

## Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis

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### SUMMARY

**BACKGROUND:** South Africa has a large burden of extensively drug-resistant tuberculosis (XDR-TB); only 15% of XDR-TB patients have successful outcomes.

**OBJECTIVE:** To describe the safety and effectiveness of bedaquiline (BDQ) in the South African BDQ Clinical Access Programme.

**DESIGN:** An interim cohort analysis.

**RESULTS:** Of the first 91 patients enrolled between March 2013 and July 2014 (with follow-up until August 2014), 54 (59%) were human immunodeficiency virus (HIV) infected. The median CD4 count was 239 cells/ $\mu$ l, and all patients were on antiretroviral therapy (ART) at initiation of BDQ; 33 had XDR-TB, 41 were pre-XDR-TB with fluoroquinolone resistance and 17 were pre-XDR-TB with resistance to an injectable. Of the 91

patients, 58 (64%) had completed 24 weeks of BDQ, 28 were still on BDQ, 3 were lost to follow-up, 1 had died and 1 had BDQ withdrawn following atrial fibrillation. Of the 63 patients with 6 months follow-up, 48 (76%) had either culture-converted or remained culture-negative after initiation of BDQ. QTcF was monitored monthly and exceeded 500 ms in three participants; this resolved in all three.

**CONCLUSION:** Interim safety and culture conversion outcomes for patients accessing BDQ in South Africa, including HIV-infected patients on ART and patients with pre-XDR- and XDR-TB, suggest that BDQ may be both efficacious and safe.

**KEY WORDS:** extensively drug-resistant tuberculosis; South Africa; compassionate access; adverse events

BETWEEN 2009 AND 2013, the number of patients being treated for drug-susceptible tuberculosis (TB) in South Africa decreased from 406 082 to 328 896.<sup>1</sup> During the same period, the number of patients who initiated treatment for either rifampicin-resistant (RMP<sup>R</sup>) or multidrug-resistant TB (MDR-TB, defined as TB resistant to both RMP and isoniazid [INH]), more than doubled, from 4143 to 10 179.<sup>1</sup> Treatment success rates for MDR-TB in South Africa remain low: 45% of the 2011 cohort was cured or completed the full 18–24 month course of treatment.<sup>1</sup> South Africa also has a large burden of extensively drug-resistant TB (XDR-TB, defined as MDR-TB with additional resistance to a fluoroquinolone and a second-line injectable drug). XDR-TB treatment outcomes are poor:<sup>2</sup> only 15% of the 2011 cohort of XDR-TB patients were reported to have a successful treatment outcome.<sup>1</sup> Several factors are linked to poor treatment success rates for RMP<sup>R</sup> TB, including the use of more toxic drugs with poorer

efficacy than those used for drug-susceptible TB. In addition, the treatment duration is a minimum of 18 months compared to the 6-month regimen for drug-susceptible TB.

Bedaquiline (BDQ), the first new anti-tuberculosis drug to have been developed in almost five decades, has a novel mechanism of action.<sup>3</sup> It was registered in the United States in late 2012 for MDR-TB based on 72-week data from a Phase II trial.<sup>4</sup> In the Phase IIIb trial, treatment with 24 weeks of BDQ in addition to a background regimen resulted in increased culture conversion at 24 weeks (79% vs. 58%) and an increased rate of cure at 120 weeks (62% vs. 44%) compared to the background regimen with placebo.<sup>5</sup> However, clinical information on the use of BDQ in patients with human immunodeficiency virus (HIV) infection and concomitant antiretroviral treatment (ART) is limited.<sup>6</sup> This information is urgently needed for the roll-out of BDQ in South Africa,

where an estimated 65% of TB cases are HIV-infected.<sup>1</sup>

The South African Medicine Control Council (MCC; Department of Health, Pretoria, South Africa) approved the BDQ Clinical Access Programme (BCAP) to treat XDR- or pre-XDR-TB patients (defined as MDR-TB with additional resistance to either a fluoroquinolone or a second-line injectable) in December 2012 to allow patients safe access to BDQ prior to registration.<sup>7</sup> Sirturo, from Janssen Pharmaceutica (Beerse, Belgium), was subsequently registered in South Africa in October 2014. To inform the roll-out of BDQ, especially among HIV-infected patients on ART, we present an interim cohort analysis of patients treated under BCAP.

