

## A REVIEW ON BEDAQUILINE IN THE TREATMENT OF MULTI-DRUG-RESISTANT TUBERCULOSIS

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### ABSTRACT

Multidrug-resistant tuberculosis (MDR-TB) presents formidable treatment challenges, and tuberculosis (TB) continues to be a major global health concern. As the first medication created especially for tuberculosis in more than 40 years, bedaquiline, an antimicrobial agent based on the diarylquinoline class, marks a significant advancement in the treatment of tuberculosis. It interferes with Mycobacterium tuberculosis's energy metabolism by targeting ATP synthase. Bedaquiline, which was approved by the FDA in 2012, has demonstrated encouraging outcomes in treating MDR-TB, even in patients who are resistant to fluoroquinolones and other first-line treatments. Its distinct pharmacokinetics and structure, which include primary excretion through feces and high bioavailability with meals, increase its effectiveness and lessen cross-resistance. The significance of suitable companion medications is highlighted by the drug's vulnerability to resistance brought on by genetic mutations. QT interval prolongation and mild to moderate side effects are safety concerns prescribed as a component of combination therapy for patients with pulmonary MDR-TB who are older than 18.

**KEYWORDS:** Multidrug-resistant tuberculosis, Bedaquiline, ATP synthase, Mycobacterium tuberculosis, fluoroquinolones, mortality.

### I. INTRODUCTION

Tuberculosis (TB) is one of the many communicable diseases has a significant position in the world as one of the numerous global causes of death.<sup>[1]</sup> Considering the most recent published World Health Organization report from 2023.

(WHO), approximately 10.6% of people had tuberculosis in 2022. million people (between 9.9 and 11.4 million), casting 3.5% more than the 10.3 million (with a range of 9.6–11.0 million) in 2021. The incidence of tuberculosis worldwide 133 new cases per 100,000 people were predicted to occur in 2022. Annually, with a 95%

confidence interval of 124–143. Between 2020 and 2022, the incidence of tuberculosis rose. 3.9%. The majority of TB cases worldwide in 2022 were concentrated in thirty nations with high rates of tuberculosis, which made 87% of the total Of these eight nations, specifically China, India, Indonesia, Nigeria, Pakistan, and the Philippines Bangladesh and the Democratic Republic of the Congo constituted two-thirds of the global total, with India having the highest percentage, 27%. The distribution of tuberculosis cases Children (0–14 years old) made up 12% of those in 2022, while 33% were of them, 55% were women and 55% were men. Mycobacterium tuberculosis caused an estimated 1.30 million fatalities

globally and almost went back to the level noted in 2019. Following the coronavirus illness the number of TB-related deaths during the COVID-19 pandemic in 2019 grew to 1.6 million in 2021 (between 1.4 and 1.5 million fatalities). from tuberculosis in 2020 and 2019, respectively.<sup>[2]</sup> The year Global case notifications increased in 2022 due to the 7.5 million cases were diagnosed and initiated last year. 70% of estimated incident cases are related to treatment. This represented a 16% rise in notifications compared to 2021 and a 5% more than in 2019. In comparison to 2021, TB mortality dropped by 7% in 2022, and it was 2% lower than in 2019 before the COVID-19 pandemic. India's combined efforts, led to a significant reduction in the Philippines and Indonesia. in the quantity of newly diagnosed cases of tuberculosis worldwide in 2020 and 2021, with each of the three nations exceeding 2019 levels in 2022.

Bedaquiline, a diarylquinoline compound with a unique anti-TB mechanism<sup>[3]</sup>, has received accelerated or conditional approval for use in MDR-TB in the USA (2012) and Europe (2014), with The WHO offers interim guidelines for its use.<sup>[4]</sup> A placebo-controlled, randomized experiment (TMC207-C208), bedaquiline treatment for 24 weeks considerably raised the culture conversion rate in MDR-TB patients.<sup>[5]</sup> Adverse events (AEs) were similar overall, but a higher the bedaquiline group experienced more deaths than the placebo group (10 (12.7%) versus 2). (2.5%), correspondingly). Based on evaluations of stage 2 of C208's interim results, Bedaquiline was made available for compassionate use in 2011 before receiving regulatory approval in 40 countries, according to analyses of the interim results of stage 2 of C208. Recently, a number of groups have shared their experiences from the Compassionate-U programs, which have given over 700 patients access globally.<sup>[6-9]</sup>

