

University of Groningen

Bedaquiline as part of combination therapy in adults with pulmonary multi-drug resistant tuberculosis

Nguyen, T. V. A.; Cao, T. B. T.; Akkerman, Onno; Tiberi, S.; Vu, D. H.; Alffenaar, Johannes

Published in:
Expert Review of Clinical Pharmacology

DOI:
[10.1080/17512433.2016.1200462](https://doi.org/10.1080/17512433.2016.1200462)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2016

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Nguyen, T. V. A., Cao, T. B. T., Akkerman, O. W., Tiberi, S., Vu, D. H., & Alffenaar, J. W. C. (2016). Bedaquiline as part of combination therapy in adults with pulmonary multi-drug resistant tuberculosis. *Expert Review of Clinical Pharmacology*, 9(8), 1025-1037. DOI: 10.1080/17512433.2016.1200462

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.



Bedaquiline as part of combination therapy in adults with pulmonary multi-drug resistant tuberculosis

T. V. A. Nguyen, T. B. T. Cao, O. W. Akkerman, S. Tiberi, D. H. Vu & J. W. C. Alffenaar

To cite this article: T. V. A. Nguyen, T. B. T. Cao, O. W. Akkerman, S. Tiberi, D. H. Vu & J. W. C. Alffenaar (2016) Bedaquiline as part of combination therapy in adults with pulmonary multi-drug resistant tuberculosis, Expert Review of Clinical Pharmacology, 9:8, 1025-1037, DOI: [10.1080/17512433.2016.1200462](https://doi.org/10.1080/17512433.2016.1200462)

To link to this article: <http://dx.doi.org/10.1080/17512433.2016.1200462>



© 2016 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group



Accepted author version posted online: 20 Jun 2016.
Published online: 27 Jun 2016.



Submit your article to this journal [↗](#)



Article views: 189



View related articles [↗](#)



View Crossmark data [↗](#)

DRUG PROFILE

 OPEN ACCESS

Bedaquiline as part of combination therapy in adults with pulmonary multi-drug resistant tuberculosis

T. V. A. Nguyen^a, T. B. T. Cao^b, O. W. Akkerman^{c,d}, S. Tiberi^e, D. H. Vu^b and J. W. C. Alffenaar^f

^aDepartment of Pharmacological, Medical and Agronomical Biotechnology, University of Science and Technology of Hanoi, Hanoi, Vietnam; ^bDepartment of Clinical Pharmacy, Hanoi University of Pharmacy, Hanoi, Vietnam; ^cUniversity of Groningen, University Medical Center Groningen, Department Pulmonary Diseases and Tuberculosis, Groningen, The Netherlands; ^dUniversity of Groningen, University Medical Center Groningen, Tuberculosis Center Beatrixoord, Haren, The Netherlands; ^eDivision of Infection, Barts Health NHS Trust, London, UK; ^fUniversity of Groningen, University Medical Center Groningen, Clinical Pharmacy and Pharmacology, Groningen, The Netherlands

ABSTRACT

Introduction: Few innovative anti-microbial products have been brought to market in recent years to combat the global multidrug resistant-tuberculosis (MDR-TB) epidemic. Bedaquiline, a novel oral diarylquinoline, was approved by the US FDA as a part of combination therapy in adults with pulmonary MDR-TB based on phase II trials.

Area covered: Pubmed searches were conducted using search terms *bedaquiline*, *diarylquinoline*, *R207910*, and *TMC207* was performed. Supplementary sources included World Health Organization, Clinicaltrial.gov, US Food and Drug Administration. Bedaquiline is an ATP synthase inhibitor specific for *M. tuberculosis* and some nontuberculous mycobacteria. It is metabolized by CYP3A4 and its drug exposure can be influenced by inducers and inhibitors of this enzyme. Phase II studies showed promising results on efficacy of bedaquiline when being used in combination with a background regimen for MDR-TB. Main safety concerns include QTc prolongation and hepatotoxicity. Phase III trials are ongoing to confirm efficacy findings from phase II studies and provide additional evidence of safety and efficacy.

Expert commentary: Critical data for long-term efficacy and safety are incomplete and scarce, supporting the cautious use of bedaquiline.

ARTICLE HISTORY

Received 1 April 2016
Accepted 8 June 2016
Published online
24 June 2016

KEYWORDS

Bedaquiline; anti-tuberculosis drugs; multidrug-resistant tuberculosis; *Mycobacterium tuberculosis*; pharmacokinetics; pharmacodynamics

1. Introduction

Tuberculosis (TB) now ranks alongside HIV as a leading infectious cause of death worldwide and is caused by infection with *Mycobacterium tuberculosis* (MTB) [1]. In 2014, an estimated 9.6 million new TB cases occurred globally, 480,000 of which being affected by multidrug resistance tuberculosis (MDR-TB) defined as TB resistant to both isoniazid and rifampicin. An estimated 190,000 died from MDR-TB in 2014 alone [1]. MDR-TB may arise from poor adherence which often occurs during the long and burdensome treatment of TB and may lead to the development of resistance and subsequent treatment failures [1]. Treatment of MDR-TB is more challenging, with second-line drugs being less effective and more toxic than isoniazid and rifampicin-based regimens. It becomes even more complex when MDR strains with additional resistance have emerged. Extensively drug-resistant tuberculosis (XDR-TB), defined as MDR-TB plus resistance to a fluoroquinolone and an injectable second-line drug, has recently been reported at an alarming rate and is even more threatening to TB control and elimination [1]. MDR/XDR-TB can be transmitted and cause primary infections. Treatment success rates in patients with MDR/XDR-TB are low. In 1269 XDR-TB patients reported in 40 countries, only 22% completed their treatment

successfully and 35% of the patients died. The treatment is long, side effects and adverse events (AEs) are common, and the treatment and management of the cases is expensive and burdensome [1]. The need for new drugs against TB thus becomes increasingly urgent.

Bedaquiline, formerly known as TMC207 or R207910, is a diarylquinoline with a novel mechanism of action [2]. It is the first new anti-TB drug approved for the treatment of TB in the United States (US) (2012) and Europe (2014) since the approval of rifampicin in 1971 in the US. Both bedaquiline and delamanid, the other anti-TB drug recently approved, have been registered for MDR-TB treatment (delamanid only in Europe). Current interim guidance for its use provided by the World Health Organization (WHO) is based on limited data collected from phase II trials [3]. Although bedaquiline showed obvious advantages with action against MDR-MTB strains, its AEs, drug–drug interactions, and the emergence of drug-resistant MTB strains should be held in consideration. Long-term safety data of this drug are rare and no phase III studies have been completed to date to make a definite conclusion on safety.

2. Overview of drug treatment for MDR-TB

Whereas the standard treatment regimen of drug-susceptible (DS) TB is a 2-month regimen of isoniazid, rifampicin,

Table 1. WHO anti-TB drugs [4].

Group	Anti-TB drug	Note
Group 1. First-line drugs	Isoniazid, Rifampicin, Pyrazinamide, Rifabutin, Rifapentine	Rifabutin and rifapentine have similar microbiological activity as rifampicin. Rifabutin is not on the <i>WHO list of essential medicines</i> ; however, it is used routinely in patients on protease inhibitors in many settings Rifapentine is part of a latent TB infection and active TB treatment in some countries but to date is not part of any WHO-endorsed treatment regimens
Group 2. Injectable anti-TB drugs	Streptomycin, Kanamycin, Amikacin, Capreomycin	There are high rates of streptomycin resistance in strains of MDR-TB; thus, streptomycin is not considered a second-line anti-TB injectable agent
Group 3. Fluoroquinolones	Levofloxacin, Moxifloxacin, Gatifloxacin	Oxifloxacin is considered a weaker agent with less anti-TB activity than other fluoroquinolones and has been removed as a choice in Group 3 drugs Gatifloxacin can have severe side effects including serious diabetes (dysglycemia). It has been removed from the market of a number of countries as safer alternatives whenever possible are available for the diseases for which the drug is labeled. However, it is widely used as a generic and is part of the 9-month Bangladesh regimen for MDR-TB
Group 4. Bacteriostatic second-line anti-TB drugs	Ethionamide, Prothionamide, Cycloserine, Terizidone, <i>Para</i> -aminosalicylic acid, <i>Para</i> -aminosalicylate sodium	Terizidone has limited program data and effectiveness data as compared to cycloserine
Group 5. Anti-TB drugs with limited data on efficacy and/or long-term safety in drug-resistance TB treatment (this group includes new anti-TB agents)	Bedaquiline, Delamanid, Linezolid, Clofazimine, Amoxicillin/clavulanate, Imipenem/cilastatin, Meropenem, High-dose isoniazid, Thioacetazone, Clarithromycin	Clavulanate is recommended as an adjunctive agent to imipenem/cilastatin and meropenem Limited data on the role of thioacetazone and clarithromycin in MDR-TB treatment have resulted in many experts not including these drugs as options for Group 5

TB: Tuberculosis.

pyrazinamide, and ethambutol, followed by a 4-month regimen of isoniazid and rifampicin, MDR-TB requires intensive, more prolonged, more toxic, and complex treatment regimens, with up to 6 second-line agents drugs, including injectable anti-TB agents (see Table 1). The total treatment duration of MDR-TB is 20 months for most patients, and even up to 2 years, depending on the patient's response to therapy [4,5]. The landscape of TB drug development has evolved dramatically over the past 10 years, and novel drugs are entering phase III trials for the treatment of MDR-TB, including bedaquiline and delamanid [6,7]. These trials aim to both shorten and simplify the treatment of drug-resistant TB. Some repurposed drugs like linezolid, clofazimine, amoxicillin/clavulanate, imipenem/cilastatin, and meropenem have demonstrated *in vitro* or *in vivo* activity and safety in humans for the treatment of MDR-TB and are classified as group 5 MDR-TB drugs by the WHO; however, they are not licensed for treatment of MDR-TB [4].

