting their treatment between January 1st 2008 and August 30th 2016 were consecutively enrolled based on their exposure to bedaquiline during the intensive and the continuation phase.

An individualised TB regimen was administered following the results of the drug susceptibility test (DST) carried out by externally quality-assured laboratories [29-31]. RR cases were managed according to the national guidelines in force in their respective countries (e.g. South Africa) [43]. Physicians were free to prescribe the accompanying anti-TB treatment to obtain the best possible regimen in their setting and, consequently, no specific protocol or method beyond local guidelines was followed.

Bedaquiline was administered at the recommended dose of 400 mg once a day for 14 days, then, 200 mg three times a week for 22 weeks. It was prescribed under programmatic conditions, expanded access and compassionate use, but not under experimental protocols of clinical trials. Adverse events were attributed to bedaquiline or to another particular drug by local attending physicians and local teams (with support of a local TB Consilium, where available), without any standardised protocols or documented level of ascertainment of the causal association. A standardized classification for the severity of the adverse events was not used.

A standardized ad-hoc e-form was used to collect epidemiological (i.e., age, place of birth and residence, gender, migrant status from a TB high-incidence country), clinical (i.e., cardiac and thyroid disorders, HIV-testing, HIV-infection status, administration of HIV drugs, previous TB diagnosis and treatment, previous treatment outcomes, radiological findings, TB therapy and related adverse events, duration of exposure to bedaquiline, delamanid, linezolid, carbapenems, adjuvant surgery, sputum smear and culture positivity at baseline, and during treatment at 30, 60, and 90 days, time to sputum smear and culture conversion, WHO treatment outcomes, duration of hospital stay), and microbiological (i.e., DST results) data from medical records.

As the latest WHO outcome definitions were introduced in 2013 and our first cohort was treated in 2008, we kept the outcome 'default' instead of 'lost to follow-up' [5].

With regard to the analysis of treatment outcomes, a sub-analysis of MDR-TB patients who started their treatment before December 31st, 2014 was performed in order to include those who could fit the definition of treatment completion and cure according to the WHO Guidelines on MDR-TB treatment [5].

A homogeneous and standardized approach to DST was not possible in all the clinical centres. The percentages reported for resistance have been calculated according to the number of cases tested for (denominator) and the number of cases resistant to (numerator) a specific drug.

The ethical approval for the retrospective collection of clinical data was obtained by the coordinating centre. The centres involved in the study requested the authorization for the treatment of their patients according to national legislation in force and, accordingly, a consent form was signed by the patient and the attending physician.

The map in Figure 1 was created using the 'worldmap' package working in R [44].

Qualitative and quantitative variables were summarised with percentages and medians (interquartile ranges –IQR). Chi-square or Fisher exact and Mann-Whitney tests were used to statistically compare qualitative and quantitative variables, respectively.

A p-value of less than 0.05 was considered statistically significant. Statistical computations were performed with Stata 13.0 (StataCorp, College Station, TX).

Results

Patients' characteristics

Demographic, epidemiological and clinical characteristics of the patients are summarised in Table 1 and Figure 1, safety and tolerability information on bedaquiline-containing regimens in Table 2, and treatment outcome results in Tables 3 (Panel A and B) and 4 (Panel A and B) .

A total of 428 culture-confirmed MDR-TB patients were recruited (Figure 1 and Electronic Annex 1).

Male (263, 61.5%) was the most prevalent gender in the cohort and the median (IQR) age was 35 (27-44) years.

The characteristics of the 428 culture-confirmed MDR-TB patients are summarised in Table 1. Migrants from high to low TB incidence countries were 45 (10.5%).

The proportion of HIV co-infected patients was 22.1%; their median (IQR) CD4 cell count was 269/mmc (168-470) and the majority (92, 97.9%) received antiretroviral therapy. The HIV co-infection prevalence in Africa, Eastern Europe and remaining settings together was 88/190 (46.3%), 0/150 (0%) and 6/85 (7.1%), respectively.

Pulmonary TB was diagnosed in 426 out of 428 (99.5%) cases, the extra-pulmonary locations being abdominal and the nervous system (2). The percentages of sputum smear and culture positive cases were 72.1% and 98.4%, respectively.

Less than half were affected by XDR-TB (195/428, 45.6%), with a median (IQR) number of drug resistances of 3 (1-5). Overall, 334/428 (78.0%) cases were previously treated for TB.

