Effectiveness and cardiac safety of bedaquiline-based therapy for drug-resistant tuberculosis: a prospective cohort study

James C.M. Brust, MD; Neel R. Gandhi, MD; Sean Wasserman, MBChB; Gary Maartens, MMed; Shaheed V. Omar, PhD; Nazir A. Ismail, PhD; Angela Campbell, MA; Lindsay Joseph, MPH; Alexandria Hahn, MS; Salim Allana, MD; Alfonso C. Hernandez-Romieu, MD; Chenshu Zhang, PhD; Koleka Mlisana, MBChB; Charle A. Viljoen, MBChB; Benjamin Zalta, MD; Ismaeel Ebrahim, MBChB; Meghan Franczek, MPH; Iqbal Master, MBChB; Limpho Ramangoaela, MBChB; Julian te Riele, MBChB; Graeme Meintjes, MBChB, PhD; for the PROBeX Study Team

1Division of General Internal Medicine, Department of Medicine, Albert Einstein College of Medicine & Montefiore Medical Center, Bronx, NY, USA
2Departments of Epidemiology & Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA
3Division of Infectious Diseases, Department of Medicine, Emory School of Medicine, Emory University, Atlanta, GA, USA
4Wellcome Centre for Infectious Diseases Research in Africa, Institute of Infectious Disease and Molecular Medicine, and Department of Medicine, University of Cape Town, Cape Town, South Africa
5Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa
6Centre for Tuberculosis, National Institute for Communicable Diseases, Johannesburg, South Africa
7Department of Molecular Medicine & Haematology, School of Pathology, Faculty of Health Sciences, University of Witwatersrand
8National Health Laboratory Services, Johannesburg, South Africa

© The Author(s) 2021. Published by Oxford University Press for the Infectious Diseases Society of America.
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.
Division of Cardiology, Department of Medicine, University of Cape Town, Cape Town, South Africa

Department of Radiology, Albert Einstein College of Medicine & Montefiore Medical Center, Bronx, NY, USA

King Dinuzulu Hospital Complex, Durban, South Africa

Jose Pearson Hospital, Port Elizabeth, South Africa

Brooklyn Chest Hospital, Cape Town, South Africa

Deceased

Corresponding Author:
James C.M. Brust, MD
Division of General Internal Medicine
Montefiore Medical Center
111 E. 210th St.
Bronx, NY 10467 USA
Tel: +1-718-920-6482
Fax: +1-718-561-5165
Email: jcmbrust@gmail.com

Main Point: Severe QTcF prolongation was uncommon among participants treated for MDR- and XDR-TB with a regimen containing both bedaquiline and clofazimine. Outcomes were favorable in this high HIV-prevalence setting. Participants receiving concurrent lopinavir-ritonavir did not experience further prolongation of the QT-interval.
ABSTRACT

Background
Bedaquiline improves treatment outcomes in patients with rifampin-resistant TB (RR-TB) but prolongs the QT-interval and carries a black-box warning by the U.S. Food and Drug Administration. The World Health Organization recommends that all patients with RR-TB receive a regimen containing bedaquiline, yet a phase 3 clinical trial demonstrating its cardiac safety has not been published.

Methods
We conducted an observational cohort study of RR-TB patients from 3 provinces in South Africa who received regimens containing bedaquiline. We performed rigorous cardiac monitoring, including electrocardiograms (ECGs) performed in triplicate at four time points during bedaquiline therapy. Participants were followed until the end of therapy or 24 months. Outcomes included final tuberculosis treatment outcome and QT-prolongation, defined as any QTcF>500 ms or an absolute change from baseline (ΔQTcF) >60 ms.

Results
We enrolled 195 eligible participants, of whom 40% had extensively drug-resistant (XDR) TB. Most participants (97%) received concurrent clofazimine. 74% of participants were cured or successfully completed treatment, and outcomes did not differ by HIV status. QTcF continued to increase throughout bedaquiline therapy, with a mean increase of 23.7 (SD 22.7) ms from baseline to month 6. Four participants experienced a QTcF>500 ms and 19 experienced a ΔQTcF>60 ms. Older age was independently associated with QT-prolongation. QT-prolongation was neither more common nor severe in participants receiving concurrent lopinavir-ritonavir.
Conclusions

Severe QT-prolongation was uncommon and did not require permanent discontinuation of either bedaquiline or clofazimine. Close QT-monitoring may be advisable in older patients.

Keywords: Bedaquiline; multidrug-resistant tuberculosis; extensively drug-resistant tuberculosis; QT-interval; HIV; clofazimine; antiretroviral therapy
BACKGROUND

Drug-resistant tuberculosis remains a major public health threat and undermines control of tuberculosis worldwide. Bedaquiline was the first antituberculosis drug from a novel class to be approved in more than 40 years [1]; its approval by the FDA and the European Medicines Agency was based upon results of 3 small Phase 2 trials [2-4]. Observational data have shown improved treatment outcomes in patients with multidrug-resistant (MDR) or extensively drug-resistant (XDR) tuberculosis who received regimens containing bedaquiline [5, 6]. Based on these data, WHO recommends that all patients with rifampin-resistant tuberculosis (RR-TB) be treated with a regimen containing bedaquiline [7].

Bedaquiline prolongs the QT-interval, resulting in concerns about its cardiac safety [8]. In the pivotal phase 2 trial, there were more deaths in the bedaquiline arm compared with placebo [9, 10]. Although the deaths were not directly attributed to bedaquiline [11], the FDA created a “black box” warning about excess mortality and QT-prolongation [12], and guidelines advise ECG monitoring in patients receiving bedaquiline [7]. A systematic review of the cardiac safety of bedaquiline reported wide variability in QT-prolongation observed, but most included studies were retrospective, based on ECGs done in routine clinical practice, and patients were receiving other QT-prolonging drugs [13]. To date, there are still no Phase 3 trial data assessing bedaquiline’s cardiac safety. WHO recommends that bedaquiline be given with clofazimine, based on improved outcomes in observational studies [7], but clofazimine also prolongs the QT-interval [14], resulting in additive QT-prolongation when combined with bedaquiline [4].