## METHODS

### *Ethics approval*

As part of the MCC process, human research ethics committee approval was secured from the University of Witwatersrand (Johannesburg), the University of Cape Town (Cape Town) and Pharma-Ethics (Centurion, South Africa; www.pharma-ethics.co.za).

### *Inclusion and exclusion criteria*

Eligible patients had to have a laboratory-confirmed diagnosis of pulmonary XDR- or pre-XDR-TB. Other criteria included age  $\geq 18$  years, negative pregnancy test and no history of habitual anti-tuberculosis treatment default. Patients with unstable medical conditions, known allergy or intolerance to BDQ or its excipients were excluded. Patients with any of the following were also excluded: serum creatinine grade  $\geq 1$  ( $>1.0 \times$  upper limit of normal [ULN]), lipase  $>1.5 \times$  ULN, aspartate aminotransferase (AST) or alanine aminotransferase (ALT)  $\geq 2.0 \times$  ULN, total bilirubin  $>1.0 \times$  ULN. Patients with a baseline QT interval corrected using the Fridericia formula (QTcF) of  $>450$  ms, clinically significant electrocardiography abnormality at screening or a family history of prolonged QT syndrome were excluded. Patients not eligible for BCAP received individualised standard of care treatment regimens and were excluded from the analysis.

### *HIV and ART regimens*

As per national HIV treatment guidelines, all HIV-infected TB patients are eligible for ART initiation regardless of baseline CD4 count.<sup>8</sup> The standard first-line ART regimen in South Africa consists of tenofovir (TDF), emtricitabine (FTC) and efavirenz (EFV).<sup>8</sup> Patients for whom a first-line regimen fails may be switched to a second-line regimen containing lopinavir/ritonavir (LPV/r), with two appropriate nucleoside reverse transcriptase inhibitors.<sup>8</sup> However, EFV co-administration with BDQ may reduce BDQ exposure and efficacy,<sup>6,9</sup> and is not recom-

mended by the manufacturer. BCAP patients on EFV were therefore switched from EFV to either nevirapine (NVP) or LPV/r.

### *Pre-XDR-/XDR-TB treatment and monitoring*

BDQ was prescribed at 400 mg once daily for 2 weeks, followed by 200 mg three times a week for 22 weeks, alongside an individualised, optimised background regimen (OBR) that included at least three second-line drugs to which the patient had proven or likely susceptibility. The OBR included a combination of some or all of the following drugs: linezolid, clofazimine (CFZ), pyrazinamide, ethambutol, high-dose INH, p-aminosalicylic acid, capreomycin, kanamycin, levofloxacin (LVX), ethionamide or terizidone, as per the South African National Tuberculosis Control Programme (NTP) guidelines<sup>10</sup> and according to availability. LVX was used instead of moxifloxacin (MFX), as it has less effect on the QT interval.<sup>11</sup> According to the interim World Health Organization (WHO) recommendations,<sup>12</sup> QTcF intervals were measured at baseline, twice in the first month and then monthly while on BDQ; liver function tests were performed at regular intervals. Severe adverse events (SAEs) were reported according to MCC requirements. Sputum cultures were taken monthly. Time to sputum culture conversion, defined as two negative cultures taken 1 month apart, was reported from the date of first negative culture.

### *Selection process*

Pre-XDR-/XDR-TB patients at five approved sites across South Africa were assessed by site investigators. The patients were presented to a National Clinical Advisory Committee consisting of clinicians with experience or expertise in RMP<sup>R</sup> TB. The Advisory Committee, Janssen Pharmaceutica and the MCC in turn approved the BDQ treatment and the OBR. The process typically lasted 2–4 weeks, during which time the OBR was initiated and treatment for other comorbid conditions optimised.