This study's (TMC207-C209) goal was to assess bedaquiline's safety, tolerability, and effectiveness when used in conjunction with a background regimen (BR) for the treatment of a larger group of patients with drug-resistant TB, including pre-XDR and XDR-TB. Here, we present the phase 2, open-label trial's final safety and efficacy data and talk about how they compare to other bedaquiline studies for MDR-TB.<sup>[10-11]</sup>

DR-TB, or drug-resistant tuberculosis, is still a frequent cause of death and an immediate threat to public health because of a contagious disease. In 2023, there were an estimated 400,000 cases of multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB) worldwide. Of the projected Four major countries accounted for more than half of all cases of MDR/RR-TB in 2023: China (7.4%), India (27%), the Russian Federation (7.5%), and Indonesia (7.4%). However, despite this burden, treatment success rates have increased to 68% worldwide as a result of countries successfully implementing bedaquiline-based, newer regimens for MDR/RR TB.<sup>[12]</sup>

The treatment is not the only factor that determines a regimen's effectiveness. success at the conclusion of therapy as well as by avoiding re disease recurrence following treatment. Recurrence following completion of TB treatment may result in a relapse due to the endogenous activation using the identical strain of *Mycobacterium tuberculosis* (M.tb) from dormant bacilli reservoirs or external reinfection with a fresh strain.<sup>[13]</sup> Inadequate TB is suggested by high relapse rates treatment, while reinfection indicates continued community transmission. Relapse and reinfection can be distinguished using genotyping techniques that identify differences in repetitive sequences in *M. tuberculosis* complex strains.<sup>[14]</sup>

More modern drugs and therapy regimens have emerged as a way of successfully controlling DR-TB. Combinations of bedaquiline (BDQ) and linezolid (LZD) in conjunction with either pretomanid (Pa) or delamanid (Dlm), as Several studies have demonstrated that high treatment success rates.<sup>[15-18]</sup> Every combination of oral, non-injectable One benefit of regimens is increased patient compliance. Just once adherence, a shorter treatment duration, and fewer toxicities as opposed to other conventional longer injectable regimens. Despite the many benefits, there isn't much evidence of the long-term These condensed oral regimens work well to stop there currence in individuals with MDR-TB, DR-TB, and MDRDR-TB Less than 1% of RRTB patients in a South African cohort were receiving shorter bedaquiline-based regimens that included levofloxacin or moxifloxacin, pyrazinamide, clofazimine, and ethambutol. Approximately 7% of patients passed away during the follow-up period following treatment.<sup>[19]</sup> Eight comorbidities, such as HIV, inadequate nutrition, and excess weight monetary TB was one of the indicators of inadequate care. results in a group of Ethiopian patients with MDR/RRTB.<sup>[20]</sup> Within In this day of shorter oral regimens and fewer medications, the necessity to determine the variables that might indicate people who might have superb response to treatment with a shorter regimen and might need a longer the length of treatment is crucial. The mitochondrial toxicities of Linezolid 600 mg leading to dose modifications such as stopping treatment, lowering dosages, or this Previous research has documented continuation. A simuImperial et al.'s lation model indicated that the dosage of linezolid reduction could lessen the likelihood of related toxicities and recommended additional research for effectiveness. Ten Here, we outline the lengthy term results following a 48-week post-treatment follow-up in a group of DR TB patients receiving bedaquiline treatment regimens based on pretomanid and linezolid in which different dosages were administered for varying lengths of time.<sup>[21]</sup>