The prevalence of drug resistance was as follows: streptomycin 185 (94.4%), pyrazinamide 145 (70.4%), fluoroquinolones 267 (64.5%), amikacin 131 (44.4%), capreomycin 127 (41.6%), kanamycin 179 (59.3%), ethionamide 135 (59.7%), para-aminosalicylic acid 70 (35.7%), linezolid 4 (10.5%), ethambutol 186 (77.5%), and cycloserine 20 (12.3%).

Treatment regimens included linezolid (82.0%), clofazimine (52.6%), moxifloxacin (58.4%), second-line injectables (45.8%), carbapenems (15.3%), and ofloxacin (1.6%).

The median (IQR) range of the administrative delay in procuring bedaquiline was 8 (0-60) days.

Patients were exposed to bedaquiline for a median (IQR) of 168 (86-180) days (Table 2). Five (1.2%) patients underwent treatment with both delamanid and bedaquiline. Adjuvant surgical therapy was performed in 55 (13%) cases.

The median (IQR range) treatment duration in the cohort was 18 (10-22) months.

Adverse events

The majority of the adverse events reported were nausea, peripheral neuropathy, and otovestibular toxicity. Adverse events potentially attributed to bedaquiline were reported in 80 of 413 (19.4%) cases where this information was provided (Table 2).

In particular, 51 of 428 (11.9%) patients discontinued bedaquiline (25 or 5.8% reporting adverse events), of these 26 (51%) did so permanently.

Although we do not have the exact information on how many cases interrupted bedaquiline due to QTcF (QT interval in the electrocardiogram corrected according to Fredericia formula) increase, 24 of 247 (9.7%) experienced QTcF prolongation >500msec.

One patient was started on bedaquiline with a baseline QTcF of 553 msec, which then decreased to 536 at week 4 and 554 at week 8. A second patient, with a baseline QTcF of 352 msec, had a transient increase (510 at week 3) and then a decline (358 at week 4); she was palliated at home as per her request. She had had no arrhythmias at any point and no evidence to suggest that her death was related to a cardiovascular event. She achieved sputum conversion (smear and culture) prior to her death.

Figure 2 summarises the median values of the QTcF interval (QT interval in the electrocardiogram corrected according to Fredericia formula) and its temporal trends in the cohort over the first twelve weeks of treatment.

The median (IQR) exposure to bedaquiline amongst the 26 patients who permanently interrupted was 69 (27.5-135) days, and 85.5 (44.3-160) days in those 33 patients who died.

Out of 33 who died, we have QT information on 19 (57.6%) and only one patient had a baseline QT >500 msec. During the follow-up none of those with a normal QT at baseline showed an increase >500 msec.

According to the information available, a single case out of 33 who died had electrocardiogram (ECG) abnormalities. During bedaquiline treatment the patient had a single QTcF measurement above 450, but below 500 msec. Two days before death this patient reported to the primary health centre complaining of weakness. The coordinating centre suggested drawing blood for electrolyte analysis; which revealed hypokalemia. Thus, the patient was transferred to the district hospital where ECG showed premature ventricular complex (PVC) bigeminy and then irreversible cardiac arrest. He died after 131 days of treatment with bedaquiline. The final ECG showed QTcF <450

msec. Thus, the revision of clinical and ECG history of the patient makes relationship between bedaquiline use and fatal arrhythmia unlikely.

Furthermore, 104 out of 348 (29.9%) cases treated with linezolid reported adverse events attributed to this drug by the attending physician; 16/58 (27.6%) of them (for whom final treatment outcome was available) permanently discontinued linezolid.

Sputum conversion and treatment outcomes

Sputum smear and culture conversion rates were 63.6% and 30.1% at 30 days; 81.1% and 56.7% at 60 days; 85.5% and 80.5% at 90 days, and 88.7% and 91.2%, at the end of the MDR-TB treatment (for those completing it) respectively. The median (IQR) time to sputum smear and culture conversion was 34 (30-60) and 60 (33-90) days (Figure 3).

Out of 247 culture-confirmed MDR-TB cases completing treatment, 71.3% achieved success (62.4% cured and 8.9% completed treatment), 13.4% died, 7.3% defaulted, and 7.7% failed (Table 3, Panel A). The treatment outcomes of the 130 patients initiating their treatment before December 31st, 2014 are reported in Table 3, Panel B.