### *Analysis and reporting*

Culture conversion by resistance pattern and HIV status was analysed using Kaplan-Meier estimates; differences in time to culture conversion were analysed using Cox proportional hazards methods. Mean and median QTcF measurements and incremental changes in QTcF measurements were analysed using logistic regression and quantile regression across all patients and according to sex, HIV status and age  $\geq 50$  years. Statistical analysis was performed using Stata, version 13 (StataCorp, College Station, TX, USA). We report results according to the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for observational cohort studies.<sup>13</sup>

**Table** Patient enrolment characteristics and drug regimens

Characteristic	n (%)
All patients	91 (100)
Age, years	
Median [IQR]	35 [26–42]
≥ 50 years	12 (13.2)
Sex	
Male	55 (60.4)
Female	36 (39.6)
Drug resistance	
XDR-TB	34 (37.4)
Pre-XDR-TB (aminoglycosides)	16 (55.0)
Pre-XDR-TB (fluoroquinolones)	41 (45.1)
HIV-infected	54 (59.3)
CD4 count, cells/mm <sup>3</sup> , median [IQR]	249.5 [130–370]
CD4 ≤ 100	8 (14.8)
On ART	54 (100)
Viral load lower than detectable limit	26 (38.9)
ART regimen (n = 54)	
TDF or AZT + 3TC + NVP	30 (55.6)
TDF or AZT + 3TC + LPV/r	9 (16.7)
D4T + 3TC + NVP	6 (11.1)
D4T + 3TC + LPV/r	9 (16.7)
Optimised background regimen including:	
Levofloxacin	76 (83.5)
Linezolid	64 (70.3)
Clofazimine	68 (74.7)

IQR = interquartile range; XDR-TB = extensively drug-resistant tuberculosis; HIV = human immunodeficiency virus; ART = antiretroviral treatment; TDF = tenofovir; AZT = zidovudine; 3TC = lamivudine; NVP = nevirapine; LPV/r = lopinavir/ritonavir; D4T = stavudine.

**RESULTS**

*Patient characteristics and enrolment*

The first 91 patients enrolled into the BCAP from March 2013 to July 2014 were included in the interim

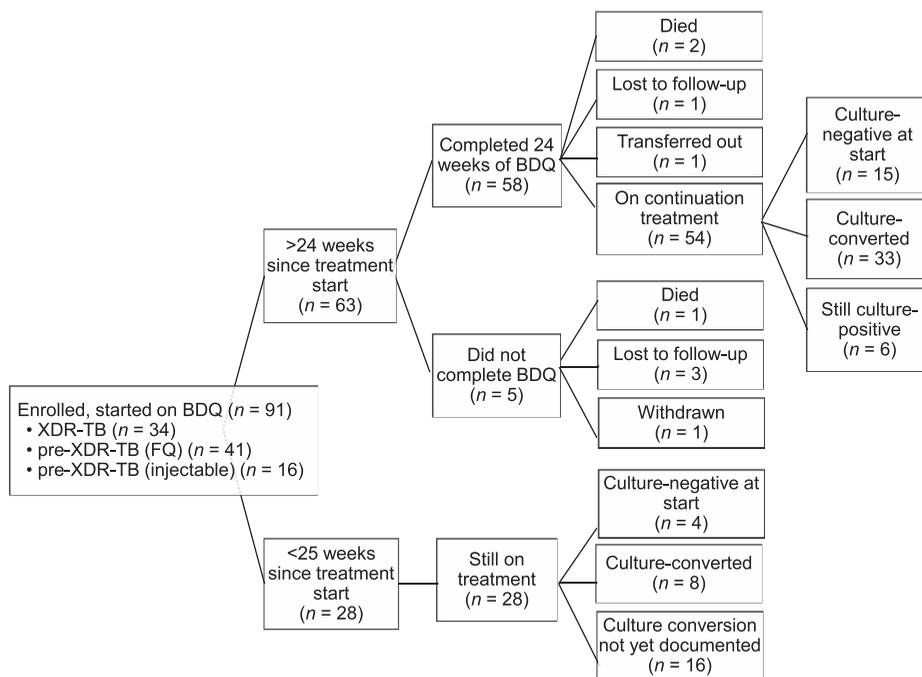
analysis and followed until the end of August 2014, representing more than 700 patient-months of follow-up. Patient baseline characteristics are presented in the Table. Of the initial cohort, 55 (60%) were male, and the median age at initiation was 35 years (interquartile range [IQR] 26–42). Fifty-four (59%) patients were HIV-infected; all were on ART at BDQ initiation, with a median baseline CD4 of 249 cells/μl (IQR 130–270). Any patients on EFV were switched to NVP or LPV/r before initiation of BDQ. At BDQ initiation, respectively 36 (67%) and 18 (33%) patients were on an ART regimen inclusive of NVP or LPV/r.