3. Introduction to the drug

Bedaquiline defines a new class of antimycobacterial compounds, the diarylquinolines due to its novel mode of action. It targets mycobacterial adenosine 5'-triphosphate (ATP) synthase, which is a critical enzyme for the generation of energy in *mycobacteria* [2]. Bedaquiline binds to this enzyme at the central region of its c subunit, halting the energy production process and inhibiting the mycobacterial reproduction, resulting in bactericidal effects for both

replicating and nonreplicating (dormant) tubercle bacilli [8–10]. Some mutations in the c subunit can lead to resistance to bedaquiline [9]. The distinct target of bedaquiline minimizes the potential for cross-resistance with existing anti-TB agents. Currently, no other drugs of the same pharmacological class are available.

4. Chemistry

The chemical name of bedaquiline (Figure 1) is (1*R*,2*S*)-1-(6-bromo-2-methoxy-3-quinolinyl)-4-dimethylamino)-2-(1-naphthalenyl)-1-phenyl-2-butanol. It is compounded with fumaric acid (1:1) as bedaquiline fumarate [2].

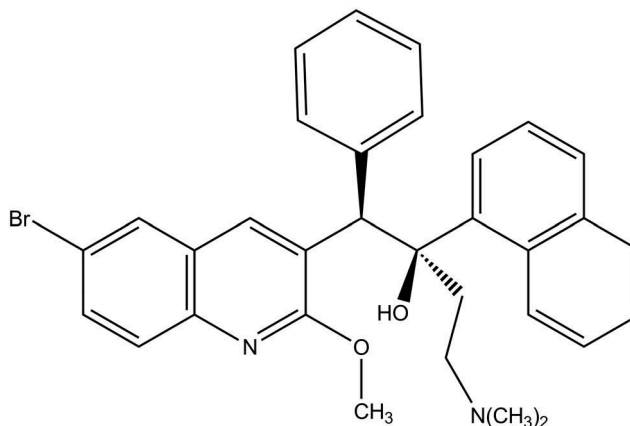


Figure 1. Structure of bedaquiline.

5. Pharmacodynamics

Bedaquiline exhibits potent *in vitro* activity against multiple strains of MTB, including DS, MDR, and XDR MTB strains with a minimal inhibitory concentration (MIC) of 0.03–0.12 mg/L. Dormant *Mycobacteria* have lower ATP supplies and are therefore more expected to be more vulnerable to further ATP depletion by bedaquiline even at nanomolar concentrations. However, this hypothesis needs to be confirmed. Bedaquiline is active within macrophages and it has remarkable sterilizing capacity that makes it an attractive drug for MDR-TB treatment [9]. The drug also possesses a good activity against *Mycobacterium avium* complex, *Mycobacterium leprae*, *Mycobacterium bovis*, *Mycobacterium marinum*, *Mycobacterium kansasii*, *Mycobacterium fortuitum*, and *Mycobacterium szulgai* and perhaps even more nontuberculous mycobacteria [8–11].

The bactericidal activity of bedaquiline was demonstrated in a study on early bactericidal activity (EBA) in treatment-naïve patients with sputum smear-positive pulmonary TB. Oral once daily administration of bedaquiline has bactericidal activity at a dose of 400 mg when administered as monotherapy for 7 days with a modest but statistically significant change in CFU (colony-forming units). Bactericidal activity at a dose of 400 mg started late but was of similar magnitude on days 4–7. The overall reduction of $-0.77 \log_{10}$ CFU over the 7-day period failed to match the high expectations fostered by the promising preclinical results [12]. A later randomized, controlled trial in MDR-TB patients treated with bedaquiline-containing regimens confirmed the moderate effect of bedaquiline up to 7 days. This trial also showed that bedaquiline appreciably accelerated the bactericidal activity of background regimen for up to 4 weeks [13]. This emphasizes the time-dependent activity of bedaquiline and its unique action mode, involving disruption of energy homeostasis, whereas bedaquiline and its *N*-desmethyl metabolite was reported to display concentration-dependent bactericidal activity in the murine model [14]. The results of this study suggest that future EBA studies with new anti-TB agents need to be extended to 14 days [13]. In a dose-ranging 14-day EBA study, all four bedaquiline dose groups (100, 200, 300, and 400 mg), preceded by loading doses, showed significant activity and this activity continued to the end of the 14-day evaluation period. Increasing the doses of bedaquiline subsequently improved the EBA [15]. The loading doses were required to counter extensive tissue distribution and to achieve adequate exposures. Recently, the delayed bactericidal response of MTB to bedaquiline was explained by a metabolic remodeling in mycobacteria triggered by bedaquiline exposure, thereby enabling transient bacterial survival [16]. In a TB murine model, the intracellular activity of bedaquiline was demonstrated to be greater than its extracellular activity due to the shorter or absent preliminary static phase [17].

Synergistic effects of bedaquiline and some other drugs have been studied in murine TB models. It is shown that bedaquiline enhances the antibacterial activity of second-line drugs [18]. Furthermore, bedaquiline synergized with pyrazinamide against MTB in mice after only 2 months of therapy [19], and the addition of bedaquiline to first- or second-line drug regimens accelerated clearance of bacilli [18]. This may help shorten treatment regimens for susceptible or MDR-TB. Concomitant treatment with verapamil *in vitro* reduced the MIC of bedaquiline 8–16-fold [20]. However,

verapamil did not reduce the MIC of bedaquiline in mice or alter efflux-based resistance [21]. The adjunctive use of verapamil was documented to increase the bactericidal activity of bedaquiline in a mouse model and protected against the development of resistant mutants *in vivo*. This synergistic effect may be due to efflux pump inhibition by verapamil, resulting in higher intracellular drug concentrations. Another approach is that oxazolidinone might increase activity of novel regimens in a mouse model of TB containing bedaquiline and pretonamid [22]. Clinical relevance should be confirmed by intervention studies on TB patients [23].

A dose of 400 mg once daily for 2 weeks followed by 200 mg thrice weekly in multidrug regimens for MDR-TB achieved plasma concentrations above 0.6 mg/L throughout the dosing interval, a target that may reach efficacy similar to 25 mg/kg in mice. The target average plasma level of 0.6 mg/L was selected based on a mouse model of TB infection but has not been validated in humans, so therapeutic concentrations in humans remain unclear [13]. In a murine model, the bactericidal activity appeared to be AUC related [14], which is consistent with the study in humans, in which bedaquiline plasma concentrations and bactericidal activity appeared to increase with dose up to 400 mg daily [15]. Results from murine models reveal that AUC is the main pharmacokinetic–pharmacodynamic driver for bedaquiline and is the parameter on which dose optimization should be based [14]. In TB-infected patients, the majority of the bactericidal efficacy is achieved by bedaquiline but not by its metabolite. It is reported that the *N*-monodesmethyl metabolite (M2) of bedaquiline has 4–6 times lower antimycobacterial activity than bedaquiline but may have a higher risk of toxicity [24].

6. Pharmacokinetics and metabolism

Bedaquiline is well absorbed orally irrespective of doses in human. The maximum plasma concentration (C_{max}) is reached after 4–6 h (T_{max}) of administration. After administration of the recommended dose of 400 mg/day, the C_{max} was 5.5 mg/L, the AUC_{0-24} was 65 mg h/L, and so the clearance was around 6.2 L/h. Interestingly, bedaquiline showed a multiphasic distribution and elimination profile with an exceedingly long terminal half-life of 5.5 months, owing to a combination of a long plasma half-life, high tissue penetration (particularly the organs affected by TB), and long half-life in tissues. This makes it suitable for intermittent drug administration. However, the long half-life could pose risk of AEs to patients even after discontinuation of therapy. The emergence of bedaquiline resistance due to low and constant exposure could be introduced as a consequence. The volume of distribution in the central compartment is approximately 164 L with plasma protein binding over 99.9%. The drug displays a linear pharmacokinetic profile, in which C_{max} and AUC increase proportionally with the dose following single doses of between 10 and 700 mg in healthy subjects and multiple doses of between 25 and 400 mg once daily in DS or MDR-TB patients. The half-life is independent of administered dose [2,13,25,26]. The effective half-life is 24 h [2], which is substantially longer than most other anti-TB drugs. Pharmacokinetics of bedaquiline is comparable in healthy subjects and patients with pulmonary TB [12]. In MDR-TB patients, after 2 weeks of 400 mg

daily, followed by 6 weeks of treatment with 200 mg 3 times weekly, mean (\pm SD) peak, minimum, and steady-state plasma concentrations of bedaquiline at week 2 were 3.27 ± 1.14 , 0.96 ± 0.56 , and 1.77 ± 0.70 mg/L, respectively, and at week 8 were 1.66 ± 0.72 , 0.62 ± 0.47 , and 0.90 ± 0.54 mg/L, respectively. The majority of patients achieved average steady-state plasma concentrations above the target of 0.60 mg/L throughout the dosing period [13].