A meta-analysis of MDR-TB cohort studies found that HIV co-infection more than doubled the adjusted odds of death [15]. Treatment with concurrent antiretroviral therapy (ART) improves these outcomes considerably [16], and is recommended in all patients with drug-resistant tuberculosis and HIV co-infection [7]. However, there are important drug-drug interactions between bedaquiline and some antiretrovirals: efavirenz is contraindicated as it induces bedaquiline metabolism, decreasing bedaquiline concentrations, and [17] lopinavir-ritonavir inhibits bedaquiline metabolism, resulting in
a nearly twofold increase in bedaquiline exposure [18]; the clinical importance of this interaction is not known.

We determined the effectiveness and cardiac safety (by rigorously assessing the QT-interval) in patients with drug-resistant tuberculosis treated with bedaquiline in a high HIV-prevalence setting.

METHODS

Setting

The Pharmacokinetics, Resistance, and Outcomes of Bedaquiline in MDR- and XDR-TB (PROBeX) study was a prospective observational cohort study conducted between 2016 and 2020 at three drug-resistant tuberculosis referral hospitals in South Africa.

During the study period, all patients with pre-XDR- and XDR-TB, as well as patients with RR-TB for whom an injectable agent was contraindicated or poorly tolerated, were treated with a modified standardized regimen, which typically included bedaquiline (400mg daily for 2 weeks followed by 200mg three times weekly), linezolid (600mg daily), clofazimine (100mg daily), levofloxacin (750-1000mg daily), ethionamide (15-20 mg/kg, max 750mg daily), terizidone (15-20 mg/kg, max 750mg daily), and pyrazinamide (20-30 mg/kg, max 1600mg daily). Bedaquiline was given for 6 months and the total tuberculosis treatment duration was 18-24 months. Para-amino salicylic acid, high-dose isoniazid, kanamycin, amikacin, ethambutol, rifabutin, and delamanid were given to some participants at the discretion of the treating provider. Study team members were not directly involved in individual treatment decisions. Many participants were already receiving tuberculosis therapy prior to bedaquiline initiation and those receiving a regimen containing moxifloxacin prior to bedaquiline initiation were changed to levofloxacin per standard of care. All HIV co-infected participants were offered ART irrespective of CD4 count. Because efavirenz is contraindicated with bedaquiline, all HIV-infected participants received either nevirapine- or lopinavir-ritonavir-based ART.
Study population and procedures

We recruited patients ≥18 years old with culture-confirmed tuberculosis who were initiating treatment with a bedaquiline-containing regimen between April 2016 and March 2018. Eligibility for bedaquiline therapy in the national tuberculosis program required a baseline QTcF ≤450 milliseconds (ms). Additionally, participants were excluded from the study if they had bedaquiline treatment, abnormal baseline creatinine (>2 times the upper limit of normal [ULN]), or abnormal alanine aminotransferase (>5 times ULN). Participants had to agree to HIV testing if their status was unknown.

Participants were followed biweekly for the first 3 months of therapy, monthly for months 4-6, and then at months 12, 18 and 24, or until 6 months after the completion of therapy, whichever was earliest. At each visit, participants were interviewed regarding current symptoms and adverse events. Study ECGs were performed by trained study staff at baseline, Month 1, Month 2, and Month 6. After participants had rested in a supine position for several minutes, three ECGs were performed at each time point, at least 5 minutes apart. All QT-intervals were manually measured by a single cardiologist (C.V.) and corrected using Fridericia’s formula. In addition, all participants had routine safety monitoring consisting of monthly (single) ECGs performed and read by clinic providers. Study staff did not review or capture clinic ECGs and decisions to stop therapy were made by clinic providers rather than the study team. Because moxifloxacin also prolongs the QT-interval, we identified participants who discontinued moxifloxacin <24 hours prior to their baseline ECG in the analysis.

Sputum samples were sent for mycobacterial culture (Mycobacterial Growth Indicator Tube, Bactec 960; MGIT) biweekly for the first 3 months, and then monthly thereafter. Bedaquiline minimum inhibitory concentrations (MICs) were measured on all available isolates, using MGIT [19], at the Centre for Tuberculosis in the National Institute for Communicable Diseases (Johannesburg). Drug-susceptibility testing (DST) for other drugs were performed at the regional reference tuberculosis laboratories.
**Outcome Measures and Analysis**

The primary effectiveness outcome of interest was cure or treatment completion according to WHO definitions [20]. The primary safety outcome was prolongation of the QTcF interval, defined as any instance of QTcF interval >500ms or an increase in QTcF (ΔQTcF) from baseline of >60ms. Secondary outcomes included: survival; time to tuberculosis culture conversion; development of resistance to bedaquiline; serious adverse events (SAEs); and any instance of QTcF >450ms or ΔQTcF >30ms. Bedaquiline resistance was defined as having an MIC >1 mcg/mL by MGIT [19].

Targeted Sanger sequencing of the *Rv0678* gene was done on isolates with phenotypic resistance to bedaquiline. Time to culture conversion was calculated, in days, from the date of bedaquiline initiation to the first of two consecutive negative cultures taken at least four weeks apart. HIV virologic suppression was defined as a viral load <150 copies/mL (the lower limit of detection of certain assays used during the study period). SAEs were defined as clinical events which resulted in death, hospitalization, or discontinuation of therapy, or laboratory abnormalities of grade 3 or 4 by the DAIDS toxicity table [21].