### Bedaquiline

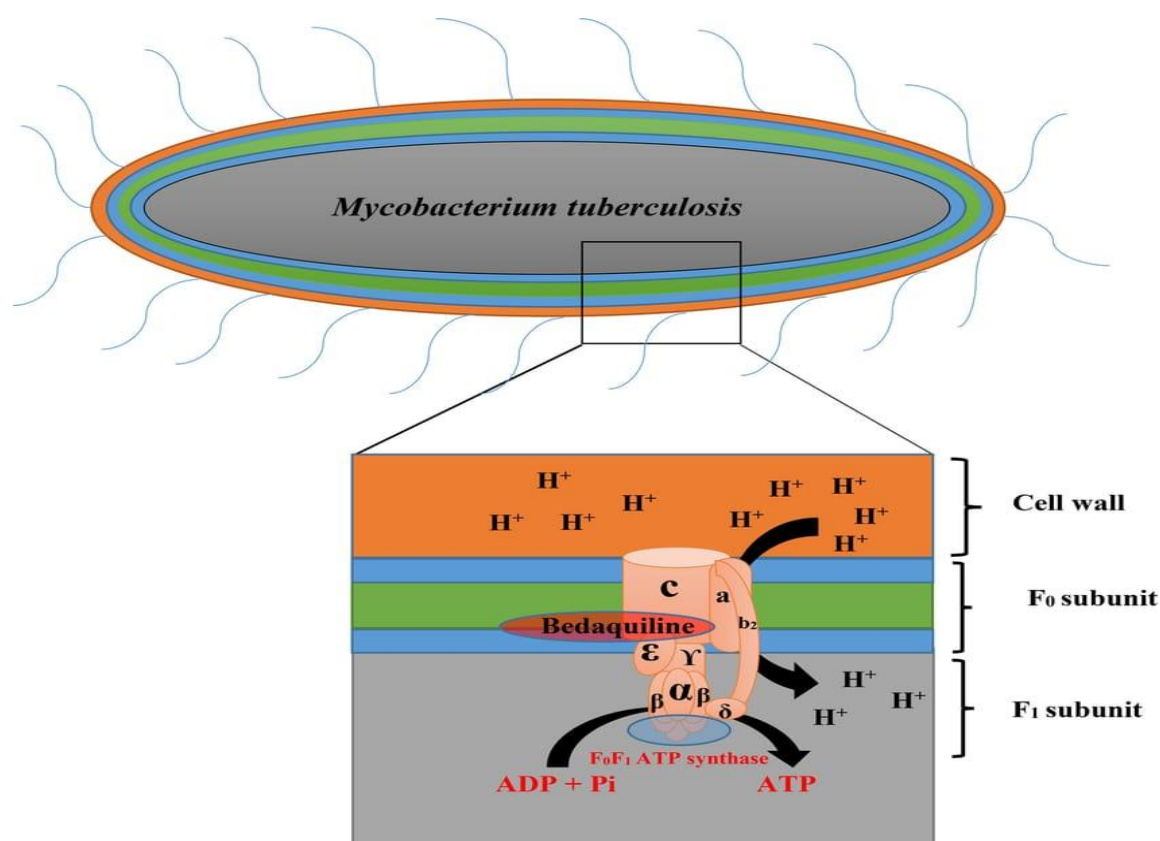
It is a novel anti-TB medication (previously called TMC-207). or R207910), a diarylquinoline medication recommended as a component of combination treatment in adults (≥18 years old) with MDR-TB in the lungs,

with a unique mechanism of action against tuberculosis-causing *Mycobacterium*. It is discovered to be successful in combating both drug-bug and drug-susceptible resistance to tuberculosis, including strains that are resistant to streptomycin, pyrazinamide, Ethambutol and moxifloxacin. It has sterilizing and bactericidal properties against various mycobacterial species, including *M. tuberculosis*, but minimal action against other bacteria. The amazing This medication's ability to sterilize also makes it appealing medication in the TB eradication strategy. It is discovered to active in macrophages and shows promise as an agent in reducing the length of anti-TBT therapy.

## II. MECHANISM OF ACTION OF BEDAQUILINE<sup>[22,23,24]</sup>

Its antimycobacterial activity is distinct and targeted. It acts by focusing on M's ATP synthase subunit C

tuberculosis, resulting in proton pump inhibition ATP synthase activity. Consequently, the substance targets metabolism of bacillary energy. ATP synthase is essential. enzyme that helps *M. tuberculosis* produce ATP. Bedaquiline's attachment to the proteolipic and oligomeric Mycobacterial ATP synthase subunit C results in suppression of ATP production. This results in the demise of mycobacteria. Unlike a number of other bacteria, which can generate enough ATP at the substrate level phosphorylation and withstand ATP synthase deletion It has been demonstrated that ATP synthase is necessary for optimal expansion of *M. tuberculosis*. Subunit C mutations.