Only phase I metabolism was observed in human. After oral administration, bedaquiline is rapidly metabolized by CYP3A4 to form its M2. Subsequently, M2 is further demethylated, likely also by CYP3A4, to a M3 metabolite with negligible antimycobacterial activity [26]. Drugs that induce CYP3A4, such as rifampicin, may decrease the plasma concentrations of bedaquiline, thus potentially reducing its therapeutic effect. Conversely, coadministration of inhibitors of these enzymes, such as protease inhibitors, macrolide antibiotics, and azole antifungals, is likely to increase concentrations of bedaquiline [26,27]. Following coadministration of bedaquiline with ketoconazole, a strong inhibitor of CYP3A, AUC and C_{\max} of bedaquiline increased by 22% and 9% (day 14 vs. day 11). The modest effects of ketoconazole on bedaquiline could be misleading. Owing to long terminal half-life of bedaquiline, steady-state concentrations were not achieved prior to pharmacokinetic sampling, so full interaction potential could not be detected during the short-term coadministration of ketoconazole. Moreover, the high protein and phospholipids binding of bedaquiline may limit the availability of bedaquiline for metabolic isoenzymes, leading to a low clearance and, accordingly, a limited impact of metabolic inhibition [25]. Using nonlinear mixed effect model, lopinavir/ritonavir was found to decrease the clearance of both bedaquiline to 35% and M2 to 58% without co-medication. The model predicted that concomitant administration of lopinavir/ritonavir would have caused a close to three- and twofold increases in average steady-state concentration ($C_{ss,avg}$) for bedaquiline and M2, respectively [28]. The significant increase of bedaquiline exposure caused by lopinavir/ritonavir was recently confirmed, but its clinical significance remains unclear [29]. The potential effect of long-term coadministration of bedaquiline and efavirenz, a CYP3A inducer, was assessed using a population pharmacokinetic model. In healthy adult volunteers, a single dose of efavirenz only minimally influenced bedaquiline pharmacokinetics [30]. However, efavirenz could reduce concentrations of bedaquiline and its main metabolite by up to 52% upon chronic coadministration. Dosing adjustments of the standard bedaquiline regimen and careful monitoring during concomitant use of efavirenz can prevent reduced exposure to bedaquiline [31]. No significant change in pharmacokinetics of bedaquiline was observed in individuals taking bedaquiline in combination with nevirapine, so bedaquiline can be coadministered with nevirapine without dose adjustments in patients coinfecting with HIV and TB [28]. The coadministration of bedaquiline with rifamycins or other potent CYP3A inducers is not recommended, even with dose adjustment, due to the risk of reduced bedaquiline exposure and a consequent loss of therapeutic efficacy [32,33]. No significant pharmacokinetic interaction with isoniazid, pyrazinamide, ethambutol, kanamycin, ofloxacin, or cycloserine was reported [34]. An overview of the drug-drug interactions is presented in Table 2.

The main metabolite M2 is primarily excreted in the stool, with only 1–4% removed in the urine. The extent of *N*-demethylation was dose independent within the dose range tested. Pharmacokinetics of M2 is also linear over the dose range of 50–400 mg.

The pharmacokinetics of bedaquiline was not affected by mild-to-moderate renal impairment (median creatinine clearance 108 mL/min, range 39.8–227 mL/min). There is no need to adjust bedaquiline dose for patients with moderate hepatic or renal impairment. Caution is recommended for those with severe renal or liver disease. Age, sex, body weight, and HIV coinfection in the absence of antiretroviral treatment did not influence its pharmacokinetics. Subjects of black ethnicity had lower concentrations of bedaquiline than other races. Notably, in light of this finding, bedaquiline did not improve treatment outcomes in one subgroup of people of African ancestry in a recent clinical trial [26]. To date, no correlation has been found between drug exposure and outcome. When taken with food, bedaquiline exposure increases approximately twofold [9]. A meal containing 22 g of fat doubled bioavailability of bedaquiline compared to its ingestion on an empty stomach. The pharmacokinetics of bedaquiline has not yet been studied in pediatric or elderly populations [26]. Penetration of bedaquiline in cerebrospinal fluid (CSF) was evaluated in one patient with MDR-TB meningitis; the undetectable low concentration of bedaquiline in CSF suggested that bedaquiline may be among second-line anti-TB drugs with poor penetration in CSF and this needs to be further explored [35].

To facilitate pharmacokinetic study, analytical method for determination of bedaquiline should be established. A method described by Rustomjee et al. using a liquid chromatography–tandem mass spectrometry (LC–MS/MS) show a wide validated analytical range from 0.001 to 2.000 mg/L for both bedaquiline and its metabolite. The method is demonstrated to be accurate and precise for application in PK study [12]. Another simple and robust LC–MS/MS method without extensive sample processing, using deuterated bedaquiline as internal standard, was recently validated [36]. The run time of this method was 2.6 min. Analytical range was 0.05–6.00 mg/L with acceptable accuracy and precision for both bedaquiline and M2 [36].

7. Drug resistance

Mutations to bedaquiline have been reported in the literature. One has to distinguish *in vitro* observations from clinical observations and data have to be interpreted carefully. Initially, mutations in *atpE*, which encodes for subunit c of ATP synthase, and in Rv0678 were found to be related to bedaquiline resistance [11,37]. Five single-point mutations within the *atpE* gene included A28V, A63P, I66M, A28P, and G61A [38]. In a larger study, it was observed that only 28% of the bedaquiline-resistant MTB bacilli carried mutations in *atpE*. The remaining 72% resistant mutant did not harbor any mutations within *atpE* and this remains unexplained [38]. This result suggested that at least one additional ATP synthase-independent mechanism of resistance to bedaquiline exists [38]. The apparent rate of mutation to high-level resistance against bedaquiline decreased with an increased drug concentration.

Table 2. Drug–drug interaction (DDI) studies on bedaquiline.

Study	Type of study	Number of subject	Key findings
Dooley et al. [30]	Two-period, sequential-design pharmacokinetic study	37	GMRs for bedaquiline with efavirenz versus bedaquiline alone were 0.82 (90% CI 0.75–0.89) for the 14-day AUC _{0–336 h} and 1.00 (90% CI 0.88–1.13) for the maximum concentration (C_{max}). For M2, the GMR was 1.07 (90% CI 0.97–1.19) for AUC _{0–336 h} and 1.89 (90% CI 1.66–2.15) for C_{max} . There were no Grade 3 or 4 clinical AEs. One subject developed asymptomatic Grade 3 serum transaminase elevation, prompting study drug discontinuation.
Svensson et al. [31]	Two-period, sequential pharmacokinetic study	37	Efavirenz concentrations stratified by CYP2B6 genotype were similar to historical data. Average steady-state concentrations of bedaquiline and M2 metabolite to be reduced by 52% (relative standard error, 3.7%) with chronic coadministration with efavirenz.
Svensson et al. [28]	Data were obtained from two DDI studies: one open-label, randomized, crossover study and one open-label, single-sequence study	32	No significant effects of nevirapine on bedaquiline pharmacokinetics were identified. Lopinavir/ritonavir decreased bedaquiline and its M2 metabolite clearances to 35% (RSE 9.2%) and 58% (RSE 8.4%) of those without co-medication.
Svensson et al. [32]	Phase I, two-arm, open-label, two-period, single-sequence study		Chronic treatment with lopinavir/ritonavir resulted in threefold (bedaquiline) and twofold (M2 metabolite) increase in exposure.
Pandie et al. [29]	Observational, parallel-group pharmacokinetic study	48	Rifamycin coadministration increased bedaquiline clearance substantially: 4.78-fold with rifampicin and 3.96-fold with rifapentine. Induction of M2 metabolite clearance was equally strong. Average steady-state concentrations of bedaquiline and M2 are predicted to decrease by 79% and 75% when given with rifampicin or rifapentine, respectively. Simulations indicated that increasing the bedaquiline dosage to mitigate the interaction would yield elevated M2 concentrations during the first treatment weeks.
Winter et al. [33]	Phase 1, open-label, single-center, two-period, single-sequence, drug interaction study	32	AUC _{0–48h} , T_{max} , $t_{1/2}$ were significantly higher in the lopinavir/ritonavir group than in the no-antiretroviral group. On multivariate analysis, bedaquiline exposure was increased by lopinavir/ritonavir, male sex, and time on bedaquiline. Bedaquiline exposure was not significantly different between the nevirapine group and the no-antiretroviral group. When coadministered with rifapentine, the GMRs and 90% CIs for the maximum observed concentration (C_{max}), area under the concentration–time curve to the last available concentration time point (AUC _{0–t}), and AUC extrapolated to infinity (AUC _{0–inf}) of bedaquiline were 62.19% (53.37–72.47), 42.79% (37.77–48.49), and 44.52% (40.12–49.39), respectively. The GMRs and 90% CIs for the C_{max} , AUC _{0–t} , and AUC _{0–inf} of bedaquiline were 60.24% (51.96–69.84), 41.36% (37.70–45.36), and 47.32% (41.49–53.97), respectively, when coadministered with rifampicin. The C_{max} , AUC _{0–t} , and AUC _{0–inf} of M2 were also altered when bedaquiline was coadministered with rifapentine or rifampicin.