Participant characteristics were compared using simple frequencies, chi-square and Wilcoxon Rank Sum tests. Survival analysis was performed using Kaplan-Meier curves and log-rank tests. The mean of the three QTcF values at each time point was used for comparison with those at other time points and participants were stratified by HIV status, receipt of lopinavir-ritonavir, and concurrent use of moxifloxacin. We used generalized estimating equations to analyze the change in mean QTcF over time and logistic regression to examine clinical predictors of QTcF prolongation.

**Ethics**

The study was approved by the institutional review boards at the University of Cape Town, Albert Einstein College of Medicine, and Emory University. All participants signed written informed consent.
RESULTS

We screened patients with presumed RR-TB, of whom 195 were eligible for enrollment (Figure 1): 80 (41%) had XDR-TB, 78 (40%) had pre-XDR-TB, and 29 (15%) had MDR-TB; 123 (63%) were HIV-infected (Table 1). The median age was 33 years (IQR 28-42) and 111 (57%) participants were female; 40% were sputum smear-positive, 77% had cavitary disease, and 128 (66%) participants had previously had tuberculosis. Nine (7%) participants had received clofazimine prior to study enrollment. During the study period, 190 (97%) received concurrent clofazimine and 179 (92%) received concurrent linezolid (Table 2). Among HIV-infected participants, the median CD4 count at enrollment was 196 cells/mm$^3$ (IQR 96-427). One hundred thirteen (90%) of the HIV-infected participants were already receiving ART at the time of enrollment (median duration 8 months). A total of 26 (23%) participants received an ART regimen containing lopinavir-ritonavir during the study. Twenty-three initiated lopinavir-ritonavir prior to starting bedaquiline and three participants initiated lopinavir-ritonavir at a later date (range: 1-4 months after bedaquiline initiation). In only 28% (28/100) of those with an available baseline viral load was this undetectable.

Tuberculosis treatment outcomes

Participants were followed for a median of 22 months after starting bedaquiline (IQR 14-24; 300 person-years). Among the 195 enrolled participants, 174 (89%) achieved sputum culture conversion; 37 (19%) converted their cultures before bedaquiline initiation. Among the 137 (70%) participants who converted after bedaquiline was started, the median time to conversion was 41 days (IQR 17-67) (Figure 2). Among all participants, 145 (74%) had a successful tuberculosis treatment outcome (cure: n=129 [66%]; completed = 16 [8%]). Eight participants (4%) experienced treatment failure; 18 (9%) interrupted treatment prematurely; and 25 (13%) died (Appendix Table S1). The proportion of participants achieving treatment success did not significantly differ by resistance category (69% MDR vs. 77% pre-XDR vs. 74% XDR [p=0.67]). Among all participants who died, the median survival time was 2.3 months (IQR 1.1-6.8) (Appendix Figure S1). Treatment outcomes did not differ between those with and without HIV (p=0.61).
QTcF Prolongation

One hundred eighty-three (94%) participants had at least one baseline (pre-bedaquiline) and one follow-up ECG and were included in the ECG analysis. The mean QTcF at baseline was 404.6ms (SD 22.1) (Table 3). One hundred twenty (66%) participants received moxifloxacin during the study or immediately prior to study enrollment. Of these, 99 (83%) stopped moxifloxacin prior to starting bedaquiline and 70 (58%) stopped at least 24 hours before starting bedaquiline. The median moxifloxacin washout period was 1 (IQR 1-2) day. The mean maximum QTcF for all participants was 434.4ms (SD 24.5). Among participants receiving clofazimine (n=179), the mean maximum QTcF was 434.8ms (SD 24.4), compared with 416.7ms (SD 27.3) in those not receiving clofazimine (n=4; p=0.15). Among participants receiving concurrent lopinavir-ritonavir, the mean maximum QTcF was 437.1ms (SD 31.0), compared with 434.0ms (SD 23.5) in those not receiving lopinavir-ritonavir (p=0.57). Among all participants, QTcF continued to increase while on bedaquiline and the mean increase in QTcF from baseline to M6 was 23.7ms (SD 22.7; p<0.001); this did not differ based on receipt of concurrent lopinavir-ritonavir (p=0.61; Figure 3).

Nineteen participants (10.4%) experienced a ΔQTcF >60ms at any time; all 19 received concurrent clofazimine, four received lopinavir-ritonavir, and two did not have a moxifloxacin washout prior to bedaquiline initiation. Four (2.2%) participants developed a QTcF >500ms; all four received concurrent clofazimine, two received lopinavir-ritonavir, and none received moxifloxacin. After adjusting for age, race, sex, weight, receipt of lopinavir-ritonavir, and concurrent moxifloxacin, age >30 years remained significantly associated with QTcF>450ms compared to those aged 21-30, with the greatest effect seen in those >50 (adjusted odds ratio [aOR] 8.3 [95%CI 2.1-32.8]; Table 4).

Table S2 (Appendix) shows the age strata for the participants experiencing QTcF >500ms or ΔQTcF >60ms.

Bedaquiline resistance

Eighty-four participants had a baseline *Mtb* isolate available for bedaquiline MIC testing. Of these, 7 (8%) had a bedaquiline MIC >1 mcg/mL prior to initiation of therapy (range 2-8 mcg/mL; Table 5). Two additional participants had a bedaquiline MIC of 4 mcg/mL at their 1-month visit, but their
baseline isolates were not available for testing. Only 1 of these 9 participants had received prior
clofazimine therapy.

Four participants were found to have a bedaquiline MIC >1 mcg/mL on treatment after the 1-month
visit (range 2-8 mcg/mL); 3 of these participants had a baseline isolate which was susceptible and the
baseline isolate was not available for the fourth participant. Of the 13 participants with an elevated
MIC at any time point, 6 were eventually cured, 3 interrupted therapy, 3 died, and 1 experienced
treatment failure. Among these 13 participants, polymorphisms were found in \textit{Rv0678} for 11 (85%).
Only two of the participants had the same polymorphism, while the other nine were unique. Among
those with resistance at baseline or month 1 (n=9), 55% achieved a successful outcome.