Sputum smear and culture conversion rates at the end of treatment were not significantly different among XDR- and MDR-TB cases (p=0.73 and 0.96, respectively).

The treatment success rates for MDR- and XDR-TB patients were higher in Eastern Europe and in settings other than in Africa (Table 4, Panel A). Table 3, Panel B summarises the treatment outcome by cohort.

Discussion

The aim of the present study was to retrospectively evaluate the effectiveness, safety and tolerability of bedaquiline-containing regimens in a large observational cohort of MDR- and XDR-TB patients treated under different conditions (programmatic, expanded access, but not recruited for experimental studies).

This is, to our knowledge, the largest study describing how safe, well tolerated and effective bedaquiline is within background regimens and the first one in the scientific literature reporting on the non-clinical trial use of bedaquiline for the treatment of M/XDR-TB patients in 5 continents.

In comparison with Menzies' data on Individual Patient Data analysis (where there was a 43% success in XDR), in our bedaquiline treated XDR-TB cohort the success rate was 71.3% [3].

In a phase 2 double blind, randomised control trial study by Diacon et al. [16] the median time to culture conversion in 79 bedaquiline-treated MDR-TB patients was 83 days; this compares with our median time of 60 days. In the study by Diacon et al. the culture conversion at the end of 24 weeks was 79% and at 120 weeks was 58% VS. 91.7% at the end of therapy in our study, and the cure rates 58% and 62.4%, respectively [16]. Regarding effectiveness, although difficult to attribute to bedaquiline given the causality of the results observed, we can report that bedaquiline-containing regimens achieved culture conversion rates exceeding 90% at the end of treatment and treatment success >70% (76.7% when only calculating patients who started their treatment before December 31st, 2014), higher than those observed in other MDR-TB cohorts [3,15,17].

Pym et al. conducted a phase 2 trial to assess safety and efficacy of bedaquiline in 233 patients, culture conversion was seen in 72.2% at 120 weeks, 8.6% of patients discontinued treatment and 6.9% of patients died [15].

Regarding safety, in Diacon's study [16] 13% of patients in the bedaquiline group died (10 of 79 VS. 2 of 81 in the placebo group) versus a very similar 33 (13.4%) out of the 247 who had an evaluable outcome in our cohort.

The most frequent adverse events in our study were nausea (31.5%), otovestibular toxicity (23.3%), peripheral neuropathy (23.3%), vomiting (21.2%) and arthralgia (20.4%), their frequencies being slightly lower than those described during Diacon et al.'s licensing study with 41% nausea, 29% vomiting and 37% arthralgia [17]. Importantly, in Diacon's study the proportion of the adverse events were similar in the group VS. placebo patients, suggesting they were probably due to the background regimen. In this context, other second-line drugs like fluoroquinolones or clofazimine might contribute to cardiologic or other adverse events [10,11,32] and invite caution and ECG monitoring.

The results of our study demonstrate that, overall, bedaquiline-containing regimens achieve a relatively higher proportion of treatment success with a relatively lower proportion of adverse events within different settings than previously described, although a standardized approach for the notification of the adverse events was not implemented across the different settings (risk of under-reporting).

Of note, culture conversion rates were higher than those reported in cohorts with an analogous degree of disease severity; with time to sputum smear and culture conversion identical or earlier to those observed in comparable cohorts; the proportion of treatment success was higher, and the percentage of adverse outcomes (death, failure) lower than those seen in available study cohorts

with the matching disease severity; adverse events due to bedaquiline requiring interruption of the drug were relatively uncommon (5.8%) [10,11].

Our study confirms that bedaquiline-containing regimens are effective, as demonstrated by the fact that a sizeable number of patients were treated with salvage regimens due to previous treatment failure, unfavourable resistance profile, toxicity, or all three.

The larger group of patients in different non-clinical trial conditions around the globe reinforces previous findings that bedaquiline is well tolerated and adverse events might be less common than previously thought.

Enthusiasm over bedaquiline and delamanid has been curtailed following concerns of potential cardiotoxicity. Both new drugs are associated with QT prolongation, which may potentially lead to arrhythmia and sudden death, a major reason why their drug combination has not been recommended. Moreover, the new drugs are likely to be associated with a fluoroquinolone and clofazimine, both known to prolong QT intervals. The specific role of the many drugs with QT prolonging potential (and their summation or synergistic effect) still needs to be fully understood.

QT prolongation occurred in 9.7% of patients. However, interruption of bedaquiline due to adverse events occurred in 25 (5.8%) patients.