GMR: Geometric mean ratios; M2: N-monodesmethyl metabolite; DDI: drug–drug interaction; RSE: root square error.

No resistant mutants were found at 3 mg/L (100× MIC of bedaquiline-susceptible MTB) [38]. Cross-resistance between clofazimine and bedaquiline through upregulation of MmpL5 in MTB was reported [21,39]. Recently, development of acquired resistance to bedaquiline and delamanid was found in the context of inadequate MDR-TB and XDR-TB treatment regimens. This serves a warning for the future rollout of new anti-TB drugs and emphasizes the need for the appropriate use of companion drugs when bedaquiline and delamanid are administered [40]. Although adequate bedaquiline susceptibility testing procedures [41] are available, a guidance document has not been established yet [42].

8. Clinical efficacy

8.1. Phase I and phase II studies

From 2005 to 2012, 11 phase I studies in 265 subjects have been conducted to evaluate pharmacokinetic characteristics, dosing regimens, drug interactions, and short-term tolerability/safety of bedaquiline. Current evidence of clinical efficacy of bedaquiline is supported by data from phase II clinical trials, primarily phase IIb studies. An overview of phase II studies is provided in Table 3.

Phase IIa trials evaluated bactericidal activity in treatment-naïve, sputum smear-positive pulmonary TB patients. A parallel-group, open-label, randomized study assessed bedaquiline's EBA of three different doses of bedaquiline (25, 100, 400 mg) compared to standard doses of rifampicin (600 mg q.d) and isoniazid (300 mg q.d) in 75 subjects for 7 days. The primary efficacy population was the intent-to-treat population. The bactericidal activity of bedaquiline was confirmed based on the reduction in CFU count over 7 days [12]. A second phase IIa, two-center, open-label, randomized clinical trial evaluating promising new combinations of two new drugs, bedaquiline and pretomanid, published recently demonstrated that this novel combination together with pyrazinamide had activity similar to that of the standard treatment regimen of HRZE over the first 14 treatment days. This was true with regard to both primary end point of activity measured by the fall in CFU counts and secondary end point determined by prolongation of time to a positive signal. Estimated activities expressed by the daily rate change in \log_{10} CFU of MTB were 0.167 (95% CI: 0.075–0.257) for bedaquiline–pretomanid–pyrazinamide and 0.051 (95% CI: 0.071–0.232) for standard treatment. The study concluded that bedaquiline–pretomanid–pyrazinamide is a potential new anti-TB regimen containing two new drugs to which no resistance in prevalent MTB strains is expected to exist [43]. However, *Mycobacterium canettii* is intrinsically resistant to pyrazinamide and might also be intrinsically resistant to pretomanid, leading to potential of bedaquiline monotherapy [44].

Phase IIb included two studies, a randomized, double-blind, placebo-controlled trial (C208) and an open-label single-arm observational study (C209). C208 consisted of two studies; stage 1 and stage 2, with two different panels of adult patients, who had newly diagnosed pulmonary MDR-TB. All subjects were sputum smear-positive, infected with MTB strains resistant to at least both rifampicin and isoniazid. Bedaquiline or placebo was added to a standard regimen for

MDR-TB. The primary efficacy end point was time to sputum culture conversion in Mycobacteria Growth Indicator Tube during the 8-week (stage 1) or 24-week (stage 2) investigational treatment period. In the exploratory trial (C208 stage 1), 23 patients received bedaquiline 400 mg daily for 2 weeks followed by 200 mg 3 times weekly for 6 weeks, and 24 patients received placebo up to 8 weeks (in combination with a background regimen). Following the 8-week trial period, patients continued their background regimen for a further 96 weeks [13]. At 4 weeks and at 8 weeks, the proportions of patients with negative sputum smears were 77% and 84% for the bedaquiline group and 57% and 68% for the placebo group, respectively. As compared with placebo, at week 8, the addition of bedaquiline to standard therapy for MDR-TB reduced time to conversion to a negative sputum culture (hazard ratio 11.8, 95%CI 2.3–61.3, $P = 0.003$). Bedaquiline increased the proportion of patients with conversion of sputum culture (48% vs. 9%) and declined rapidly the mean \log_{10} CFU count in the sputum compared with the placebo [13]. At 24 weeks, efficacy was significantly better in the bedaquiline group (hazard ratio 2.25, 95% CI 1.08–4.71, $P = 0.031$); 81% in the bedaquiline arm and 65% receiving placebo were sputum culture negative. Treatment success rates were similar at 104 weeks, 52.4% and 47.8% in the bedaquiline and placebo arms, respectively. After week 24, 9.5% (bedaquiline, two subjects) versus 17.4% (placebo, four subjects) of subjects were considered to have had relapse [45]. The data showed the potential of bedaquiline for MDR-TB, and this supported the start of stage 2 of the trial.

In the C208 stage 2, which provides the pivotal data, 160 newly MDR-TB, smear-positive patients were randomized to receive either 400 mg of bedaquiline once daily for 2 weeks, followed by 200 mg 3 times weekly for 22 weeks, or placebo, both in combination with a standard regimen. Patients were followed for 120 weeks. At week 24, the median time to sputum culture conversion was faster in the bedaquiline group than in the placebo group (83 vs. 125 days, $P < 0.001$). Bedaquiline increased the rate of culture conversion at 24 weeks (79% vs. 58%, $P = 0.008$) and at 120 weeks (62% vs. 44%, $P = 0.04$). On the basis of WHO definition, cure rates at 120 weeks were 58% in the bedaquiline and 32% in the placebo group ($P = 0.003$). Five subjects (7.6%) in the bedaquiline group and eight subjects (12.1%) in the placebo group experienced relapse [46].

The trial C209 was performed in 233 patients with newly diagnosed MDR-TB or who previously failed treatment for MDR-TB, including pre-XDR-TB (44 subjects) and XDR-TB (37 subjects). HIV-infected subjects could participate if their antiretroviral regimen could be switched to a triple nucleotide reverse transcriptase inhibitor regimen, zidovudine, lamivudine, and abacavir (trizivir), or if antiretroviral therapy could be discontinued. Patient profiles were more like the typical patient with MDR-TB than those in the C208 trials. The dose, treatment, and follow-up duration are the same as in the C208 stage 2. After bedaquiline treatment, participants were followed for a further 96 weeks during which the background regimen was completed. Efficacy analysis was based on the modified intention to treat population ($n = 205$) that excluded patients with DS TB or patients with negative cultures at

Table 3. Clinical phase II studies on bedaquiline.

Study	Type of study	Study population	Number of subjects	Key results
Rustomjee et al. [12]	Phase IIa, parallel-group, open-label, randomized study	Treatment-naïve sputum smear positive adult patients	75	Oral administration of 400 mg bedaquiline q.d. as monotherapy for 7 days resulted in a decline in CFU from day 4 onward Severe AEs did not occur The majority of patients achieved average steady-state plasma concentrations above the target of 0.6 mg/L throughout the dosing period Most AEs were mild or moderate Increases in the QTc interval were observed in both treatment groups but were more pronounced in the bedaquiline group. None of the absolute values for QTc interval were greater than 500 ms Bedaquiline significantly reduced the time to culture conversion over 24 weeks (hazard ratio: 2.253; 95% CI: 1.08–4.71; $P = 0.031$)
Diacon et al. [13]	Phase IIa, randomized, multicenter, placebo-controlled study	Newly diagnosed multidrug-resistant pulmonary tuberculosis	47	Nausea occurred in 26% of patients receiving bedaquiline and none receiving placebo. Other AEs bilateral hearing impairment, extremity pain, acne, and non-cardiac chest pain occurred at a similar frequency in both groups of patients Mean (standard deviation) daily fall in log ₁₀ CFU over 14 days of 0.040 (0.068), 0.056 (0.051), 0.077 (0.064), and 0.104 (0.077) in the 100, 200, 300, and 400-mg bedaquiline groups, respectively The linear trend for dose was significant ($P < 0.001$) Activity in the 400-mg dose group was greater than that in the 100-mg group ($P < 0.014$) All bedaquiline groups showed significant bactericidal activity that was continued to the end of the 14-day evaluation period
Diacon et al. [45]	2 year follow-up of the previous randomized, placebo-controlled study [13]		47	
Diacon et al. [15]	A phase II, two-center, double-blinded, centrally randomized trial	Sputum smear-positive pulmonary tuberculosis patients	68	
Diacon et al. [45]	Phase IIb, randomized, double-blind, placebo-controlled study	Newly diagnosed, smear-positive, multidrug-resistant tuberculosis patients	160	Bedaquiline reduced the median time to culture conversion and increased the rate of culture conversion at 24 weeks and at 120 weeks Cure rates at 120 weeks were 58% in the bedaquiline group and 32% in the placebo group ($P = 0.003$). The overall incidence of AEs was similar in the two groups Ten deaths occurred in the bedaquiline group and two in the placebo group, with no causal pattern evident
Diacon et al. [46]	Phase IIa, two-center, open-label, randomized study	Treatment-naïve, sputum smear-positive pulmonary tuberculosis patients	105	Over the first 14 days of treatment, novel combination of bedaquiline–pretomanid–pyrazinamide has similar activity to the current anti-TB treatment regimen
Pym et al. [47]	Phase II, multicenter, open-label, single-arm study	Newly diagnosed or previously treated patients with multidrug-resistant tuberculosis	233	In the efficacy population ($n = 205$), culture conversion (missing outcome classified as failure) was 72.2% at 120 weeks, and 73.1%, 70.5%, and 62.2% in MDR-TB, pre-XDR-TB, and XDR-TB patients, respectively Only two patients had clinically significant QTcF prolongation (>500 ms), and both were taking clofazimine and one also had hypokalemia