\textbf{Serious adverse events}

Overall, SAEs were common, with 84 (43%) participants experiencing a clinical or laboratory AE that
required temporary or permanent discontinuation of one or more antituberculosis medications. Most
(n=56) discontinuations were due to linezolid-associated AEs, but bedaquiline was stopped in 9 (5%)
participants, due to: QT-prolongation (n=5), rash (n=1), abdominal pain (n=1), non-specific T-wave
abnormality (n=1) and unknown (n=1). Four of the five participants who stopped because of QT-
prolongation also stopped clofazimine, although all four eventually restarted both drugs and the fifth
participant restarted bedaquiline. Only one of these five participants experienced a $\Delta$QTcF >60ms and
none experienced a QTcF >500ms by study ECGs. The participant with rash temporarily stopped all
tuberculosis medications. Four (2%) participants experienced a grade 3 or 4 elevation in ALT and all
four resolved spontaneously without any discontinuation in therapy, potentially representing hepatic
adaptation. Participants receiving concurrent lopinavir-ritonavir and bedaquiline were no more likely
to experience clinical or laboratory SAEs than those who received other ART regimens (p=0.61).
DISCUSSION

In this prospective cohort study, we followed participants with RR-TB who were treated with bedaquiline to rigorously assess their treatment outcomes and cardiac safety. Treatment outcomes were generally favorable, as has been shown by others [5, 6, 22, 23]. Few participants experienced a QTcF >500ms or an absolute increase of >60ms from baseline, suggesting that bedaquiline, even in combination with clofazimine, may be safe. This is an important finding, given WHO’s recommendation that most patients with RR-TB be treated with both bedaquiline and clofazimine. The largest increase in QTcF was at Month 1, but the QTcF continued to increase for the duration of bedaquiline therapy, suggesting that it may not have plateaued when bedaquiline was stopped at 6 months. As more patients are treated with bedaquiline worldwide and, potentially with courses longer than 6 months [24, 25], QT-monitoring in the later months of therapy will be important to ensure that the QTcF does not reach dangerous levels. Older age, particularly >50 years, was associated with QT-prolongation and may warrant close cardiac monitoring.

Nearly all of our study participants received both bedaquiline and clofazimine. Participants treated with both bedaquiline and clofazimine had a longer QTcF at all study visits, compared with those who did not receive clofazimine, but this comparison is limited by the small number of participants who did not receive clofazimine. The QTcF among participants concurrently treated with clofazimine was also longer than the QTcF in participants in other studies who received bedaquiline without clofazimine [3, 26].

Lopinavir-ritonavir reduces bedaquiline clearance, leading to ~2-fold increase in steady-state concentration [18], but until now, the clinical importance of this interaction was unknown. We found that participants who received concurrent therapy did not experience a significant prolongation in QTcF compared with participants treated with bedaquiline who did not receive lopinavir-ritonavir. This is likely because lopinavir-ritonavir has a minimal effect on plasma concentrations of bedaquiline’s M2 metabolite [27], which is responsible for the QT-prolongation seen with bedaquiline [28, 29].
Bedaquiline discontinuations were uncommon (5%) and frequently temporary. Although most study participants had a successful treatment outcome, 15% of the 99 participants tested for bedaquiline resistance had an elevated MIC to bedaquiline at some time point: some had resistant isolates at baseline while others developed resistance during therapy or following a treatment interruption. The presence of bedaquiline resistance at baseline is concerning and has been seen in other studies [30, 31]. Prior exposure to clofazimine may generate polymorphisms in Rv0678 and cross-resistance to bedaquiline [32], but very few participants in our study had previously received clofazimine. While these variants could represent spontaneous polymorphisms, it is also possible that bedaquiline resistance is already being transmitted. We used a consensus definition of resistance based on an MIC cutoff of 1.0 mcg/mL when measured by MGIT, but importantly, this definition was developed without clinical outcomes [19, 33]. A clinical definition of resistance is challenging in multidrug therapy, because participants may have a favorable outcome despite bedaquiline resistance if the background regimen contains a sufficient number of active drugs, as we observed in some patients in this study.

A strength of our study is the precision with which we performed and analyzed ECGs; ECGs were timed and performed in triplicate, and all QTcF intervals were measured by a cardiologist. We also reported the use of moxifloxacin at baseline and the duration of the washout period, to have a more precise estimate of the incremental effect of bedaquiline (and clofazimine). Our study has several limitations. First, we were reliant on self-report of adverse events and clinician notes from the handwritten medical record. Some adverse events may, therefore, have been incompletely captured. We restricted our analysis, however, only to serious adverse events—particularly those requiring a change in therapy and/or hospitalization, as these adverse events would have been unlikely to go unnoticed in the medical record. Second, Mtb isolates were only available from two of the three study sites. Third, participants were followed for a maximum of 24 months and we therefore did not capture information on relapse following treatment completion. Fourth, we used an outcome of QTcF >450ms and ΔQTcF >30ms from baseline in our predictors analysis due to the small number of participants.
who experienced the more clinically important outcomes of QTcF >500 or ΔQTcF >60ms. These alternate endpoints are approved by the FDA [34] but are not as clearly associated with sudden cardiac death. We did not test differing monitoring strategies and we are thus unable to recommend a monitoring schedule for clinical care. Our study ECGs were performed in triplicate and read by a cardiologist, which is important for research but is not feasible for routine monitoring.