Although information on QT is available in 64% of cases, and the timing of their assessment not standardised, it seems the majority of cases died for non heart-related reasons. A more accurate assessment of the adverse events (from data collection to detailed clinical investigation) will allow for evaluation of the relationship between death and QT prolongation. Unfortunately, our data is not standardised and, therefore, heterogeneous.

Close monitoring of drug safety should be implemented widely, particularly for rare adverse events. A comprehensive, population-level pharmacological surveillance in the post-marketing phase might allow a better assessment of the safety and tolerability profile of bedaquiline, alone or in combination with other potentially cardiotoxic anti-TB drugs [45].

The importance of implementing active tuberculosis drug-safety monitoring and management (aDSM) when bedaquiline is used programmatically cannot be over emphasised [45].

We underline the importance of using, in future studies, a standardised ECG monitoring protocol allowing to exclude inter- and intra-day variability in QTc measurements. For study purposes, 24 hour Holter monitoring is probably the best strategy to assess the true impact of drugs on QTc. This is clearly not feasible under programmatic conditions.

The strengths of the study are the large sized cohort, the inclusion of cases from several countries (ranging from 7.7% of all patients receiving bedaquiline in the United Kingdom to 100% of bedaquiline-treated patients in Argentina, Australia/Victoria State, Greece, Peru, Russian

Federation/Arkhangelsk Oblast and Spain), and the detailed information collected from the participating centres. The large sample size allows, for the first time, to compare treatment outcomes from different settings.

Some variables, like the drug-resistance patterns, the number of previous anti-TB treatment cycles and the HIV seroprevalence varied among the settings participating in the study.

The observational and retrospective design of the study however has inbuilt limitations (recent guideline changes, different resource settings, different standards of care, dataset differences) so that the research findings need to be confirmed by larger randomised controlled clinical trials and well-designed observational prospective studies.

Furthermore, several sources of bias may confound the reliability of the findings: missing random selectivity of the patients, heterogeneity between recruited geographic settings, different levels of completeness of collected data (especially adverse events and their severity), non-standardised DST methods for several drugs, background regimen variability between countries which differed over time (mainly later generation fluoroquinolones), different TB/HIV co-infection prevalence and availability of anti-retroviral drugs.

The effectiveness of bedaquiline might be over-estimated owing to the additive and/or synergistic role played by other effective drugs (e.g., carbapenems, linezolid, etc.) [7,23-25,27-31]. New experimental studies should be implemented to really assess the critical effect of bedaquiline, as well as delamanid, in new combination therapies.

The different operating procedures adopted in various settings, as well as the heterogeneous drug resistance patterns, may underestimate the real benefits of the bedaquiline-containing regimens. However, stratified analyses allowed us to better assess the heterogeneity related to time and geographical factors. The new information provided by this observational study allows clinicians managing difficult-to-treat TB cases in programmatic conditions to better understand how to use bedaquiline in case the minimum number of active drugs necessary to design an effective regimen is lacking [1,5,11].

Although new compounds will soon become available to support the move towards TB Elimination [46], bedaquiline confirms its ‘core drug’ characteristics to manage MDR- and XDR-TB cases even in field conditions, and eventually to be used in newly designed anti-TB regimens of the future. Whilst it is crucial to recommend the use of bedaquiline in difficult-to-treat cases, WHO guidelines should be followed assiduously so as to reduce the emergence and spread of bedaquiline-resistant *Mycobacterium tuberculosis* strains.

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Table 1. Demographic, epidemiological, and clinical characteristics of 428 culture-confirmed multidrug-resistant tuberculosis patients exposed to bedaquiline-containing regimens.