Thirty-four patients had confirmed XDR-TB, 41 had pre-XDR-TB with resistance to a fluoroquinolone and 16 had pre-XDR-TB with resistance to a second-line injectable. The prescribed OBR included CFZ in 68, LVX in 76 and linezolid in 63 patients.

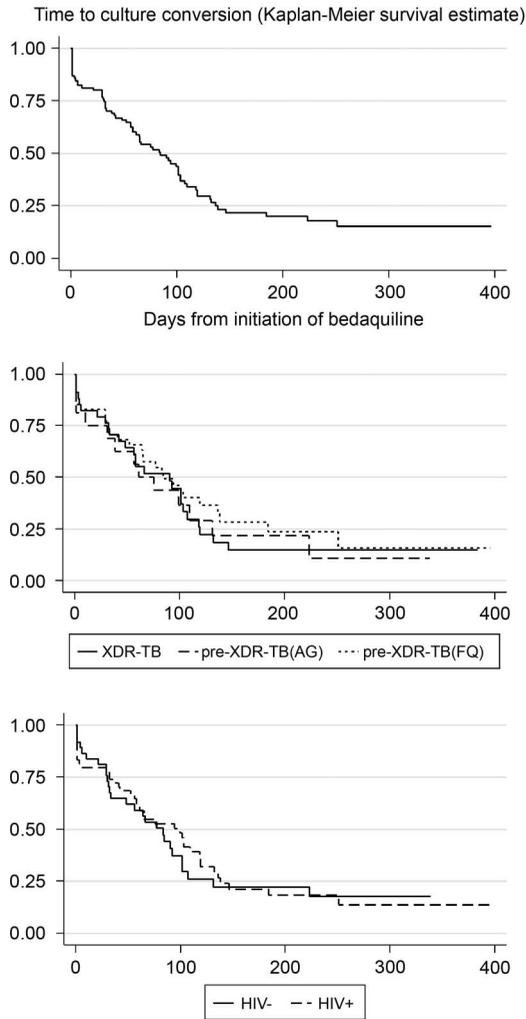
*Culture conversion and interim results*

As of the end of August 2014, 58/91 (64%) patients had completed a full course of 24 weeks of BDQ, and 28 were still on BDQ treatment. Three patients were lost to follow-up within the first 6 months, one patient died while on BDQ and one patient had BDQ withdrawn following an episode of atrial fibrillation (OBR was continued). Of the 58 patients who completed the full course of BDQ, 54 were still on continuation phase treatment. Of the remaining four, one transferred out, one was lost to follow-up and two died following completion of BDQ.

Figure 1 shows the culture conversion and interim results of patients included in this analysis. As BDQ



**Figure 1** Interim outcomes for XDR- and pre-XDR-TB patients enrolled in the national BDQ Clinical Access Programme. XDR-TB = extensively drug-resistant tuberculosis; BDQ = bedaquiline; FQ = fluoroquinolone.



**Figure 2** Time to culture conversion (Kaplan-Meier survival estimates). XDR-TB = extensively drug-resistant tuberculosis; AG = aminoglycoside; FQ = fluoroquinolone; HIV = human immunodeficiency virus.

initiation followed initiation of the OBR, 16/58 patients who completed 24 weeks of BDQ had negative cultures before the addition of BDQ to the OBR. Among the 42 patients (72% of 58) who were culture-positive when starting BDQ, culture conversion was rapid (median 45 days, IQR 26–66.5). Kaplan Meier curves indicating proportion of the cohort ( $n=42$ ) culture converting by days since BDQ initiation according to HIV status and pre-XDR or XDR-TB drug resistance are presented in Figure 2. Time to culture conversion was not statistically significantly affected by HIV infection status or drug resistance patterns (Cox proportional hazard univariate analysis, data not shown). Of the 39 patients who completed 24 weeks of BDQ and who had positive cultures at initiation of BDQ, 6 (15%) had not culture converted at the time of the analysis. In total, 48/63 (76%) patients with 6 months of follow-up had either culture converted or remained culture-negative at 6 months after initiation of BDQ.