Our findings suggest that the combination of bedaquiline and clofazimine is safe and that life-threatening QTcF prolongation is rare. Our study adds to the literature establishing the cardiac safety of bedaquiline when given with other QT-prolonging medications [35, 36], including a randomized controlled trial to evaluate the cardiac safety of concomitant bedaquiline and delamanid. An important population of HIV-infected patients worldwide will require protease inhibitor-based ART; therefore, demonstrating the safety of lopinavir-ritonavir with bedaquiline has important implications for clinical practice. In just eight years, bedaquiline has transformed the treatment of MDR- and XDR-TB. Several clinical trials are currently underway to identify the optimal combination of partner medications. Defining the drug-drug interactions with bedaquiline and their clinical implications is essential for the tuberculosis community to optimize the use of this important drug.
NOTES

Acknowledgments:
We are grateful to the study team at the University of Cape Town for their tireless efforts in data collection, record abstraction, participant recruitment and interviews. We thank the doctors and staff of Brooklyn Chest Hospital, Jose Pearson Hospital and King Dinuzulu Hospital for their outstanding clinical management of the study participants and support of the study. We thank Cindy Hayes, Tania Dolby, and Keeren Lutchminarain for their assistance with obtaining laboratory specimens. We thank Pauline Harrington, Krystalyn Martin, and Zahraa Mohamed for their contributions to data cleaning and analysis, and Jonathan Smith for his assistance with the study figures. Finally, we thank the participants who consented to participate in this study as well as their families.

Disclaimer
The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of this report. The opinions, findings and conclusions expressed in this manuscript reflect those of the authors alone and do not necessarily represent the official position of the U.S. Department of Health and Human Services.

Funding
This study was funded by the US National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH): R01AI114304 (to JCMB). It was also supported in part by NIH/NIAID grants, R01AI145679 (to JCMB), K24AI155045 (to JCMB), K24AI114444 (to NRG), Einstein-Rockefeller-CUNY CFAR P30AI124414, Emory CFAR P30AI050409, Emory TBRU U19AI11211, Einstein/Montefiore ICTR UL1TR001073 and the Atlanta CTSI UL1TR000454. SW is supported by the European & Developing Countries Clinical Trials Partnership (Grant number CDF1018), Wellcome Trust (Grant number 203135/Z/16/Z), and NIH (K43TW011421, [PI Wasserman]). GrM was supported by the Wellcome Trust (098316, 214321/Z/18/Z, and 203135/Z/16/Z), and the South African Research Chairs Initiative of the Department of Science and Technology and National Research Foundation (NRF) of South Africa (Grant No 64787). Additional
support was provided by the South African Medical Research Council through its TB and HIV Collaborating Centres Programme, with a grant (RFA# SAMRC-RFA-CC: TB/HIV/AIDS-01-2014) funded by the National Department of Health.

**Potential conflicts of interest:**

All  No reported conflicts.
REFERENCES

1. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Sirturo NDA 204384 approval letter, 28 December 2012. Retrieved 3 July 2020, from www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/204384Orig1s000ltr.pdf.

2. Diacon AH, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N Engl J Med 2009; 360(23): 2397-405.

3. Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med 2014; 371(8): 723-32.

4. Pym AS, Diacon AH, Tang SJ, et al. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. Eur Respir J 2016; 47(2): 564-74.

5. Schnippel K, Ndjeka N, Maartens G, et al. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. Lancet Respir Med 2018.

6. Collaborative Group for the Meta-Analysis of Individual Patient Data in MDRTB treatment, Ahmad N, Ahuja SD, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018; 392(10150): 821-34.

7. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. WHO/CDS/TB/20197; Geneva 2019.

8. Centers for Disease Control and Prevention. Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate (Sirturo) for the Treatment of Multidrug-Resistant Tuberculosis. MMWR 2013; 62 (No RR-9):1-12.

9. Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med 2014; 371(8): 723-32.

10. Cox E, Laessig K. FDA approval of bedaquiline--the benefit-risk balance for drug-resistant tuberculosis. N Engl J Med 2014; 371(8): 689-91.
11. Food and Drug Administration (U.S). Anti-infective drugs advisory committee meeting briefing document TMC207 (bedaquiline). Treatment of patients with MDR-TB. NDA 204-384. 2012 November 28. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM329260.pdf.

(Accessed 2013 Nov 13).

12. Moro ML, Gori A, Errante I, et al. An outbreak of multidrug-resistant tuberculosis involving HIV-infected patients of two hospitals in Milan, Italy. Italian Multidrug-Resistant Tuberculosis Outbreak Study Group. AIDS 1998; 12(9): 1095-102.

13. Pontali E, Sotgiu G, Tiberi S, D’Ambrosio L, Centis R, Migliori GB. Cardiac safety of bedaquiline: a systematic and critical analysis of the evidence. Eur Respir J 2017; 50(5): 1701462.

14. Diacon AH, Dawson R, von Groote-Bidlingmaier F, et al. Bactericidal activity of pyrazinamide and clofazimine alone and in combinations with pretomanid and bedaquiline. Am J Respir Crit Care Med 2015; 191(8): 943-53.

15. Bisson GP, Bastos M, Campbell JR, et al. Mortality in adults with multidrug-resistant tuberculosis and HIV by antiretroviral therapy and tuberculosis drug use: an individual patient data meta-analysis. Lancet 2020; 396(10248): 402-11.

16. Brust JCM, Shah NS, Mlisana K, et al. Improved Survival and Cure Rates With Concurrent Treatment for Multidrug-Resistant Tuberculosis-Human Immunodeficiency Virus Coinfection in South Africa. Clin Infect Dis 2018; 66(8): 1246-53.

17. Svensson EM, Aweeka F, Park JG, Marzan F, Dooley KE, Karlsson MO. Model-based estimates of the effects of efavirenz on bedaquiline pharmacokinetics and suggested dose adjustments for patients coinfected with HIV and tuberculosis. Antimicrob Agents Chemother 2013; 57(6): 2780-7.
18. Pandie M, Wiesner L, McIlerson H, et al. Drug-drug interactions between bedaquiline and the antiretrovirals lopinavir/ritonavir and nevirapine in HIV-infected patients with drug-resistant TB. J Antimicrob Chemother 2016; 71(4): 1037-40.