## III. PHARMACODYNAMICS AND ANTIMICROBIALS PROPERTIES<sup>[25,26,27,28,29]</sup>

According to in vitro research, bedaquiline significantly inhibits Drug-resistant and drug-sensitive mycobacteria TB at a minimum inhibitory concentration (MIC) of 0.03. Each liter contains 0.12 milligrams/L. It has been suggested that dormant mycobacteria have lower ATP store(these mycobacteria have mild ATP synthase activity which is necessary for their survival) which makes these microorganisms more vulnerable to further ATP depletion from bedaquiline even at nanomolar concentrations. This action turns it into an effective sterilizer that fights mycobacteria and a better than other

first-line anti-TB drugs. The inhibitory effect of medication has been shown to be significant and powerful. Against nontuberculous louslous mycobacteria (NTM), As an example, *M. avium*, *M. intracellulare*, *M. abscessus*, and *M. ulcerans*. In these conditions, it is almost as active as in *Mycobacterium tuberculosis*. It also has good activity against MAC, *M. leprae*, *M. bovis*, *M. marinum*, *M. fortuitum*, *M. Kansasii*, *M. szulgai*. It was found Ordered that it takes two to four days for its antibacterial properties to become apparent. For instance, this lag time may result from its mode of action. delayed intracellular pH disruption and ATP depletion balance. A

significant bactericidal impact has been reported four to seven days after starting the course of treatment.

### **DLM synergy with BDQ**

Every 14 days, the electrocardiogram (ECG) was repeated while the patient's condition was closely monitored, one significant risk factor for severe cardiac arrhythmias is a QTc interval greater than 500 ms. Healthcare providers should stop treating patients who exhibit this sign and closely monitor them.<sup>[35]</sup> In addition to adjusting electrolyte balance, serum albumin levels, and ECG QT wave duration, the use of BDQ was resumed after nearly a month, which resulted in a negative sputum smear and culture during the two-month follow-up. Additionally, Ferlazzo et al.<sup>[36]</sup> carried out a thorough investigation in 2018 to assess the safety and effectiveness of the combined treatment strategy involving BDQ and DLM regimens in patients with MDR-TB in South Africa, India, and Armenia. The effectiveness and safety of these treatment combinations in various geographic contexts were clarified by this retrospective cohort study. The study's findings imply that BDQ and DLM combined therapy does not have a synergistic or additive effect on QTc prolongation.

### **PZA's synergy with BDQ**

PZA primarily targets vital bacterial functions like ribosomal translation and proton drive. Combining BDQ with other substances may suppress bioenergetic processes and potentially deplete cellular energy stores because BDQ inhibits ATP synthase.<sup>[37]</sup> The first study on the efficacy of BDQ in the intravenous infection of Swiss mice found that the combination therapy of BDQ and PZA is more bactericidal than the traditional first-line therapy and has a synergistic effect during the sterilization phase.<sup>[38]</sup> A recent study on the response of BALB/c and C3HeB/FeJ mice to treatment with BDQ and PZA administered either separately or in combination showed that the bacterial load in the lungs decreased after four weeks of treatment. Additionally, co-administration of BDQ and PZA demonstrated potent synergistic effects that enhanced bactericidal efficacy in vitro. BDQ's inhibitory effect on energy metabolism, when paired with PZA, produced a synergistic effect that decreased *Mycobacterium bovis* BCG, a model for bactericidal activity.

Additionally, the results of a randomized EBA (early bactericidal activity) trial involving therapy-naïve patients with sputum smear-positive, drug-susceptible pulmonary tuberculosis were reported by Iacon et al. BDQ, BDQ-PZA, PA-824-PZA, BDQ-PA-824, PA-824-moxifloxacin (MFX)-PZA, or standard anti-TB drugs were administered to the participants as the control group. PA-824-MFX-PZA's mean 14-day EBA was comparable to that of standard medications and significantly higher than the other combinations.<sup>[39]</sup> They seemed to be safe and well-tolerated. A single inflection points at 6.5 days caused a delay in the start of BDQ activity. This result is explained by PZA's enhancement

of BDQ activity, which results in a synergistic increase in both BDQ and PZA activities as opposed to BDQ acting alone. Although there was no apparent contradiction, the addition of PA-824 to BDQ seemed to have little to no effect on BDQ activity.

