Early access to bedaquiline for extensively drug-resistant (XDR) and pre-XDR tuberculosis

To the Editor:

Globally in 2016, 19% of previously treated tuberculosis (TB) cases and 4.1% of newly diagnosed cases were reported to be resistant to isoniazid and rifampicin (multidrug-resistant (MDR)-TB) or rifampicin alone (rifampicin-resistant TB) [1]. In 2017, 8.5% of MDR-TB cases were caused by extensively drug-resistant (XDR)-TB [1], defined as MDR-TB with additional resistance to a fluoroquinolone (FQ) and a second-line injectable drug (SLI) (amikacin, kanamycin or capreomycin). TB drug resistance, especially XDR-TB, is associated with poorer treatment outcomes [1–3].

Based on phase 2 clinical data, bedaquiline (TMC207), a diarylquinoline antimycobacterial, was granted accelerated or conditional approval in various countries for MDR-TB [4, 5]. Compassionate-use and expanded-access programmes have made bedaquiline available in 95 countries worldwide [6, 7]. "Real-world" data have shown bedaquiline achieves high culture conversion and treatment success rates in patients with MDR-TB and XDR-TB, with a low proportion of adverse events (AEs) [8–13]. In a large-scale study, all-cause mortality was lower in patients treated with bedaquiline (12.6%) than in those who received alternative treatments (24.8%) [14].

The primary objective of study TMC207TBC3001 (www.clinicaltrials.gov identifier number NCT01464762) was to provide early access to bedaquiline for adult patients (⩾18 years of age) with confirmed sputum smear- or culture-positive TB and drug susceptibility testing results, performed locally as per the local standard of care, demonstrating pulmonary pre-XDR-TB (MDR-TB with additional FQ or SLI resistance) or XDR-TB. The secondary objective was to evaluate safety, tolerability and microbiological status. Enrolled patients had limited to no treatment options and were unable/ineligible to participate in any other bedaquiline study. Results of the 120-week final analysis are presented here.

Patients received bedaquiline for 24 weeks (400 mg orally once daily for 2 weeks and 200 mg orally three times weekly for 22 weeks) with an investigator-selected background regimen (BR) in accordance with national TB programme guidelines. The BR was chosen using three or more drugs to which the TB isolate was known (based on drug-susceptibility testing from within the previous 6 months) or likely (based on known treatment history) to be susceptible, and administered under supervision using the directly observed treatment short-course for MDR-TB (DOTS-Plus). After completing the 24-week bedaquiline plus BR treatment, participants continued to receive BR only for ⩽96 weeks. Clinic visits were at 2, 4, 12, 24, 28, 48, 72, 96 and 120 weeks. Safety, tolerability and microbiological status were assessed throughout. Patients who prematurely withdrew from the study were rigorously followed up to verify survival, unless consent was withdrawn.

The study protocol was reviewed by an independent ethics committee or institutional review board. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent.

Sample size calculation was not performed and no statistical hypotheses were tested. Unless stated otherwise, safety and efficacy analyses were performed on the intent-to-treat (ITT) population, which included all patients who had one or more intake of bedaquiline, regardless of their protocol compliance.

Cite this article as: Vasilyeva I, Mariandyshev A, Kazennyy B, *et al*. Early access to bedaquiline for extensively drug-resistant (XDR) and pre-XDR tuberculosis. *Eur Respir J* 2019; 54: 1802208 [https://doi.org/10.1183/13993003.02208-2018].

TABLE 1 Patient characteristics, disposition, and safety and efficacy analysis outcomes during 120 weeks

Patient characteristics	**ITT population (N=57)**
Age at screening years	28.0 (18–61)
Sex	
Female	33 (57.9%)
Male	24 (42.1%)
Previous use of second-line drugs[#]	
No	4 (7.0%)
Yes	53 (93.0%)
Extent of resistance of *M. tuberculosis* strain at screening	
Pre-XDR	27 (47.4%)
FQ-resistant	14 (24.6%)
SLI-resistant	13 (22.8%)
XDR	30 (52.6%)

Resistance to other TB therapies at baseline	**n with observation/N tested**
Cycloserine	3/27
Ethambutol	44/55
Ethionamide	31/41
Linezolid	0/5
PAS	4/30
Prothionamide	1/2
Pyrazinamide	20/22

Discontinuations	**ITT population (N=57)**
Total discontinuations	14 (24.6%)
Discontinuations due to AEs	5 (8.8%)
Deaths	3 (5.3%)
Discontinued bedaquiline	2[¶] (3.5%)
Lost to follow-up	2 (3.5%)
Noncompliance	1 (1.8%)
Withdrawal of consent	2 (3.5%)
Patient moved city/country	4 (7.0%)

Deaths	**Case 1**	**Case 2**	**Case 3**
Infection subtype	Pre-XDR-TB (FQ resistant)	Pre-XDR-TB (SLI resistant)	XDR-TB
Considered related to bedaquiline or BR	No	No	No
Time since last bedaquiline intake days	441	442	411
QTcF at week 24 ms	414	436	310
Sputum culture conversion	No	No	Yes
Treatment phase	Post-investigational[+]	Post-investigational[+]	Follow-up
Considered TB-related	Yes[§]	Yes[§]	No[f]