#### QT interval monitoring and reported severe adverse events

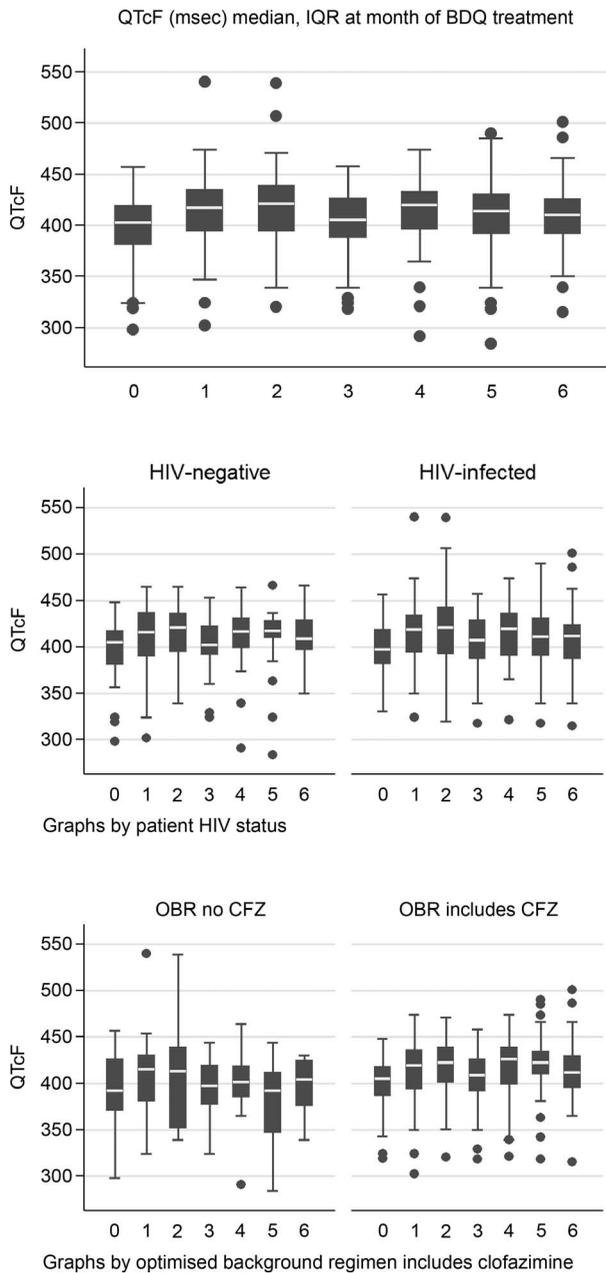
One patient developed atrial fibrillation on BDQ and was taken off the drug, but continued treatment with the OBR; the patient subsequently transferred out and died after 5 months of unknown causes. At initiation of BDQ, the median QTcF was 403 ms (IQR 381–419); after 24 weeks on treatment ( $n=51$ ), median QTcF was 410 ms (IQR 392–425.5). Of the 24 patients with a maximal QTcF increase of  $>50$  ms over 6 months, the QTcF exceeded 500 ms, probably or possibly due to BDQ, in three. BDQ was temporarily withdrawn in one patient; in all three the QTcF decreased to below 500 ms and there were no clinical sequelae. Figures 3 and 4 display box plots of the median and IQR of QTcF and monthly increments in QTcF, respectively, for all patients and disaggregated by HIV status and inclusion of CFZ in the OBR; the lack of an increasing trend in QTcF can be seen in the plots. Quantile and logistic regression of median QTc and incremental QTc indicated no significant increase across all patients and by HIV status, age  $\geq 50$  years, and sex with months of BDQ treatment (data not shown). In quantile regression, CFZ was significantly associated with an 18.4 ms increase in QTcF; however, patients on CFZ were not more likely to experience a QTcF increase of  $>50$  ms ( $\chi^2$  test of proportions,  $P=0.630$ ).