CFU: Colony-forming units; AE: adverse event; QTc: corrected QT.

screening and/or baseline. The median time to culture conversion was 57 days, which was shorter than the one in the C208 studies (83 days) because the majority of patients were receiving second-line therapy at baseline. Consistent with the C208 results, the sputum culture conversion rate was 79.5% at 24 weeks and 72.2% at 120 weeks, and it was 73.1%, 70.5%, and 62.2% in patients with MDR-TB, pre-XDR-TB, and XDR-TB, respectively. A percentage of 85.3 of 24-week responders were still responders at 120 weeks. This showed that culture conversion at 24 weeks was sustained and associated with a high likelihood of response at 120 weeks, corroborating the observation that the 24-week culture conversion rate is predictive for long-term MDR-TB treatment outcome. Seven patients (3.4%) experienced relapse [26,47].

A pediatric phase II, multicenter, single-arm study has been planned to evaluate the pharmacokinetics, safety, tolerability, and antimycobacterial activity of bedaquiline in combination with background regimen (ClinicalTrials.gov identifier: NCT02354014). Furthermore, a randomized, open-label phase II trial evaluating the safety, tolerability, and pharmacokinetics of bedaquiline and delamanid, alone and in combination, for drug-resistant pulmonary TB is also planned but not yet open for recruitment (ClinicalTrials.gov identifier: NCT02583048).

8.2. Phase III studies

Currently, several phase III trials are ongoing that may confirm the efficacy findings from phase II trials and provide additional safety data. A phase III study assessing the safety and efficacy of bedaquiline plus pretomanid plus linezolid in patients with drug-resistant pulmonary TB is now recruiting patients with a planned enrollment of 200 subjects (ClinicalTrials.gov identifier: NCT02333799). Furthermore, an open-label, randomized, placebo-controlled trial is also recruiting participants to evaluate a new treatment regimen of linezolid, bedaquiline, levofloxacin, pyrazinamide, and ethionamide/high-dose isoniazid compared to the conventional empiric injection-based regimen of 21–24 months treatment for patients with MDR-TB (ClinicalTrials.gov identifier: NCT02454250). The evaluation of a standard treatment regimen of anti-TB drugs including locally used WHO-approved MDR-TB regimen, moxifloxacin, clofazimine, ethambutol, pyrazinamide, isoniazid, prothionamide, kanamycin, levofloxacin, and bedaquiline for patients with MDR-TB is planned but not yet open for participant recruitment (ClinicalTrials.gov identifier: NCT02409290).

8.3. Experience from compassionate use

Based on analyses of interim results of trial C208 stage 2, bedaquiline was made available for compassionate use in 2011. The first evidence on the compassionate use of bedaquiline to treat MDR/XDR-TB cases was the management of two XDR-TB patients with bedaquiline at the Italian TB Reference Centre [48]. After achieving culture conversion after 2 months (58 and 63 days) on linezolid, meropenem, and amoxicillin/clavulanate, the patients were exposed to bedaquiline for a total of 180 days without major AEs. Both subjects achieved consistent bacteriological conversion and radiological

improvements and then moved to the continuation phase of treatment with a plan to continue for 24 months [48]. Data on bedaquiline use in 91 XDR-TB patients from the Expanded Access Programme in South Africa showed 76% of patients with sputum culture conversion or persistently negative cultures observed at 6 months [49]. A recent interim analysis of compassionate use of bedaquiline in 35 MDR-TB subjects showed that after 6 months of bedaquiline treatment, sputum culture conversion was observed in 28 of 29 (97%) patients who were culture positive initially and the median time to sputum culture conversion was 85 (8–235) days. Only two patients needed to stop bedaquiline during the course of therapy [50]. The use of bedaquiline in a series of five Indian XDR-TB patients also showed striking improvement, with microbiological conversion [51]. The use of bedaquiline as a substitute for linezolid in the first XDR-TB case in the US was reported to allow the successful completion of adequate XDR-TB therapy with good tolerability and a favorable outcome 10 months after the treatment completion [52].

In a case report on a pericardial XDR-TB patient receiving bedaquiline at week 14 when full drug sensitivity testing became available for 24 weeks, culture negative was remained at the end of her planned 2-year treatment regimen with no specific AEs [53]. Bedaquiline treatment for 18 months was reported firstly in one XDR-TB patient and showed no recurrence of sputum smear or culture positivity, gradual weight gain, and resolution of active inflammatory changes on serial CT scans and the patient was graded as cured [54].

9. Safety and tolerability

The phase IIb trial data were pooled to increase the likelihood of detecting AEs due to higher number of subjects per pooled treatment group and to increase sample size for subgroup analyses. The most frequently reported AEs in the pooled bedaquiline (Any bedaquiline) group (>20.0% of subjects) were nausea (35.3%), arthralgia (29.4%), headache (23.5%), hyperuricemia (22.5%), and vomiting (20.6%). Most AEs were grade 1 or 2 in severity. The incidence of grade 3 or 4 AEs was 27.5% in the Any bedaquiline group and 22.9% in the pooled placebo (Any placebo) group. Hyperuricemia was the most frequently reported grade 3 or 4 AE, which occurred in 10.8% of participants in the Any bedaquiline group and 13.3% in the Any placebo group. Other grade 3 or 4 AEs were reported in <3.0% of subjects in both groups. A higher incidence of serious AEs was observed in the Any bedaquiline group, with seven (6.9%) subjects compared to two (1.9%) subjects in the Any placebo group. However, the overall number of AEs leading to permanent discontinuation was low and balanced in both groups [26]. AEs of interest included AEs related to the liver, pancreas, QT prolongation, muscle, and skin. The number of patients with AEs related to skeletal, muscle, pancreas, and stomach was similar in both groups.

9.1. Prolongation of corrected QT interval

Bedaquiline prolongs corrected QT (QTc) interval. No Torsade de Pointes events and no fatalities from sudden death were reported. The pooled analysis of C208 trials showed that mean

QTc increased in both pooled groups, but mean increases were more pronounced in the Any bedaquiline group and observed from the first assessment after Day 1 onward. Increase in QTc became gradually larger over the first 8 weeks of taking bedaquiline and then remained stable until week 24. Over 24 weeks of bedaquiline treatment, mean increase in QTc was 15.4 ms compared to 6.2 ms in the placebo group and it became less pronounced after 24 weeks of bedaquiline dosing period [26].

The safety finding in the C209 trial revealed that increases in QTc were larger in patients receiving concomitant clofazimine ($n = 17$) than those without concomitant clofazimine use ($n = 177$) [47]. Mean increase in QTc from baseline was also previously reported to be larger in patients receiving bedaquiline in combination with clofazimine than in those receiving only bedaquiline, although this was not associated with clinically relevant arrhythmias [55]. QTc > 500 ms was observed in two subjects, both of whom received clofazimine. The QTc was between 450 and 500 ms for 22.5% of patients taking bedaquiline and 6.7% of patients taking placebo. The maximum change in QTc from baseline was 14.2 ms and this decreased to <10 ms after stopping bedaquiline [47].

When bedaquiline is given with other QT-prolonging anti-TB drugs, the effect on the QT interval could be additive, complicating efforts to optimize multidrug treatment for MDR-TB. Pyrazinamide, moxifloxacin, and clofazimine can potentially cause QT prolongation as well. In a study evaluating the combination of bedaquiline, pyrazinamide, and clofazimine, an increase from baseline of ≥ 60 ms in QTc was reported for two patients (13.3%) and no QTc ≥ 500 was reported. However, QT prolongations remained within acceptable safety limits [43].

In addition, coadministration of verapamil with bedaquiline is a promising strategy not only for improving MDR-TB treatment efficacy and reducing bedaquiline dosing, but also for reducing the risk of QTc prolongation. Verapamil, which has effects of extending the PR interval and reducing the QTc interval, has been shown to be able to limit or even abrogate the negative cardiac effects of bedaquiline [56].