Safety analysis	
Treatment duration weeks	97.7 (2.1–131.1)
Any AE regardless of cause or severity	50 (87.7%)
Most common (>15%) AEs regardless of cause or severity	
AST increased	28 (49.1%)
ALT increased	15 (26.3%)
Eosinophilia	13[##] (22.8%)
Any AE leading to discontinuation of bedaquiline	2[##] (3.5%)
Any AE at least possibly related to bedaquiline	6 (10.5%)
Most common AEs (>2%) at least possibly related to bedaquiline[¶¶]	
AST increased	4 (7.0%)
ALT increased	2 (3.5%)
ECG QT interval prolonged	2 (3.5%)
Any serious AE[++]	8[##] (14.0%)
Any grade 3 or 4 AE[§§]	15[##] (26.3%)
Most common (>5%) grade 3 or 4 AEs	

Continued

TABLE 1 Continued

Safety analysis	
ALT increased, grade 3	5[##] (8.8%)
AST increased, grade 3	4[##] (7.0%)
Sputum culture conversion over time	**n with observation/N tested**
Week 24	31/36 (86.1%)
Week 72	17/20 (85.0%)
Week 120	6/6 (100%)
Last visit	39/43 (90.7%)

Data are presented as median (range) unless otherwise stated. ITT: intent-to-treat; XDR: extensively drug-resistant; FQ: fluoroquinolone; SLI: second-line injectable; TB: tuberculosis; PAS: para-aminosalicylic acid; AE: adverse event; BR: background regimen; QTcF: QT interval corrected for heart rate using Fridericia's method; AST: aspartate aminotransferase; ALT: alanine aminotransferase. [#]: second-line drugs are all anti-TB drugs excluding rifampicin, isoniazid, pyrazinamide, streptomycin and ethambutol. [¶]: discontinued bedaquiline due to toxic nephropathy and depression considered not related to bedaquiline by the investigator. The BR was permanently withdrawn due to depression and temporarily withdrawn due to toxic nephropathy. Depression and toxic nephropathy were considered possibly and very likely to be related to the BR, respectively, by the investigator. [+]: 96-week post-bedaquiline+BR treatment phase during which patients received BR alone. [§]: pulmonary haemorrhage. [f]: acute myocardial infarction. [##]: none was considered at least possibly related to bedaquiline by the investigator. [¶¶]: each of the other AEs at least possibly related to bedaquiline occurred in only one patient: hypercreatininaemia, hyperuricaemia, haematuria, leukocyturia, proteinuria, dermatitis and hypotension. [++]: asthma, pulmonary haemorrhage, appendicitis, pulmonary TB, psychotic disorder or cervix carcinoma stage 0. [§§]: events were graded according to the Division of Microbiology and Infectious Diseases Adult Toxicity Table [15].

Of 61 screened patients, 57 were recruited and received bedaquiline plus BR (ITT population) at three sites in Russia (n=54) and one site in Lithuania (n=3). All patients were Caucasian and HIV negative, with a median (range) age of 28 (18–61) years (table 1); 57.9% were female. Most patients (93%) had previously used second-line TB drugs. Pre-treatment, 47.4% had pre-XDR-TB (24.6% FQ resistant and 22.8% SLI resistant) and 52.6% had XDR-TB.

The most frequently used TB drugs in the BR (>40%) during the 120-week study were FQs (100%; levofloxacin 82.5% (47 out of 57) and moxifloxacin 57.9% (33 out of 57), with some patients switching from levofloxacin to moxifloxacin or *vice versa*), para-aminosalicylic acid (PAS) (89.5%, 51 out of 57), pyrazinamide (87.8%, 50 out of 57), capreomycin (84.2%, 48 out of 57), linezolid (66.7%, 38 out of 57), terizidone (61.4%, 35 out of 57) and cycloserine (54.4%, 31 out of 57). Prothionamide, ethambutol, amikacin sulfate, kanamycin, gatifloxacin, ofloxacin and amoxicillin/clavulanate were used by <40% of patients.

By 120 weeks, 43 patients had completed the study (75.4%) and 14 discontinued (24.6%) (table 1). During 120 weeks, most AEs were grade 1 or 2 in severity and 10.5% were considered by the investigator to be related to bedaquiline. Observed grade 3–4 (26.3%) and serious AEs (14%) were not considered to be related to bedaquiline. The most frequent AEs, regardless of cause or severity, were increased aspartate aminotransferase (AST) and alanine aminotransaminase (ALT), and eosinophilia (table 1). Acknowledging the small study size and limitations of comparing across studies, no new clinically relevant safety findings were noted, and the pattern and severity of AEs was generally similar to that reported in the phase 2b bedaquiline studies [4, 5]. While elevated AST and ALT, and eosinophilia occurred more frequently than in the phase 2b studies [4, 5], grade 3 ALT/AST increases were of similar incidences and no grade 4 increases were reported. None of the eosinophilia AEs or grade 3 increases in ALT or AST were considered by the investigator to be related to bedaquiline, and none led to bedaquiline discontinuation. Furthermore, most patients with ALT/AST increases were using PAS, which may be associated with hepatotoxicity and drug-induced hepatitis [16], and two of these patients had a medical history of hepatitis C.