Variables		
Median (IQR) age		35 (27-44)
Male, n (%)		263/428 (61.5)
Median (IQR) body weight at admission, kg		56 (47-65)
Median (IQR) height, cm		169 (160-176)
Migrant, n (%)		45/428 (10.5)
Employed, n (%)		110/413 (26.6)
Prisoner, n (%)		23/413 (5.6)
Pregnant, n (%)		1/133 (0.8)
Thyroid disease, n (%)		12/413 (2.9)
Heart disease, n (%)		40/318 (12.6)
Pre-existing ECG abnormality, n (%)		13/318 (4.1)
Alcoholism, n (%)		132/363 (36.4)
Drug abuse, n (%)		75/413 (18.2)
Methadone use, n (%)		0/318 (0.0)
Diabetes, n (%)		26/413 (6.3)
HIV infection testing, n (%)		425/428 (99.3)
HIV-positive, n (%)		94/425 (22.1)
Median (IQR) CD4 count at baseline, mmc		269 (168-470)
Median (IQR) nadir CD4+ cell counts, mmc		222 (160-402)
Anti-retroviral therapy exposure, n (%)		92/94 (97.9)
Prior anti-TB therapy, n (%)		334/428 (78.0)
Median (IQR) n times treated >1 month		2 (1-2)
Prior TB treatment outcome, n (%)	*Success*	68/263 (25.9)
	Cured	41/263 (15.6)
	Completed	27/263 (10.3)
	Defaulted	35/263 (13.3)
	Transferred out	20/263 (7.6)
	Failed	140/263 (53.2)
Pulmonary surgery, n (%)		55/423 (13.0)
Previous MDR-TB, n (%)		169/317 (53.3)
Pulmonary involvement, n (%)		426/428 (99.5)
Extra-pulmonary involvement, n (%)		11/428 (2.6)
Radiology involvement, n (%)	*Cavitary lesion*	81/331 (24.5)
	Bilateral pulmonary involvement with cavitary lesions	147/331 (44.4)
	Bilateral pulmonary involvement	56/331 (16.9)
	Noncavitary nonbilateral pulmonary	47/331 (14.2)
Sputum-smear positive, n (%)		305/423 (72.1)
Sputum culture positive, n (%)		421/428 (98.4)
Resistance to streptomycin, n (%)		185/196 (94.4)

Resistance to ethambutol, n (%)	186/240 (77.5)
Resistance to pyrazinamide, n (%)	145/206 (70.4)
Resistance to fluoroquinolones, n (%)	267/414 (64.5)
Resistance to amikacin, n (%)	131/295 (44.4)
Resistance to capreomycin, n (%)	127/305 (41.6)
Resistance to kanamycin, n (%)	179/302 (59.3)
Resistance to ethionamide, n (%)	135/226 (59.7)
Resistance to cycloserine, n (%)	20/163 (12.3)
Resistance to para-aminosalicylic acid, n (%)	70/196 (35.7)
Resistance to linezolid, n (%)	4/38 (10.5)
Resistance to rifabutin, n (%)	32/35 (91.4)
XDR-TB, n (%)	195/428 (45.6)
MDR/XDR-TB contacts, n (%)	105/411 (25.6)
Median (IQR) hospital stay	179 (92-280)

IQR: interquartile range; XDR-TB: extensively drug-resistant tuberculosis; MDR: multidrug-resistant

Table 2. Safety and tolerability profile of bedaquiline-containing regimens in a cohort of 428 culture-confirmed MDR-TB patients.

Interruption of bedaquiline, n (%)	51/428 (11.9)
Interruption of bedaquiline due to adverse events, n (%)	25/428 (5.8)
Adverse events presumably due to bedaquiline, n (%)	80/213 (19.4)
Bedaquiline restarted if interrupted, n (%)	25/69 (36,2)
Median (IQR) total bedaquiline exposure, days	168 (86-180)
Creatinine >1.4x ULN, n (%)	91/411 (22.1)
Lipase >1.6x ULN, n (%)	1/239 (0.4)
ALT >3x ULN, n (%)	92/413 (22.3)
Bilirubin >2x ULN, n (%)	47/413 (11.4)
Median (IQR) albumin, gr/dl	36 (30-40)
Potassium <3.4 or >5.6 mmol/L, n (%)	98/412 (23.8)
Magnesium <0.59 mmol/L, n (%)	21/199 (10.6)
Calcium <1.75 mmol/L, n (%)	23/302 (7.6)
Nausea, n (%)	130/413 (31.5)
Neuropathy peripheral, n (%)	96/412 (23.3)
Oto-vestibular toxicity, n (%)	96/412 (23.3)
Vomiting, n (%)	87/411 (21.2)
Anaemia, n (%)	86/412 (20.9)
Arthralgia, n (%)	84/412 (20.4)
Skin rash, n (%)	63/412 (15.3)
Diarrhoea, n (%)	56/412 (13.6)
Renal failure, n (%)	47/413 (11.4)
Thrombocytopenia, n (%)	41/413 (9.9)
Neutropenia, n (%)	40/413 (9.7)
Lymphocytopenia, n (%)	40/413 (9.7)
QT prolongation, n (%)	24/248 (9.7)
Hypothyroidism, n (%)	38/410 (9.3)
Psychiatric disorder, n (%)	29/413 (7.0)
Tendinopathy, n (%)	18/413 (4.4)
Optic neuropathy, n (%)	10/413 (2.4)
Deep vein thrombosis, n (%)	7/412 (1.7)
Pancreatitis, n (%)	4/318 (1.3)
Hallucinations, n (%)	2/411 (0.5)
Stroke, n (%)	1/318 (0.3)