The report on compassionate use of bedaquiline was in two XDR-TB patients for 6 months and reported no QTc prolongation [48]. An absence of notable adverse effects such as prolonged QTc was also noted in five Indian MDR/XDR-TB patients receiving bedaquiline [51]. During the bedaquiline treatment under compassionate use in 35 French MDR-TB patients, the QTc interval increased by a median of 1.96 ms (range, -64 – 71 ms). Overall, increases of QTc ≥ 60 ms from baseline were observed in 20% of patients and three (9%) patients had a QTc value >500 ms. Bedaquiline was discontinued in two (6%) patients due to persistent QTc prolongation. No cardiac arrhythmia was documented [50]. In the interim analysis of 91 XDR-TB patients in the South African Bedaquiline Clinical Assess Programme, of whom 54 were HIV infected and all were on antiretroviral treatment at bedaquiline initiation, QTc was monthly monitored and exceeded 500 ms in 3 patients. Bedaquiline was temporarily withdrawn in one patient; in all three, the QTcF decreased to below 500 ms and there were no clinical sequelae. Atrial fibrillation while on bedaquiline was developed in one patient, leading to the discontinuation of the drug [49].

9.2. Hepatic events

The pooled data analysis of C208 studies revealed that higher incidence of hepatic events was observed in the Any bedaquiline group compared to the Any placebo group (8.8% vs. 1.9%, $P = 0.03$). Transaminases increased in the majority of these reported events of which all but two resolved. One patient met the laboratory criteria for Hy's law at week 32 (treatment-emergent serum alanine aminotransferase [ALT] or aspartate aminotransferase (AST) $>$ threefold upper limit of normal [ULN] with serum total bilirubin >2 times ULN and recovered, but this was confounded by reported alcoholic hepatitis and concurrent intake of hepatotoxic background medications [including paraaminosalicylic acid and ethionamide]) [26,47]. In a detailed analysis over 120 weeks in the single-arm C209, four (1.7%) patients were identified to have hepatic events related to bedaquiline. One of these four did not resolve, but the patient also had hepatitis C infection. One patient had grade ≥ 3 hepatic-related AEs due to bedaquiline use [47]. Permanent discontinuation of bedaquiline due to bedaquiline-related hepatic disorders was documented in three (2.9%) patients in the Any bedaquiline group. In the C208 stage 2 trial, one patient receiving bedaquiline died due to hepatitis/hepatic cirrhosis [26].

The study on compassionate use of bedaquiline in a French cohort of 35 MDR-TB patients reported that mild liver enzyme AST/ALT elevation (\geq twofold baseline) occurred in 5 (14%) patients. Severe liver enzyme elevation (\geq fivefold baseline), confounded by the concomitant use of hepatotoxic compounds (pyrazinamide, fluoroquinolones, and *para*-aminosalicylic acid), occurred in two additional patients (6%) and did not lead to bedaquiline discontinuation. In these two patients, liver enzymes peaked after 3 months of bedaquiline treatment and reverted to normality during the subsequent month [50]. No hepatotoxicity was reported as a severe AE in 91 pre-XDR-/XDR-TB patients in the South Africa Bedaquiline Clinical Access Programme treated with bedaquiline and antiretroviral drugs [49].

9.3. Death

In the trial C208 stage 1, two patients died in the bedaquiline group (one died during the trial and one died after withdrawing prematurely) and two patients died in the placebo group (both died after withdrawing prematurely) [26].

In the trial C208 stage 2, 10 deaths occurred in the bedaquiline group and 2 deaths in the placebo group [46]. TB was the cause of death in 5 of the 10 bedaquiline deaths and both placebo deaths. Of 10 deaths in the bedaquiline arm, 4 deaths occurred during long-term survival follow-up of premature withdrawals. No deaths were considered to be related to bedaquiline in both stages of the trial C208. The reason for the imbalance in death between the two arms in the second stage is unclear [46].

Amongst 233 participants in the trial C209, 16 deaths (6.9%) were reported by the trial cutoff date (120 weeks), 4 of which occurred after withdrawal from the study. Of the 12 remaining deaths, 3 occurred during the bedaquiline treatment and 9 during the 96-week follow-up period. TB-related

diseases were causes of death in 11 patients (68.8%). None of deaths were related to bedaquiline, except for renal impairment that was judged doubtfully related to bedaquiline [26,47].

In the compassionate access cohorts, 3 deaths were reported in the South African Bedaquiline Clinical Access Programme [49] and 1 death was reported in the French cohort of 35 MDR-TB patients but none of them were considered to be related to bedaquiline [50].

10. Cost-effectiveness

The cost-effectiveness of introducing bedaquiline in MDR-TB treatment regimens in six low- and middle-income countries (Russia, Estonia, Philippines, Peru, Nepal, and China) was assessed by the WHO, using outcomes from published literature and initial results from bedaquiline clinical trial program [57]. It was concluded that bedaquiline is highly likely to be cost-effective in most environments, with cost-savings in environments which have high MDR-TB treatment costs [57].

In high-income countries, patients are almost always hospitalized with lengthy period of hospital stay and incur significant costs to health-care systems. Wolfson et al. developed a comprehensive model looking at cost-effectiveness of bedaquiline plus background regimen in the United Kingdom and reported that bedaquiline is likely to be cost-effective and cost-saving, compared with the current MDR-TB standard of care [58]. This was also confirmed in a recent study examining cost-effectiveness of bedaquiline in the German health-care system [59].

11. Regulatory affairs

Bedaquiline is the first new anti-TB drug to be introduced into the market in more than 40 years. The approval of the US FDA and the European Medical Agency was based on results of phase IIb clinical trials. Due to QTc prolongation and significant excess mortality, the FDA required a black-box warning on the bedaquiline package insert [60]. A phase III multicenter, randomized, double-blind, placebo-controlled trial of bedaquiline in subjects with sputum smear-positive pulmonary MDR-TB was required to confirm efficacy findings from phase II trials and provided additional evidence on safety of bedaquiline and it was initially scheduled to start recruiting subjects in 2013.

Because no phase III trial has been completed, the potential interim guidance issued by WHO [3] is provisional until further efficacy and safety data, particularly from phase III trial, become available. The WHO document specified the essential conditions for the bedaquiline use and is targeted at national TB programs, public health agencies, as well as public and private partners involved in planning, implementing, and monitoring MDR-TB control activities. A WHO implementation plan has been developed to assist countries in the preparation and conduct of necessary activities for the introduction of bedaquiline [61].

12. Conclusion

Bedaquiline, a new anti-TB drug, belongs to the diarylquinoline family and has an appealingly novel action mechanism. Its recommended dosing regimen is 400 mg daily for 2 weeks and then 200 mg thrice weekly for a total of 6 months. Its long half-life will increase the risks of acquired bedaquiline resistance if drugs are discontinued or have mismatched half-lives and long dosing interval [60]. Though bedaquiline has shown excellent efficacy in phase II clinical trials, its EBA during the first week of chemotherapy is minimal. There was a linear increase in bactericidal activity with increasing dose over 14 days of treatment. The predominant AEs included hepatic disorders and cardiac QTc prolongation. The risk of QTc prolongation could be additive when bedaquiline is coadministered with other QTc prolonging medications. In addition, conditions and medications associated with hepatotoxicity could pose additional hepatotoxic risks in patients receiving bedaquiline. This suggests careful monitoring, particularly in patients with preexisting liver disease and/or regular alcohol use. The death rate in the group of patients receiving bedaquiline in the phase IIb trial was 5 times higher than among patients who did not receive bedaquiline (10 of 79 vs. 2 of 81 patients) but the reasons for this remain unclear, resulting in a black-box warning on its label and raising concerns about drug safety. Mortality related to bedaquiline use needs to be further investigated. Additionally, caution should be paid when bedaquiline is used in combination with antiretroviral drugs due to potential drug interactions. Coadministration of bedaquiline with rifampicin or other potent CYP3A4 inducers is not recommended due to the risk of reduced plasma concentration of bedaquiline. A few studies reported clinical evidence on efficacy and safety of bedaquiline in non-trial settings as part of compassionate use or expanded access programs. Overall, bedaquiline was well tolerated and safe. The high rate of culture conversion and the low mortality rate in these cohorts are promising findings, highlighting the potential of bedaquiline to improve outcome in patients with MDR or XDR-TB. However, it is premature to make any conclusions on the efficacy of bedaquiline as part of combination therapy for MDR-TB treatment. Critical safety data for bedaquiline are incomplete. Well-designed, randomized studies in large populations are required to confirm effectiveness findings and provide additional long-term safety data for bedaquiline.