None of the three deaths were considered to be bedaquiline or BR related by the investigator (table 1), or associated with a QT interval corrected for heart rate using Fridericia's method (QTcF) >450 ms. Two deaths occurred during the post-investigational phase (441–442 days after last bedaquiline intake); both were due to pulmonary haemorrhage and considered to be TB related by the investigator. Neither patient had culture converted (table 1). The third death occurred after week 120 (411 days after bedaquiline) and was due to an acute myocardial infarction (table 1). Overall mortality was 5%, compared with 7% in C209 [5], 12% in C208 stage 2 [4] and 15% in a large meta-analysis of patients with MDR-TB [17].

Bedaquiline was associated with a small QTcF prolongation at week 24 (mean change from baseline +1.4 ms) that gradually declined after bedaquiline treatment ended. AEs related to QTcF prolongation considered possibly related to bedaquiline by the investigator were reported in only two patients, starting 15 and 94 days, respectively, after bedaquiline treatment. Neither event was grade 3 or 4, or considered serious. Both events resolved with no action required (mean change in QTcF at 24 weeks was −15 ms and +123 ms, respectively). No events of ventricular arrhythmia or torsades de pointes were reported. None of the patients received clofazimine with bedaquiline, or had a clinically significant QTcF prolongation >500 ms or other ECG abnormalities.

In the 45 patients (ITT) who had a positive baseline TB culture and available post-baseline results, sputum culture conversion at 24 weeks was 68.9% (31 out of 45) overall, 72.7% (16 out of 22) in pre-XDR-TB and 65.2% (15 out of 23) in XDR-TB patients. Only 16 patients had sputum culture data reported at 120 weeks; six were negative and 10 were reported as "not done". Table 1 shows the analysis censoring for assessments that were not done and "unknown". The efficacy results support observations from the phase 2b and real-world bedaquiline studies [4, 5, 8–10].

A strength of the trial was its design, which reflected routine clinical practice and included a high proportion of difficult-to-treat patients. Most patients had previously received second-line TB drugs (93% *versus* 86% in C209 [5]) and >50% had XDR-TB (*versus* 16% in C209). However, the study did not have strictly defined data collection goals, so a large amount of microbiological data were missing, especially towards the end of treatment, as is expected during MDR-TB therapy in the real-world setting. Aside from the small study size, other limitations were the lack of a comparator arm or inclusion of HIV-positive patients.

In conclusion, bedaquiline added to a BR was generally well tolerated and efficacious over 120 weeks, as measured by traditional endpoints in patients infected with pre-XDR-TB and XDR-TB. These findings support the inclusion of bedaquiline in an individualised BR for the treatment of MDR-TB, including XDR-TB, across a broad spectrum of patients.

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Received: June 26 2018 | Accepted after revision: April 05 2019

Acknowledgements: We would like to express gratitude to the patients and their families for their participation and support during the study. We would also like to thank the study centre staff and public health authorities for their support. We are grateful to all the Janssen study personnel, as well as Nyasha Bakare and other Janssen staff members for their review of this letter, and Chris Liu, previously a contractor with Johnson & Johnson, who was involved in the data analysis. Medical writing support was provided by Ian Woolveridge of Zoetic Science, an Ashfield company, Macclesfield, UK; this support was funded by Janssen.

This study is registered at www.clinicaltrials.gov with identifier number NCT01464762. The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

Author contributions: I. Vasilyeva, A. Mariandyshev, B. Kazennyy and E. Davidavičienė all participated in recruiting significant numbers of patients to the trial and reported data for those patients. N. Lounis and S. Keim had significant involvement in the study conception or design, and/or contributed to acquisition, analysis or interpretation of data. All authors were involved in the development of this letter and interpretation of data, have read and approved the final version, and have met the criteria for authorship as established by the International Committee of Medical Journal Editors.

Conflict of interest: I. Vasilyeva has nothing to disclose. A. Mariandyshev has nothing to disclose. B. Kazennyy has nothing to disclose. E. Davidavičienė has nothing to disclose. N. Lounis is an employee of Janssen Pharmaceutical Companies of Johnson & Johnson. S. Keim reports is an employee of and holds shares in Janssen Pharmaceutical Companies of Johnson & Johnson.

Support statement: This study was sponsored by Janssen. The study sponsor was involved in the design and conduct of the trial, and in the collection and analysis of the data. The corresponding author had full access to the clinical trial report and final responsibility to submit the manuscript for publication. Funding information for this article has been deposited with the Crossref Funder Registry.

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