### **BDQ and Pretomanid Synergy**

Pretomanid (PA-824), an oral nitroimidazo-oxazine, has become a novel antimycobacterial medication since 2019. It can be used alone or in conjunction with other innovative agents to treat tuberculosis.<sup>[40]</sup> By preventing the synthesis of mycolic acid, PA-824 eliminates active MTB by preventing the formation of cell walls. PA-824 works well against non-replicating bacilli in hypoxic or anaerobic environments.<sup>[41]</sup> The combined effects of BDQ and PA-824 in treating tuberculosis in mouse models and patients with pulmonary TB have been investigated in a number of studies.<sup>[42]</sup> The antagonistic interaction between PA-824 and BDQ has been studied in a number of studies, and the results show that BDQ plus PA-824 is as effective as traditional first-line therapy for two to three months. However, it was found that BDQ monotherapy was more effective than combination therapy during the first month.<sup>[43,44]</sup> A number of studies involving the addition of PA-824 to BDQ-containing treatment regimens have been started in recent years due to encouraging clinical data on enhancing bactericidal activity, preventing acquired BDQ resistance, and decreasing relapse time in drug-susceptible isolates.<sup>[45]</sup> For the treatment of pulmonary RR, MDR, or pre-XDR-TB patients 14 years of age or older, PA-824 is currently approved for use in BDQ-PA-LZD-MFX (BP<sub>a</sub>LM) and BDQ-PA-LZD (BP<sub>a</sub>L) combination regimens.<sup>[46, 47]</sup>

## **IV. BACTERIAL RESISTANCE<sup>[48,49,50,51]</sup>**

It has been discovered that resistance is linked to twopoint mutations: A63P and D32V. This section of the gene codes the ATP's membrane-spanning domain. subunit of synthase C. It has been discovered that the gene ATP synthase subunit C is encoded by *atpE*, and it possesses an amino acid sequence that is extremely conserved. The mutations (at position 63, where proline replaces alanine or the methionine at position 66. replaces leucine) of the *atpE* gene prevents the binding of the medication to the ATP synthase enzyme's c subunit. It is believed that the medication has a binding pocket around Glu61 is an amino acid residue. Mutations at these sites interfere with the access of bedaquiline to its target site residue 61. This leads to either natural or acquired resistance. Natural resistance is mainly seen in NTM, while acquired resistance is mainly seen in *M. tuberculosis*.

## **V. ADVERSE DRUG REACTIONS, DOSAGE DRUG INTERACTIONS, WARNINGS, AND CONTRAINDICATIONS**

Dosage 400 mg once daily with food for weeks one and two, week 3–24:200 mg three times a week with food, for a total dosage of 600 mg every week.<sup>[52,53]</sup> The side

effects of TMC207 are not severe. and comprise diarrhea in 26% of patients and nausea in 13% of patients, along with additional conditions like arthralgia, pain in extremities, and hyperuricemia in a tiny percentage of patients.

At 400 mg per day, it was linked to a low adverse event rate. The most often reported incidents were diarrhea (7%) and rash (7%) following a 100 mg dosage. somnolence (7%) in the 400 mg dose. Two patients treated with 400 mg, died 14 and 34 days after the end of bedaquiline treatment, but neither of the deaths (one from hemoptysis and the other from complications of TB and Bedaquiline was thought to be the cause of AIDS).

The electrocardiogram showed increase in the QT interval, but no pathologically prolonged QT or corrected QT values were reported. Most of adverse events were of mild or moderate in nature; nausea, diarrhea, arthralgia, dizziness, hyperuricemia and eye disorders were more frequently observed in patients treated with bedaquiline. Incidence of nausea was significantly higher in bedaquiline group.<sup>[54,55]</sup> However, only a limited number of patients have been exposed to this drug, so that the full side-effect profile is unclear.

#### **Important precautions and contraindications are**<sup>[48, 54, 55, 52, and 53]</sup>

Before beginning treatment, an ECG should be performed and at least 2, 12, and 24 weeks after starting treatment. Baseline levels of potassium, calcium, and magnesium in the serum should be monitored and corrected if abnormal. When the medication is taken with other QT medications, there is a higher chance of QT prolongation if the drug is coadministered with other QT prolonging drugs e.g. macrolides, fluoroquinolones etc.