13. Expert commentary

Given the emergence of MDR-TB, with the challenge of limited treatment options and low cure rates, it is crucial to develop new, shorter, and safer treatment regimens. To obtain success, the development of new anti-TB drugs with novel mechanisms of action and activity against drug-resistant TB is urgently required. The introduction of bedaquiline into the treatment regimens for MDR-TB represents considerable progress in research and drug development of new anti-TB drugs. Findings reported in clinical trials demonstrated improved efficacy with the addition of bedaquiline when compared to standard therapy alone for MDR-TB. It should be noted that

the approval of bedaquiline was based on trials that evaluated using the surrogate marker of culture conversion rather than the gold standard of durable cure after completion of therapy [62]. The primary end point of time to culture conversion may predict non-relapsing cure in clinical trials of DS TB [63] but has poor prognostic value at individual patient level and has not been validated for MDR-TB patients [64]. The scarcity of current clinical evidence supports the cautious use of bedaquiline. Before results from phase III studies are published, efficacy and safety data could be collated from compassionate studies. Currently, cohorts of pre-XDR or XDR-TB patients are collected in high-burden countries under five conditions recommended by interim WHO guidance including strict pharmacovigilance monitoring. Once data from those cohorts are integrated, more consolidated conclusions on the role of bedaquiline can be obtained.

Ideally, drug approvals should be based on evidence collected from large randomized studies measuring actual clinical outcomes. Nevertheless, the pivotal data on bedaquiline were reported in limited studies with small sample sizes. The accelerated approval from the FDA was based solely on 2 phase IIb studies of 440 MDR-TB patients. Thus, critical data for long-term efficacy and safety are needed for bedaquiline as for many other antimicrobial drugs that used for MDR-TB treatment.

14. Five-year review

Until further research evidence is available, the use of bedaquiline must be carefully controlled to prevent the spread of drug resistance and closely monitored for AEs and drug interactions. In the future, studies on bedaquiline should focus on various combination therapies with new and existing drugs to shorten MDR/XDR-TB treatment.

Key issues

- Bedaquiline is a new anti-tuberculosis (TB) drug and approved as part of combination therapy in pulmonary multidrug resistant tuberculosis (MDR-TB) by the US FDA in 2012.
- Bedaquiline has a new mechanism of action: inhibition of mycobacterial ATP synthetase, resulting in depletion of cellular energy stores.
- Bedaquiline has a very long half-life, however it takes 4–7 days for onset of bactericidal activity
- Evidence from phase II trials showed that bedaquiline was well tolerated and had good efficacy when being used along with a background regimen for MDR-TB.
- There are two important black box warnings for this drug: prolongation of QT interval and increased mortality with bedaquiline as compared to placebo treatment.
- Given incomplete and scarce data, phase III trials are currently ongoing to confirm safety and efficacy findings from phase II studies.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes

employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

Papers of special note have been highlighted as:

- of interest
 - of considerable interest
1. WHO. Global tuberculosis report 2015. World Health Organization [cited 2016 Jan 28]. Available from: http://www.who.int/tb/publications/global_report/en/
 2. Andries K, Verhasselt P, Guillemont J, et al. A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. *Science*. 2005;307(5707):223–227.
 3. WHO. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis - interim policy guidance. WHO [cited 2016 Feb 1]. Available from: http://apps.who.int/iris/bitstream/10665/84879/1/9789241505482_eng.pdf
 4. WHO. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. World Health Organization [cited 2016 Jan 29]. Available from: http://www.who.int/tb/publications/pmdt_companionhandbook/en/
 5. Loddenkemper R, Sotgiu G, Mitnick CD. Cost of tuberculosis in the era of multidrug resistance: will it become unaffordable? *Eur Respir J*. 2012;40(1):9–11.
 6. Kakkar AK, Dahiya N. Bedaquiline for the treatment of resistant tuberculosis: promises and pitfalls. *Tuberculosis*. 2014;94(4):357–362.
 7. Esposito S, Bianchini S, Blasi F. Bedaquiline and delamanid in tuberculosis. *Expert Opin Pharmacother*. 2015;16(15):2319–2330.
 8. Harmanjit S, Navreet Kaur N, Nipunjot G, et al. Bedaquiline: a new weapon against MDR and XDR-TB. *Int J Basic Clin Pharmacol*. 2013;2(2):96–102.
 9. Matteelli A, Carvalho ACC, Dooley KE, et al. TMC207: the first compound of a new class of potent anti-tuberculosis drugs. *Future Microbiol*. 2010;5(6):849–858.
 10. Koul A, Vranckx L, Dendouga N, et al. Diarylquinolines are bactericidal for dormant *Mycobacteria* as a result of disturbed ATP homeostasis. *J Biol Chem*. 2008;283(37):25273–25280.
 11. Huitric E, Verhasselt P, Andries K, et al. In vitro antimycobacterial spectrum of a diarylquinoline ATP synthase inhibitor. *Antimicrob Agents Chemother*. 2007;51(11):4202–4204.
 12. Rustomjee R, Diacon AH, Allen J, et al. Early bactericidal activity and pharmacokinetics of the diarylquinoline TMC207 in treatment of pulmonary tuberculosis. *Antimicrob Agents Chemother*. 2008;52(8):2831–2835.
 13. Diacon AH, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. *N Engl J Med*. 2009;360(23):2397–2405.
 - **The first phase II, randomized, placebo-controlled trial of 8-week bedaquiline added to the standard therapy for multidrug resistance tuberculosis (MDR-TB); bedaquiline reduced the time to culture conversion and increased the proportion of patients with conversion of sputum culture. Most adverse events were mild-to-moderate, and only nausea occurred significantly more frequently among patients in the TMC207 group than among patients in the placebo group (26% vs. 4%, $P = 0.04$).**
 14. Rouan M-C, Lounis N, Gevers T, et al. Pharmacokinetics and pharmacodynamics of TMC207 and its N-Desmethyl metabolite in a murine model of tuberculosis. *Antimicrob Agents Chemother*. 2012;56(3):1444–1451.
 15. Diacon AH, Dawson R, Von Groote-Bidingmaier F, et al. Randomized dose-ranging study of the 14-day early bactericidal activity of bedaquiline (TMC207) in patients with sputum microscopy smear-positive pulmonary tuberculosis. *Antimicrob Agents Chemother*. 2013;57(5):2199–2203.
 16. Koul A, Vranckx L, Dhar N, et al. Delayed bactericidal response of *Mycobacterium tuberculosis* to bedaquiline involves remodelling of bacterial metabolism. *Nat Commun*. 2014;5:3369.