Table 3. Treatment outcome and conversion rates of 428 culture-confirmed multidrug-resistant tuberculosis patients exposed to bedaquiline-containing regimens (Panel A) and treatment outcomes of 130 MDR-TB patients starting their treatment with bedaquiline-containing regimens before December 31st, 2014 (Panel B).

Panel A

Variables		
Sputum smear conversion 30 days, n (%)		206/324 (63.6)
Sputum culture conversion 30 days, n (%)		117/389 (30.1)
Sputum smear conversion 60 days, n (%)		257/317 (81.1)
Sputum culture conversion 60 days, n (%)		213/376 (56.7)
Sputum smear conversion 90 days, n (%)		265/310 (85.5)
Sputum culture conversion 90 days, n (%)		298/370 (80.5)
Sputum smear conversion at the end of treatment, n (%)		126/140 (90.0)
Sputum culture conversion at the end of treatment, n (%)		191/208 (91.8)
Median (IQR) time to sputum smear conversion, days		34 (30-60)
Median (IQR) time to sputum culture conversion, days		60 (33-90)
Treatment outcome, n (%)	*Success*	176/247 (71.3)
	Cured	154/247 (62.4)
	Completed	22/247 (8.9)
	Died	33/247 (13.4)
	Defaulted	18/247 (7.3)
	Failure	19/247 (7.7)
	Transferred out	1/247 (0.4)
Median (IQR) months of treatment after MDR-TB diagnosis		18 (10-22)
Mean (SD) body weight at the end of treatment, kg		61.9 (13.9)

IQR: interquartile range; MDR-TB: multidrug-resistant tuberculosis; SD: standard deviation

Panel B

Treatment outcome	
Treatment success, n (%)	100/130 (76.9)
Cured, n (%)	86/130 (66.2)
Completed, n (%)	14/130 (10.8)
Died, n (%)	8/130 (6.2)
Defaulted, n (%)	6/130 (4.6)
Failed, n (%)	16/130 (12.3)

Table 4. Treatment outcomes of 428 culture-confirmed MDR- and XDR-TB patients exposed to bedaquiline-containing regimens in different settings (Panel A) and stratified by cohort (Panel B).

Panel A

Treatment outcome	Africa	Eastern Europe	Other settings
Total cohort	**(n=113)**	**(n=85)**	**(n=49)**
Treatment success	73 (64.6)	65 (76.5)	38 (77.6)
Cured	73 (64.6)	54 (63.5)	27 (55.1)
Completed	-	11 (12.9)	11 (22.5)
Died	27 (23.9)	3 (3.5)	3 (6.1)
Defaulted	9 (8.0)	8 (9.4)	1 (2.0)
Failure	3 (2.7)	9 (10.6)	7 (14.3)
Transferred out	1 (0.9)	-	-
MDR-TB	**(n=62)**	**(n=39)**	**(n=27)**
Treatment success	36 (58.1)	28 (71.8)	22 (81.5)
Cured	36 (58.1)	20 (51.3)	11 (40.7)
Completed	-	8 (20.5)	11 (40.7)
Died	17 (27.4)	3 (7.7)	1 (3.7)
Defaulted	7 (11.3)	3 (7.7)	1 (3.7)
Failure	1 (1.6)	5 (12.8)	3 (11.1)
Transferred out	1 (1.6)	-	-
XDR-TB	**(n=51)**	**(n=46)**	**(n=22)**
Treatment success	37 (72.6)	37 (80.4)	16 (72.7)
Cured	37 (72.6)	34 (73.9)	16 (72.7)
Completed	-	3 (6.5)	-
Died	10 (19.6)	-	2 (9.1)
Defaulted	2 (3.9)	5 (10.9)	-
Failure	2 (3.9)	4 (8.7)	4 (18.2)
Transferred out	-	-	-