There were also three reports of severe psychosis, mood disorder and delusion; all three patients were receiving terizidone; none of these events were attributed to BDQ. One of the three patients committed suicide following completion of 6 months of BDQ. The third death in the cohort was reported as being from haemoptysis due to post-TB lung damage 4 months after completing BDQ. No hepatotoxicity was reported as an SAE, although most HIV-infected patients were changed to an ART regimen including NVP. Furthermore, no instances of severe renal dysfunction were reported as SAEs, including no reports for the 26 patients who were on an ART regimen including TDF. In total, 9/91 patients experienced 20 reported SAEs during the follow-up period.

## DISCUSSION

These interim results from the BCAP represent one of the largest cohorts reported, particularly among patients with TB-HIV co-infection, and increase our understanding of the concomitant use of BDQ and ART.

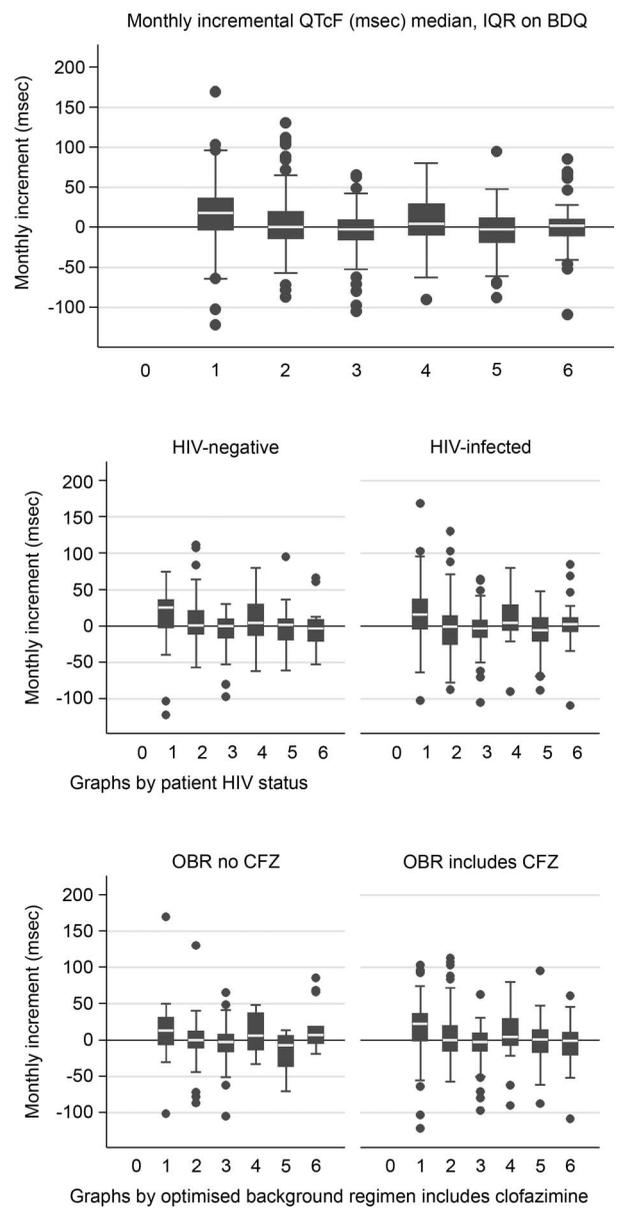
The high rate of culture conversion and the low mortality rate are promising early findings in this highly resistant group of TB patients, 59% of whom were HIV-infected. The 76% of patients with sputum culture conversion or persistently negative cultures



**Figure 3** Median QTcF (in ms) and IQR at month of BDQ treatment. HIV = human immunodeficiency virus; OBR = optimised background regimen; CFZ = clofazimine; IQR = interquartile range; BDQ = bedaquiline.

observed at 6 months is especially striking, given that in the 2012 South African NTP MDR-TB cohort the culture conversion rate was only 56% at 6 months. There were only three deaths—none of which were reported as being probably or possibly related to BDQ—among the 63 BCAP patients who reached at least 6 months of follow-up (5%), while 11% of the 2012 South African NTP MDR-TB cohort died within 6 months.

Median increases in the QTc interval were small or non-existent in the group as a whole, and resolved for the three patients whose QTcF exceeded 500 ms.