19. Ismail NA, Omar SV, Joseph L, et al. Defining Bedaquiline Susceptibility, Resistance, Cross-Resistance and Associated Genetic Determinants: A Retrospective Cohort Study. EBioMedicine 2018; 28: 136-42.

20. World Health Organization. Definitions and reporting framework for tuberculosis -- 2013 revision. Geneva, WHO/HTM/TB/20132013.

21. Division of AIDS (DAIDS). Table for grading the severity of adult and pediatric adverse events. Version 1.0/Clarification 1. http://rcc.tech-res.com/safetyandpharmacovigilance (accessed November 28, 2013).

22. Zhao Y, Fox T, Manning K, et al. Improved treatment outcomes with bedaquiline when substituted for second-line injectable agents in multidrug resistant tuberculosis: a retrospective cohort study. Clin Infect Dis 2018.

23. Tack I, Dumicho A, Ohler L, et al. Safety and effectiveness of an all-oral, bedaquiline-based, shorter treatment regimen for rifampicin-resistant tuberculosis in high HIV burden rural South Africa: a retrospective cohort analysis. Clin Infect Dis 2020.

24. Guglielmetti L, Jaspard M, Le Du D, et al. Long-term outcome and safety of prolonged bedaquiline treatment for multidrug-resistant tuberculosis. Eur Respir J 2017; 49(3).

25. Furin J, Lessem E, Cox V. Recommending prolonged bedaquiline use for the treatment of highly resistant strains of tuberculosis. Eur Respir J 2017; 50(5).

26. Conradie F, Diacon AH, Ngubane N, et al. Treatment of Highly Drug-Resistant Pulmonary Tuberculosis. N Engl J Med 2020; 382(10): 893-902.

27. Brill MJ, Svensson EM, Pandie M, Maartens G, Karlsson MO. Confirming model-predicted pharmacokinetic interactions between bedaquiline and lopinavir/ritonavir or nevirapine in patients with HIV and drug-resistant tuberculosis. Int J Antimicrob Agents 2017; 49(2): 212-7.

28. Sirturo [package insert]; Janssen Therapeutics; Titusville, NJ; 2012.
29. Li H, Salinger DH, Everitt D, et al. Long-Term Effects on QT Prolongation of Pretomanid Alone and in Combinations in Patients with Tuberculosis. Antimicrob Agents Chemother 2019; 63(10).

30. Nimmo C, Millard J, Brien K, et al. Bedaquiline resistance in drug-resistant tuberculosis HIV co-infected patients. Eur Respir J 2020; 55(6).

31. Villellas C, Coeck N, Meehan CJ, et al. Unexpected high prevalence of resistance-associated Rv0678 variants in MDR-TB patients without documented prior use of clofazimine or bedaquiline. J Antimicrob Chemother 2017; 72(3): 684-90.

32. Ismail N. Emerging resistance: the South African perspective. 50th Union World Conference on Lung Health, 30 October - 2 November 2019, Hyderabad, India 2019.

33. Kaniga K, Aono A, Borroni E, et al. Validation of Bedaquiline Phenotypic Drug Susceptibility Testing Methods and Breakpoints: a Multilaboratory, Multicountry Study. J Clin Microbiol 2020; 58(4).

34. U.S. Food and Drug Administration. International Conference on Harmonisation; E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. Available at https://www.fda.gov/media/71372/download (accessed Oct 19, 2020). 2005.

35. Dooley KE, Rosenkranz SL, Conradie F, et al. QT effects of bedaquiline, delamanid, or both in patients with rifampicin-resistant tuberculosis: a phase 2, open-label, randomised, controlled trial. Lancet Infect Dis 2021.

36. Kempker RR, Mikiashvili L, Zhao Y, et al. Clinical Outcomes Among Patients With Drug-resistant Tuberculosis Receiving Bedaquiline- or Delamanid-Containing Regimens. Clin Infect Dis 2020; 71(9): 2336-44.
Table 1: Participant characteristics