MDR-TB: multidrug-resistant tuberculosis; XDR-TB: extensively drug-resistant tuberculosis

Panel B

Treatment outcome	2008-09	2010-11	2012-14
Treatment success, n (%)	-	5/9 (55.6)	89/116 (76.7)
Cured, n (%)	-	5/9 (55.6)	77/116 (66.4)
Completed, n (%)	-	0/9 (0.0)	12/116 (10.3)
Died, n (%)	-	2/9 (22.2)	7/116 (6.0)
Defaulted, n (%)	-	2/9 (22.2)	4/116 (3.5)
Failed, n (%)	-	0/9 (0.0)	16/116 (13.8)

Figure 1. Global distribution of MDR-/XDR-TB cases treated with regimens containing bedaquiline, 2009-2016 (N=428 cases in 25 study sites, see Electronic Annex 1 for details).

Figure 2. Median values of the QTcF interval and its temporal trends in the cohort in the initial 12 weeks of treatment

Median values

	Baseline	Week 4	Week 8	Week 12
Median (IQR) QTcF, msec	401.5 (372.0-437.0)	424.0 (395.0-456.0)	430.0 (401.0-450.0)	425.5 (389.0-449.0)

Temporal trends

Legend
The coloured dots indicate outlier patients
IQR: interquartile range; QTcF: QT interval in the electrocardiogram corrected according to Fredericia formula
Few patients underwent electrocardiogram after week 12.

Figure 3. Sputum smear and culture conversion rates of 428 culture-confirmed multidrug-resistant tuberculosis patients exposed to bedaquiline-containing regimens.

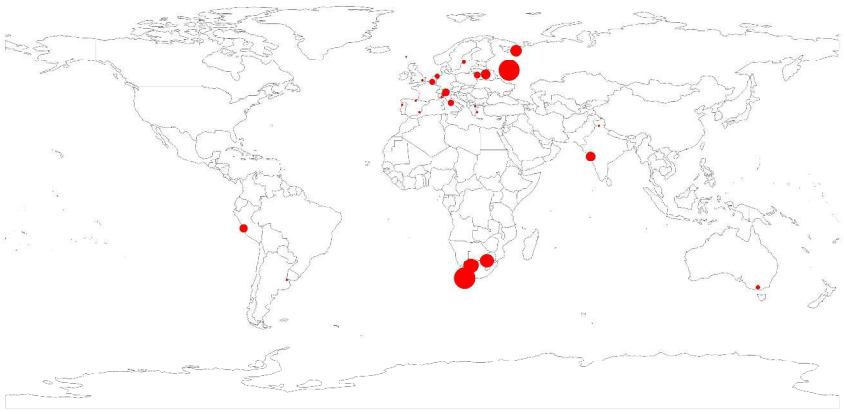

Figure 1. Global distribution of MDR-/XDR-TB cases treated with regimens containing bedaquiline, 2009-2016 (N=428 cases in 25 study sites, see Electronic Annex 1 for details).
Figure 1
1763x881mm (72 x 72 DPI)

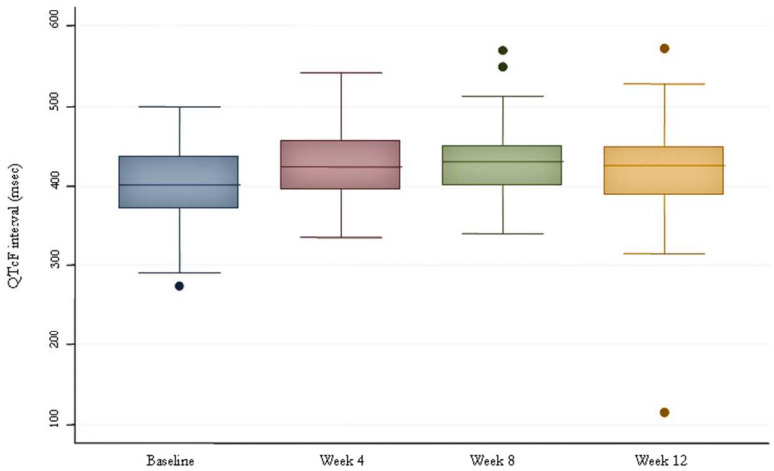

Figure 2. Median values of the QTcF interval and its temporal trends in the cohort in the initial 12 weeks of treatment

The coloured dots indicate outlier patients
IQR: interquartile range; QTcF: QT interval in the electrocardiogram corrected according to Fredericia formula
Few patients underwent electrocardiogram after week 12.