**Figure 4** Monthly median incremental QTcF (in ms) and IQR on BDQ. HIV = human immunodeficiency virus; OBR = optimised background regimen; CFZ = clofazimine; IQR = interquartile range; BDQ = bedaquiline.

However, the baseline QTc interval was measured while most patients were on MFX, which increases the QTc by 10–15 ms. Follow-up QTcF interval measurements were performed after patients on MFX were switched to LVX, which causes a minimal QTc increase (<5 ms). The fact that the QTc interval did not change significantly from baseline may be because BDQ and MFX both increase the QTc interval to a similar extent.

No severe hepatotoxicity or renal dysfunction was reported during the study period, including for HIV-infected patients on ART regimens containing NVP and TDF. The safety and efficacy of BDQ in the BCAP

is similar to that reported in other early and compassionate access cohorts.<sup>14,15</sup>

### Limitations

This study is an observational prospective cohort of a clinical access programme and was not designed to show whether differences to the South African NTP standard regimens are significant. Other changes since the 2012 cohort reported here may have improved the overall culture conversion rate for South Africa, such as rapid diagnosis of RMP<sup>R</sup> TB using Xpert<sup>®</sup> MTB/RIF (Cepheid, Sunnyvale, CA, USA) and the Geno-Type<sup>®</sup> MTBDR (Hain Lifescience, Nehren, Germany) polymerase chain reaction test, which has reduced the time from presumption of TB to initiation of appropriate treatment in drug-resistant TB patients.<sup>16,17</sup> Furthermore, the OBR for many patients in the BCAP included linezolid, another drug that has shown improved culture conversion rates for XDR-TB.<sup>18,19</sup> These early results are encouraging for the South African NTP, which has targeted an MDR-TB success rate of 60% by 2016.

The exclusion criteria for patients accessing BDQ were strict, potentially introducing selection bias, and the toxicity monitoring was intense, which limits generalisability to programmatic roll-out outside of a clinical access programme. However, the implementing sites are in the South African public sector, and lessons learned from experiences at these sites may inform and influence monitoring requirements for NTP BDQ patients. This BCAP was unique in that HIV-infected patients were included regardless of ART status. Ours is the largest reported cohort with concomitant BDQ and ART, which can inform policy on the use of BDQ in patients with TB-HIV co-infection.

A final limitation is that these are interim results and the period of follow-up is relatively short for pre-XDR- and XDR-TB treatment. In the Phase IIb BDQ trial, there were 10 deaths in the BDQ arm and only two in the placebo arm, with most occurring after completion of the 24 weeks of BDQ.<sup>5</sup> Two deaths occurred in the BCAP following completion of BDQ; further monitoring is therefore required and planned. Furthermore, we cannot yet comment on treatment outcomes at 2 years and the risk of relapse after treatment completion. However, at 120 weeks the overall cure rate in the BDQ arm of the Phase IIb trial was significantly higher (62% vs. 44%);<sup>5</sup> at the end of 2014, BCAP clinicians and patients celebrated the first cure in the programme—a BCAP patient who completed BDQ treatment, completed the OBR and remained culture-negative.

### CONCLUSION

The interim outcomes for the first 91 pre-XDR-/XDR-TB patients enrolled in the BDQ clinical access

programme in South Africa show high rates of early sputum culture conversion. Of the 91 patients, 54 were HIV-infected and all were on ART at BDQ initiation. In this setting, HIV infection did not affect the time to culture conversion or risk of non-conversion. QTc prolongation was modest, despite concomitant use of CFZ in most patients. These data support the expansion of the programme to allow for wider access to BDQ for patients with RMP<sup>R</sup> TB and are being used to inform the inclusion of BDQ in the South African NTP.

### Acknowledgements

The authors are grateful to the staff and patients at all the BCAP sites included in this interim analysis and to the clinicians, staff and patients at all the newly participating BCAP sites.

BDQ under BCAP was provided by Janssen Pharmaceutical. Janssen also provided travel support to BCAP investigators to attend the 45<sup>th</sup> Union World Conference on Lung Health in Barcelona, Spain. Janssen did not have any role in the collection, analysis and interpretation of data; in the writing of the report; or the decision to submit the paper for publication.