17. Dhillon J, Andries K, Phillips PPJ, et al. Bactericidal activity of the diarylquinoline TMC207 against *Mycobacterium tuberculosis* outside and within cells. *Tuberculosis*. 2010;90(5):301–305.
18. Lounis N, Veziris N, Chauffour A, et al. Combinations of R207910 with drugs used to treat multidrug-resistant tuberculosis have the potential to shorten treatment duration. *Antimicrob Agents Chemother*. 2006;50(11):3543–3547.
19. Ibrahim M, Andries K, Lounis N, et al. Synergistic activity of R207910 combined with pyrazinamide against murine tuberculosis. *Antimicrob Agents Chemother*. 2007;51(3):1011–1015.
20. Gupta S, Tyagi S, Bishai WR. Verapamil increases the bactericidal activity of bedaquiline against *Mycobacterium tuberculosis* in a mouse model. *Antimicrob Agents Chemother*. 2014;59(1):673–676.
21. Andries K, Villellas C, Coeck N, et al. Acquired resistance of *Mycobacterium tuberculosis* to bedaquiline. *PLoS One*. 2014;9(7):e102135.
22. Tasneen R, Betoudji F, Tyagi S, et al. Contribution of oxazolidinones to the efficacy of novel regimens containing bedaquiline and pretomanid in a mouse model of tuberculosis. *Antimicrob Agents Chemother*. 2015;60(1):270–277.
23. Gupta S, Cohen KA, Winglee K, et al. Efflux inhibition with verapamil potentiates bedaquiline in *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother*. 2014;58(1):574–576.
24. Mesens N, Verbeeck J, Rouan M-C. Elucidating the role of M2 in the preclinical safety profile of TMC207. Presented at: 38th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease; 2007 Nov 8–12; Cape Town, South Africa.
25. van Heeswijk RPG, Dannemann B, Hoetelmans RMW. Bedaquiline: a review of human pharmacokinetics and drug–drug interactions. *J Antimicrob Chemother*. 2014;69(9):2310–2318.
26. Janssen Briefing Document. TMC207 (bedaquiline): treatment of patients with MDR-TB: NDA 204-384. US Food and Drug Administration [cited 2016 Jan 29]. Available from: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM329260.pdf>
27. Fox GJ, Menzies D. A review of the evidence for using bedaquiline (TMC207) to treat multi-drug resistant tuberculosis. *Infect Dis Ther*. 2013;2(2):123–144.
28. Svensson EM, Dooley KE, Karlsson MO. Impact of lopinavir-ritonavir or nevirapine on bedaquiline exposures and potential implications for patients with tuberculosis-HIV coinfection. *Antimicrob Agents Chemother*. 2014;58(11):6406–6412.
29. Pandie M, Wiesner L, McIlleron 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):1037–1040.
30. Dooley KE, Park J-G, Swindells S, et al. Safety, tolerability, and pharmacokinetic interactions of the antituberculous agent TMC207 (bedaquiline) with efavirenz in healthy volunteers: AIDS clinical trials group study A5267. *J Acquir Immune Defic Syndr*. 2012;59(5):455–462.
31. Svensson EM, Aweeka F, Park J-G, et al. Model-based estimates of the effects of efavirenz on bedaquiline pharmacokinetics and suggested dose adjustments for patients coinfecting with HIV and tuberculosis. *Antimicrob Agents Chemother*. 2013;57(6):2780–2787.
32. Svensson EM, Murray S, Karlsson MO, et al. Rifampicin and rifapentine significantly reduce concentrations of bedaquiline, a new anti-TB drug. *J Antimicrob Chemother*. 2015;70(4):1106–1114.
33. Winter H, Egizi E, Murray S, et al. Evaluation of the pharmacokinetic interaction between repeated doses of rifapentine or rifampin and a single dose of bedaquiline in healthy adult subjects. *Antimicrob Agents Chemother*. 2015;59(2):1219–1224.
34. CDC. Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (sirturo) for the treatment of multidrug-resistant tuberculosis [cited 2016 Jan 29]. CDC. Available from: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6209a1.htm>
35. Akkerman OW, Odish OFF, Bolhuis MS, et al. Pharmacokinetics of bedaquiline in cerebrospinal fluid and serum in multidrug-resistant tuberculous meningitis. *Clin Infect Dis*. 2016;62(4):523–524.
36. Alffenaar J-WC, Bolhuis M, van Hateren K, et al. Determination of bedaquiline in human serum using liquid chromatography-tandem mass spectrometry. *Antimicrob Agents Chemother*. 2015;59(9):5675–5680.
37. Petrella S, Cambau E, Chauffour A, et al. Genetic basis for natural and acquired resistance to the diarylquinoline R207910 in mycobacteria. *Antimicrob Agents Chemother*. 2006;50(8):2853–2856.
38. Huitric E, Verhasselt P, Koul A, et al. Rates and mechanisms of resistance development in *Mycobacterium tuberculosis* to a novel diarylquinoline ATP synthase inhibitor. *Antimicrob Agents Chemother*. 2010;54(3):1022–1028.
39. Hartkoorn RC, Uplekar S, Cole ST. Cross-resistance between clofazimine and bedaquiline through upregulation of MmpL5 in *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother*. 2014;58(5):2979–2981.
40. Bloemberg GV, Keller PM, Stucki D, et al. Acquired resistance to bedaquiline and delamanid in therapy for tuberculosis. *N Engl J Med*. 2015;373(20):1986–1988.
41. Torrea G, Coeck N, Desmaretz C, et al. Bedaquiline susceptibility testing of *Mycobacterium tuberculosis* in an automated liquid culture system. *J Antimicrob Chemother*. 2015;70(8):2300–2305.
42. Salfinger M, Migliori GB. Bedaquiline: 10 years later, the drug susceptibility testing protocol is still pending. *Eur Respir J*. 2015;45(2):317–321.
43. 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):943–953.
44. Feuerriegel S, Köser CU, Richter E, et al. *Mycobacterium canettii* is intrinsically resistant to both pyrazinamide and pyrazinoic acid. *J Antimicrob Chemother*. 2013;68(6):1439–1440.
45. Diacon AH, Donald PR, Pym A, et al. Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence of drug resistance. *Antimicrob Agents Chemother*. 2012;56(6):3271–3276.
- **The 2-year follow-up results of the first randomized placebo-controlled study by Diacon et al. [13]: Bedaquiline significantly reduced the time to culture conversion over 24 weeks (hazard ratio: 2.253; $P = 0.031$). With the exception of nausea reported in 26% of patients receiving bedaquiline and none receiving placebo, adverse events occurred at a similar frequency in both groups of patients.**
46. Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med*. 2014;371(8):723–732.
- **The second phase II, randomized controlled trial of bedaquiline given for 24 weeks in combination with a background regimen for MDR-TB; bedaquiline reduced the time to culture conversion from 125 to 83 days ($P < 0.001$) and increased the rate of culture conversion at 24 weeks (79 vs. 58%, $P = 0.008$) and 120 weeks (62 vs. 44%, $P = 0.04$). Cure rates at 120 weeks were 58% in the TMC207 group and 32% in the placebo group ($P = 0.003$). Ten deaths occurred in the bedaquiline group and two in the placebo group, with no causal pattern evident.**
47. Pym AS, Diacon AH, Tang S-J, et al. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. *Eur Respir J*. 2015;47(2):564–574.
- **A phase II, multicenter, open-label, single-arm trial to confirm the safety and efficacy of bedaquiline: In the efficacy population ($n = 205$), culture conversion (missing outcome classified as failure) was 72.2% at 120 weeks, and 73.1%, 70.5%, and 62.2% in MDR-TB, pre-XDR-TB, and XDR-TB patients, respectively. Adverse events were generally those commonly associated with MDR-TB treatment. Two patients with an increase in QTcF interval >500 ms were both taking clofazimine and one had concurrent hypokalemia.**

48. Tiberi S, De Lorenzo S, Centis R, et al. Bedaquiline in MDR/XDR-TB cases: first experience on compassionate use. *Eur Respir J.* **2014**;43(1):289–292.
49. Ndjeka N, Conradie F, Schnippel K, et al. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. *Int J Tuberc Lung Dis.* **2015**;19(8):979–985.
50. Guglielmetti L, Le Dû D, Jachym M, et al. Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort. *Clin Infect Dis.* **2015**;60(2):188–194.
- A phase II, multicenter, open-label, single-arm trial to confirm the safety and efficacy of bedaquiline: In the efficacy population (n = 205), culture conversion (missing outcome classified as failure) was 72.2% at 120 weeks, and 73.1%, 70.5%, and 62.2% in MDR-TB, pre-XDR-TB, and XDR-TB patients, respectively. Adverse events were generally those commonly associated with MDR-TB treatment. Two patients with an increase in QTcF interval >500 ms were both taking clofazimine and one had concurrent hypokalemia.**
51. Udhwadia ZF, Amale RA, Mullerpattan JB. Initial experience of bedaquiline use in a series of drug-resistant tuberculosis patients from India. *Int J Tuberc Lung Dis.* **2014**;18(11):1315–1318.
52. Danckers M, Lesko MB, Adamson R, et al. Compassionate use of bedaquiline in the treatment of pulmonary XDR-TB. *Int J Tuberc Lung Dis.* **2014**;18(12):1522–1523.
53. van Halsema C, Humphreys S, Bonington A. Extensively drug-resistant tuberculosis: early access to bedaquiline for a UK patient. *Eur Respir J.* **2014**;43(1):292–294.
54. Lewis JM, Hine P, Walker J, et al. First experience of effectiveness and safety of bedaquiline for 18 months within an optimised regimen for XDR-TB. *Eur Respir J.* **2016**;47:1581–1584.
55. Dannemann BR, Bakare N, De Marez T, et al. Corrected QT interval (QTcF) prolongation in a phase 2 open-label trial of TMC207 plus background regimen as treatment for MDR-TB: effect of co-administration with clofazimine. Abstract at ICCAC; **2012**.
56. Srikrishna G, Gupta S, Dooley KE, et al. Can the addition of verapamil to bedaquiline-containing regimens improve tuberculosis treatment outcomes? A novel approach to optimizing TB treatment. *Future Microbiol.* **2015**;10(8):1257–1260.
57. Vassall A. Cost-effectiveness of introducing bedaquiline in MDR-TB regimens - an exploratory analysis. WHO [cited **2016** Mar 20]. Available from: http://who.int/tb/challenges/mdr/CEA_bdqreport_final.pdf
58. Wolfson LJ, Walker A, Hettle R, et al. Cost-effectiveness of adding bedaquiline to drug regimens for the treatment of multidrug-resistant tuberculosis in the UK. *PLoS One.* **2015**;10(3):e0120763.
59. Wolfson LJ, Gibbert J, Wirth D, et al. Cost-effectiveness of incorporating bedaquiline into a treatment regimen for MDR/XDR-TB in Germany. *Eur Respir J.* **2015**;46(6):1826–1829.
60. Leibert E, Danckers M, Rom WN. New drugs to treat multidrug-resistant tuberculosis: the case for bedaquiline. *Ther Clin Risk Manag.* **2014**;10:597–602.
61. WHO. Introduction of bedaquiline for the treatment of multidrug-resistant tuberculosis at country level - implementation plan. WHO [cited **2016** Feb 1]. Available from: <http://www.who.int/tb/publications/Bedaquiline-implementation-plan/en/>
62. Avorn J. Approval of a tuberculosis drug based on a paradoxical surrogate measure. *JAMA.* **2013**;309(13):1349–1350.
63. Wallis RS, Pai M, Menzies D, et al. Biomarkers and diagnostics for tuberculosis: progress, needs, and translation into practice. *Lancet.* **2010**;375(9729):1920–1937.
64. Horne DJ, Royce SE, Gooze L, et al. Sputum monitoring during tuberculosis treatment for predicting outcome: systematic review and meta-analysis. *Lancet Infect Dis.* **2010**;10(6):387–394.