Figure 2
101x76mm (240 x 240 DPI)

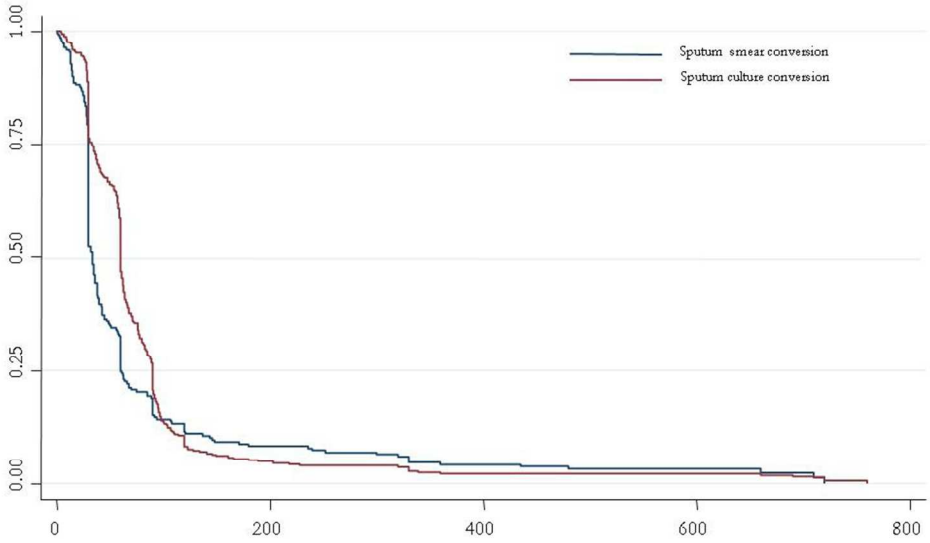

Figure 3. Sputum smear and culture conversion rates of 428 culture-confirmed multidrug-resistant tuberculosis patients exposed to bedaquiline-containing regimens.
Figure 3
174x127mm (150 x 150 DPI)

Electronic Annex 1. Proportion of cases treated with bedaquiline per country/state during the study period out of 428 confirmed MDR-/XDR TB cases.

Country	Number of sites	Cases included in the present study, *n (% of the total cases;* n=428)	Proportion of cases treated with BDQ during the study period out of the total cases in the same Country/State (%)	MDR-TB, *n(%)* (n=233)	XDR-TB *n (%)* (n=195)	Known outcome *n (%)* (n=247)
Argentina	1	1 (0.2)	100%	-	1 (0.5)	1 (0.4)
Australia (State of Victoria)	1	4 (0.9)	100%	2 (0.9)	2 (1.0)	1 (0.4)
Belarus	2	30 (7.0)	16.1%	9 (3.9)	21 (10.8)	-
Belgium	1	7 (1.6)	53.8%	6 (2.6)	1 (0.5)	2 (0.8)
Greece	2	2 (0.5)	100%	-	2 (1.0)	2 (0.8)
India	2	21 (4.9)	40.4%	8 (3.4)	13 (6.7)	17 (6.9)
Italy	4	26 (6.1)	66.7%	17 (7.3)	9 (4.6)	9 (3.6)
Netherlands	1	5 (1.2)	71.4%	3 (1.3)	2 (1.0)	3 (1.2)
Peru	1	15 (3.5)	100%	15 (6.4)	-	10 (4.1)
Portugal	1	1 (0.2)	50%	-	1 (0.5)	1 (0.4)
Russian Federation	2	120 (28.0) of whom: - Moscow Oblast 90 (21.0) - Arkhangelsk Oblast 30 (7.0)	8.8% of whom: - Moscow Oblast 38.1% - Arkhangelsk Oblast 100%	53 (22.8)	67 (34.4)	85 (34.4)
South Africa	3	190 (44.4)	11.6%	117 (50.2)	73 (37.4)	113 (45.8)
Spain	2	2 (0.5)	100%	2 (0.9)	-	-
Sweden	1	3 (0.7)	27.3%	1 (0.4)	2 (1.0)	3 (1.2)
United Kingdom	1	1 (0.2)	7.7%	-	1 (0.5)	-

MDR-TB: multidrug-resistant tuberculosis; XDR-TB: extensively drug-resistant tuberculosis; Bdq: bedaquiline