Declaration of interests: NN, DM and YP are officials of the South African Department of Health; their responsibilities include recommending guidelines for the treatment of drug-resistant TB and approving procurement of medications for use by the South African NTP. The remaining authors have no conflicts of interest to declare.

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## RESUME

**CONTEXTE :** L'Afrique du Sud est lourdement frappée par des cas de tuberculose ultrarésistante (TB-XDR) ; seulement 15% des patients TB-XDR guérissent.

**OBJECTIF :** Décrire la sécurité et l'efficacité de la bedaquiline (BDQ) dans le cadre du programme sud-africain d'accès clinique à la BDQ.

**SCHEMA :** Une analyse de cohorte.

**RÉSULTATS :** Des 91 premiers patients enrôlés entre mars 2013 et juillet 2014 (avec un suivi jusqu'en août 2014), 54 (59%) étaient infectés par le virus de l'immunodéficience humaine (VIH), le compte de CD4 était à 239 cellules/ $\mu$ l et tous étaient sous traitement antirétroviral (ART) lors de la mise en route de la BDQ ; 33 avaient une TB-XDR, 41 avaient une TB pré-XDR résistante à la fluoroquinolone et 17 une TB pré-XDR résistante aux injectables. Sur 91 patients, 58 (64%) ont

achevé les 24 semaines de BDQ ; 28 sont toujours sous BDQ, 3 patients ont été perdus de vue, 1 est décédé et enfin, une fibrillation atriale a obligé l'arrêt de la BDQ chez 1 patient. Des 63 patients suivis pendant 6 mois, 48 (76%) ont soit eu une conversion de culture ou leur culture est restée négative après la mise en route de la BDQ. Le QTcF a été suivi chaque mois et a excédé 500 ms chez trois participants, mais il est revenu à la normale chez tous ces patients.

**CONCLUSIONS :** Les résultats en termes de sécurité et de conversion de culture pour les patients, notamment ceux VIH positifs sous ART, ceux avec pré-TB-XDR et TB-XDR, ayant eu accès à la BDQ en Afrique du Sud, suggèrent que la BDQ pourrait être à la fois efficace et sûre.

## RESUMEN

**MARCO DE REFERENCIA:** Suráfrica soporta una considerable carga de morbilidad por tuberculosis extremadamente drogoresistente (TB-XDR); solo 15% de los pacientes con diagnóstico de TB-XDR alcanza desenlaces favorables.

**OBJETIVO:** Describir la seguridad toxicológica y la eficacia de la bedaquilina (BDQ) en el marco del Programa de Acceso Clínico a la Bedaquilina en Suráfrica.

**MÉTODO:** Fue este un análisis provisional de cohortes.

**RESULTADOS:** De los primeros 91 pacientes que se incorporaron al estudio de marzo del 2013 a julio del 2014 (con un seguimiento hasta agosto del 2014), 54 (59%) padecían infección por el virus de la inmunodeficiencia humana (VIH) y presentaban una mediana del recuento de linfocitos CD4 de 239 células/ $\mu$ l, y todos recibían tratamiento antirretrovírico (ART) al comenzar la BDQ. Treinta y tres pacientes tenían un diagnóstico de TB-XDR, 41 pacientes de TB pre-XDR

por resistencia a la fluoroquinolona y 17 de TB pre-XDR por resistencia a un medicamento inyectable de segunda línea. De los 91 pacientes, 58 (64%) completaron 24 semanas de BDQ; 28 seguían recibiendo al final del análisis, 3 pacientes se perdieron durante el seguimiento, 1 paciente falleció y se interrumpió la BDQ en 1 paciente por fibrilación auricular. De los 63 pacientes con un seguimiento de 6 meses, 48 (76%) habían convertido el cultivo o continuaban con un cultivo negativo después de haber iniciado la BDQ. Se vigiló cada mes el intervalo QTcF y se observó que en tres participantes excedía 500 ms, pero se resolvió espontáneamente en todos los casos.

**CONCLUSIÓN:** El análisis provisional de la seguridad toxicológica y la conversión de los cultivos de los pacientes con TB-XDR o pre-XDR, incluidos los pacientes infectados por el VIH que seguían un ART, y que recibieron BDQ en Suráfrica, indica que este medicamento puede ser eficaz y también seguro.