- ☐ There is history of Torsade de Pointes or congenital long QT syndrome
- ☐ There are low levels of serum magnesium, calcium, or potassium

Stop taking bedaquiline if any of the following happens: Clinically significant ventricular arrhythmia QTcF interval longer than 500 ms Bedaquiline is metabolized by CYP3A4; concurrent use of strong CYP3A4 inducers, including rifampin, rifapentine, Rifabutin) ought to be avoided since they may lower bedaquiline-related treatment failure. Combining CYP3A4 inhibitors may result in an increase in systemic concentrations and cause an increase in detrimental effects; concurrent use of strong CYP3A4 inhibitors such as ketoconazole, ciprofloxacin, and other quinolones should be avoided, but, if necessary, it shouldn't exceed more than 14 consecutive days. The drug has shown synergistic effects of pyrazinamide (in vitro).

Use during pregnancy: Pregnancy has been assigned category B, no damage to the growing fetus was

discovered in preclinical research, but there aren't many human studies, and More information is needed.

**Hepatic Disease:** Usually, there is no need to change the dosage. in individuals who have mild to moderate liver impairment. has not been investigated in individuals with severe hepatic disease and should be used with caution in these patients. only when the advantages surpass the dangers.

**Renal Disease:** The majority of research was done in individuals with healthy kidneys, so sufficient information is not available. Patients do not need to change their dosage. with moderate to mild renal impairment, but ought to be When treating patients with severe renal disease, use caution.

Clinical data about the combined application of Antiretroviral drugs and bedaquiline in HIV/MDR-TB coinfecting people and limited clinical data about the Use of bedaquiline in HIV/MDR-TB Individuals with co-infections not using antiretroviral drugs.<sup>[52,53]</sup> Patients who are at least eighteen years old are currently recommended to use it. years old, making it unsuitable for kids. No. For senior patients over 65, adequate information is available, more experiments are needed to determine its safety and effectiveness in elderly patients.<sup>[52,53]</sup>

#### **Novel 9-month all-oral treatment plans**

Five 9-month, all-oral regimens for treating MDR-TB without fluoroquinolone resistance were evaluated in the end TB clinical trial.<sup>[56]</sup> These regimens included combinations of drugs like bedaquiline, levofloxacin or moxifloxacin, linezolid, clofazimine, delamanid, and pyrazinamide. When compared to the longer all-oral bedaquiline-containing regimens (≥18 months) recommended by the WHO, three regimens were found to be safe and non-inferior in efficacy.

#### **The financial effects of treating tuberculosis**

The economic effects of new DS-TB regimens have not been thoroughly studied. However, research indicates that shorter DS-TB regimens may save money for patients and healthcare systems.<sup>[57]</sup> On the other hand, shorter or all-oral MDR-TB regimens may lower the cost of purchasing medications.<sup>[58,59]</sup> BPaL and other shorter regimens reduced costs by 15–32%, demonstrating that shorter regimens were more economical than longer ones.<sup>[60,61]</sup> To validate these results in various contexts, more economic research is required.

## **IX. CONCLUSION**

Bedaquiline has emerged as a breakthrough in the management of multidrug-resistant tuberculosis (MDR-TB), addressing one of the most critical challenges in global public health. By specifically inhibiting ATP synthase in Mycobacterium tuberculosis, it introduces a novel mechanism of action that is effective even against strains resistant to conventional first-line drugs. The

inclusion of Bedaquiline in combination treatment regimens has significantly improved patient outcomes, including faster sputum culture conversion, higher treatment success rates, and the potential for shorter and more tolerable therapy durations. This has marked a shift toward more effective and patient-friendly MDR-TB treatment strategies. However, the use of Bedaquiline requires careful clinical monitoring due to possible adverse effects, particularly cardiotoxicity such as QT interval prolongation. Rational use, adherence to guidelines, and pharmacovigilance are essential to maximize its benefits while minimizing risks and preventing the development of further drug resistance. In conclusion, Bedaquiline represents a major advancement in MDR-TB therapy and plays a crucial role in strengthening global tuberculosis control efforts, offering renewed hope for improved management and eventual eradication of the disease.

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