| Characteristics                      | Total cohort (n=195) | Durban (n=89) | Port Elizabeth (n=47) | Cape Town (n=59) |
|--------------------------------------|---------------------|---------------|-----------------------|------------------|
| **Demographic**                      |                     |               |                       |                  |
| Age, median (IQR)                    | 33 (28-42)          | 32 (27-39)    | 35 (30-42)            | 29 (26-43)       |
| Female Sex                           | 111 (57)            | 55 (62)       | 21 (45)               | 35 (59)          |
| **Race**                             |                     |               |                       |                  |
| Black                                | 160 (82)            | 89 (100)      | 38 (81)               | 33 (56)          |
| Mixed race                           | 33 (17)             | 0 (0)         | 9 (19)                | 24 (41)          |
| White                                | 2 (1)               | 0 (0)         | 0 (0)                 | 2 (3)            |
| **Clinical**                         |                     |               |                       |                  |
| BMI, kg/m², median (IQR)             | 20 (18-23)          | 21 (18-22)    | 19 (17-23)            | 19 (18-24)       |
| <18                                  | 55/193 (28)         | 23 (26)       | 14 (30)               | 18 (32)          |
| 18-25                                | 103/193 (53)        | 51 (57)       | 26 (55)               | 26 (46)          |
| 25-30                                | 21/193 (11)         | 8 (9)         | 4 (9)                 | 9 (16)           |
| >30                                  | 14/193 (7)          | 7 (8)         | 3 (6)                 | 4 (7)            |
| HIV-infected                         | 123 (63)            | 66 (74)       | 28 (60)               | 29 (49)          |
| Receiving ART                        | 113 (92)            | 66 (100)      | 23 (82)               | 24 (83)          |
| ART regimen included lopinavir       | 26 (23)             | 11 (17)       | 3 (13)                | 12 (50)          |
| Median duration of ART at enrollment, months | 8              | 8             | 29.5                  | 5                |
| Median CD4 count at enrollment baseline, cells/mm³ (IQR) | 196 (96-427) | 185 (105-433) | 196 (105-575) | 210 (72-353) |
| Undetectable HIV viral load at enrollment | 28%             | 30%           | 13%                   | 17%              |
| Diabetes                             | 10 (5)              | 3 (3)         | 5 (11)                | 2 (3)            |
| Current/former smoker                | 62 (32)             | 9 (10)        | 21 (45)               | 32 (54)          |
| Alcohol use in the past year         | 73 (37)             | 14 (16)       | 29 (62)               | 30 (51)          |
| QTcF at baseline, milliseconds, mean (SD) | 404.6 (22.1)       | 408.1 (24.0)  | 401.9 (20.1)          | 401.5 (20.2)     |
| **Tuberculosis**                     |                     |               |                       |                  |
| Tuberculosis Resistance category     |                     |               |                       |                  |
| MDR                                  | 29 (15)             | 21 (24)       | 7 (15)                | 1 (2)            |
| pre-XDR                              | 78 (40)             | 34 (38)       | 10 (21)               | 34 (58)          |
| XDR                                  | 80 (41)             | 28 (31)       | 30 (64)               | 22 (37)          |
| Other RR-TB<sup>a</sup>              | 8 (4)               | 6 (7)         | 0 (0)                 | 2 (3)            |
| Sputum smear positive,               | 73/181 (40)         | 32/85 (38)    | 19/45 (42)            | 22 (37)          |
| Previous tuberculosis episode        | 128 (66)            | 57 (64)       | 26 (51)               | 45 (75)          |
| Median number of prior tuberculosis episodes (IQR) | 2 (2-3)           | 2 (2-3)       | 2 (2-2)               | 3 (2-3)          |
| Previous drug-susceptible tuberculosis | 60<sup>b</sup> (48) | 18 (32)       | 18 (75)               | 23 (51)          |
### Previous drug-resistant tuberculosis

| History of prior treatment with CFZ | 66 (52) | 39 (57) | 6 (25) | 22 (49) |
|-------------------------------------|---------|---------|--------|---------|
| Duration of prior treatment with CFZ, median months (IQR) | 9 (7) | 3 (3) | 2 (8) | 4 (9) |
|                                      | 2 (1-10.5) | 3c | Unknown | 1 (1-18) |

| Baseline chest radiograph           | (n=125) | (n=63) | (n=45) | (n=17) |
|-------------------------------------|---------|--------|--------|--------|
| Cavitary lesion                     | 96 (77) | 42 (67) | 40 (89) | 14 (82) |
| Bilateral disease                   | 71 (57) | 32 (51) | 28 (62) | 11 (65) |

*Five participants had only Xpert results with no additional susceptibility test results.

*Details on previous treatment available for n=126.

*Duration of prior clofazimine treatment unknown for 2 of the 3 participants.

**ART** = antiretroviral therapy; **SD** = standard deviation; **CFZ** = clofazimine; **IQR** = interquartile range; **MDR** = multidrug-resistant; **XDR** = extensively drug-resistant; **RR** = rifampin-resistant
Table 2: Anti-tuberculosis drugs received after enrollment

| Drug name                  | Number (%) of participants receiving drug |
|----------------------------|--------------------------------------------|
| Bedaquiline                | 195 (100)                                  |
| Clofazimine                | 190 (97)                                   |
| Pyrazinamide               | 184 (94)                                   |
| Levofloxacin               | 183 (94)                                   |
| Linezolid                  | 179 (92)                                   |
| Para-aminosalicylic acid   | 173 (89)                                   |
| Terizidone                 | 161 (83)                                   |
| Ethambutol                 | 93 (48)                                    |
| Moxifloxacin\(^a\)         | 49 (25)                                    |
| High-dose isoniazid        | 74 (38)                                    |
| Ethionamide                | 63 (32)                                    |
| Kanamycin or amikacin      | 16 (8)                                     |
| Delamanid                  | 11 (6)                                     |
| Rifabutin                  | 5 (3)                                      |

\(^a\)32 of these participants received moxifloxacin concurrently with bedaquiline for at least 24 hours. Forty of the 49 participants were changed from levofloxacin to moxifloxacin following completion of the 6-month course of bedaquiline.
Table 3: ECG findings

|                          | All patients (n=183) | BDQ only (n=4) | BDQ and CFZ (n=179) | BDQ and LPV/r (+/- CFZ) (n=23) | BDQ without LPV/r (n=160) |
|--------------------------|----------------------|----------------|---------------------|--------------------------------|--------------------------|
| Mean QTcF (SD), milliseconds, baseline | 404.6 (22.2)         | 398.8 (21.1)   | 404.7 (22.2)        | 405.1 (20.3)                  | 404.5 (22.5)             |
| Mean QTcF (SD), Month 1  | 418.7 (24.3)         | 403.5 (20.2)   | 419.1 (24.4)        | 425.5 (35)                    | 417.8 (22.5)             |
| Mean QTcF (SD), Month 2  | 421.2 (25.4)         | 429.2 (13.6)   | 421.0 (25.6)        | 411.9 (16.8)                  | 422.3 (26.1)             |
| Mean QTcF (SD), Month 6  | 427.6 (22.1)         | -              | 427.6 (22.1)        | 427.5 (22.3)                  | 427.6 (22.2)             |
| Mean maximum QTcF (SD), all participants | 434.4 (24.5)         | 416.7 (27.3)   | 434.8 (24.4)        | 437.1 (31.0)                  | 434.0 (23.5)             |
| Receiving MFX prior to BDQ initiation, n | 117                  | 2              | 115                 | 13                             | 104                      |
| Stopped MFX prior to initiating BDQ, n (%) | 96 (82)              | 2 (100)        | 94 (82)             | 11 (85)                       | 85 (82)                  |
| Median duration of MFX washout prior to baseline ECG, days (IQR) | 1 (0-2)              | 1 (1-69)       | 1 (0-2)             | 1 (0-2)                       | 1 (0-2)                  |
| Mean (SD) QTcF increase from baseline to Month 6 | 23.7 (22.7)          | -              | 23.7 (22.7)         | 26.4 (22.2)                   | 23.4 (22.9)              |
| Number of participants with mean QTcF increase >60 ms, n (%) | 8 (4.4)              | 0 (0)          | 8 (4.5)             | 2 (8.7)                       | 6 (3.8)                  |
| Number of participants with mean QTcF increase >30 ms, n (%) | 61 (33.3)            | 1 (25)         | 60 (33.5)           | 6 (26.1)                      | 55 (34.4)                |
| Number of participants with QTcF >500 ms, n (%) | 4 (2)                | 0 (0)          | 4 (2.2)             | 2 (8.7)                       | 2 (1.3)                  |
| Number of participants with QTcF >450 ms, n (%) | 42 (23)              | 0 (0)          | 42 (23.5)           | 5 (21.7)                      | 37 (23.1)                |

SD=standard deviation; IQR=interquartile range; MFX=moxifloxacin; BDQ=bedaquiline; CFZ=clofazimine; LPV/r=lopinavir-ritonavir
Table 4: Multivariable logistic regression analysis of potential predictors of QTcF prolongation

| Variable                        | QTcF >450 ms |          | ΔQTcF>30 ms |          |
|---------------------------------|--------------|----------|-------------|----------|
|                                 | aOR | 95% CI   | aOR | 95% CI   |
| Male sex                        | 1.3 | 0.6-2.7  | 1.2 | 0.6-2.2  |
| Black race                      | 3.2 | 0.97-10.41 | 1.5 | 0.7-3.2  |
| Age                             |     |          |     |          |
| 21-30 years^a (n=45)            | Ref |          | Ref |          |
| 31-40 years (n=72)              | 3.4 | 1.0-10.9 | 1.6 | 0.8-3.5  |
| 41-50 years (n=43)              | 3.8 | 1.1-13.9 | 1.6 | 0.7-3.9  |
| >50 years (n=23)                | 8.3 | 2.1-32.8 | 1.9 | 0.7-5.3  |
| Weight (per kg increase)        | 0.99| 0.95-1.02| 0.98| 0.96-1.01|
| Concurrent lopinavir-ritonavir  | 0.82| 0.3-2.6  | 0.86| 0.32-1.81|
| Concurrent moxifloxacin^b       | 1.4 | 0.5-3.6  | 0.89| 0.3-2.2  |

^Youngest study participant was 21 years old
^Includes participants who received moxifloxacin concurrently with bedaquiline for at least one day, or who discontinued moxifloxacin <24 hours prior to initiating bedaquiline. CI=confidence interval; Bold denotes statistical significance.
Table 5: Participants having at least one *M. tuberculosis* isolate with a bedaquiline MIC>1 mcg/mL.

| Participant ID | Visit resistant isolate obtained | MIC to BDQ | \(Rv0678\) | Cavitation on baseline chest radiograph | Prior CFZ Treatment outcome |
|----------------|----------------------------------|------------|------------|----------------------------------------|-----------------------------|
| **Resistance at baseline** |                                |            |            |                                        |                             |
| A              | Baseline                         | 4          | 144_insC   | -                                      | No                          | Cure                        |
| B              | Baseline                         | 4          | 144_insC   | Yes                                    | No                          | Interruption/LTFU            |
| C              | Baseline                         | 4          | T437C      | -                                      | No                          | Cure                        |
| D              | Baseline                         | 2          | Wt         | -                                      | No                          | Interruption/LTFU            |
| E              | Baseline                         | 8          | 139_142_insGATC | Yes                                    | No                          | Cure                        |
| F              | Baseline                         | 4          | 138_insG   | Yes                                    | Yes (unknown duration)     | Treatment completion        |
| G              | Baseline                         | 4          | A202C      | Yes                                    | No                          | Died                        |
| **Emergent resistance on therapy** |                                |            |            |                                        |                             |
| H              | Month 10                         | 8          | 349_insC   | Yes                                    | No                          | Cure                        |
| I              | Month 17                         | 4          | A202G      | Yes                                    | No                          | Death (after interruption)  |
| J              | Week 6                           | 2          | Wt         | Yes                                    | Yes (unknown duration)     | Interruption/LTFU            |
| **Resistance on therapy but no available baseline isolate** |                                |            |            |                                        |                             |
| K              | Month 6                          | 4          | 141_insT/139_insG | -                                      | No                          | Died                        |
| L              | Month 1                          | 4          | 144_insG   | -                                      | No                          | Failure                     |
| M              | Month 1                          | 4          | 198_insG   | Yes                                    | No                          | Cure                        |

\(\sim\)=unavailable chest radiograph; MIC=minimum inhibitory concentration; BDQ=bedaquiline; CFZ=clofazimine. Wt=wild type; LTFU=lost to follow-up.
FIGURE LEGENDS

Figure 1: Enrollment flowchart

Figure 2: Kaplan-Meier plot of time to sputum culture conversion among participants with positive culture at time of bedaquiline initiation (n=158), stratified by HIV status.

Figure 3: QTcF intervals from baseline to month 6 overall and stratified by receipt of lopinavir-ritonavir. Numbers below plots represent the number of available paired ECGs at each visit.
Figure 2

Proportion achieving culture conversion

Time (Days)

0.0  0.2  0.4  0.6  0.8  1.0

0  50  100  150  200  250  300  350  400  450  500  550  600  650  700

HIV-negative  HIV-positive
