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Advantages and Disadvantages of New Drugs: **Bedaquiline** and **Delamanid** in the Treatment of Multi-drug Resistant *M. Tuberculosis*

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Introduction

"The End TB Strategy "

Tuberculosis (TB) is a major public health problem that is becoming increasingly concerning in global

In 2018, the World Health Organization (WHO) estimated 10.0 million cases of TB

The burden of disease is very heterogeneous among countries, with the global average being around 130 new cases per 100,000 population per year.

- According to the WHO, almost 500,000 cases of rifampicin-resistant TB (RR-TB) were diagnosed in 2019, of which 78 % were multidrug-resistant TB (MDR-TB) that is resistant to both isoniazid and rifampicin

In 2021 alone, there were 450,000 new patients with MDR-TB

An estimated 25,000 to 32,000 children develop MDR/RR-TB each year

MDR/RR TB is one of the leading causes of death worldwide

and has been drawn attention for its severe form in children

Among MDR-TB cases, 10 % are additionally resistant to fluoroquinolone and second-line injectables, that is, extensively drug-resistant tuberculosis (XDR-TB)

India, China and the Russian

The MDR-TB epidemics in these countries are associated with persistent obstruction in socioeconomic development

MDR/RR TB is difficult to treat due to the lack of effective drugs, which are costly, require a long treatment period and potential for adverse effects

Studies showed that MDR-TB treatment drugs such an aminoglycosides can cause irreversible ototoxicity, hepatotoxicity, and neurological side effects

After fifty years of stagnation in identifying new targets and drugs to treat TB, new drugs, bedaquiline and delamanid, have showed promising efficacy in adults

- In 2022, the WHO revised the guidelines for TB treatment in children and adults, recommending the use of new drugs bedaquiline and delamanid to treat MDR-TB

Treatment of TB in children using of the new drug bedaquiline and delamanid

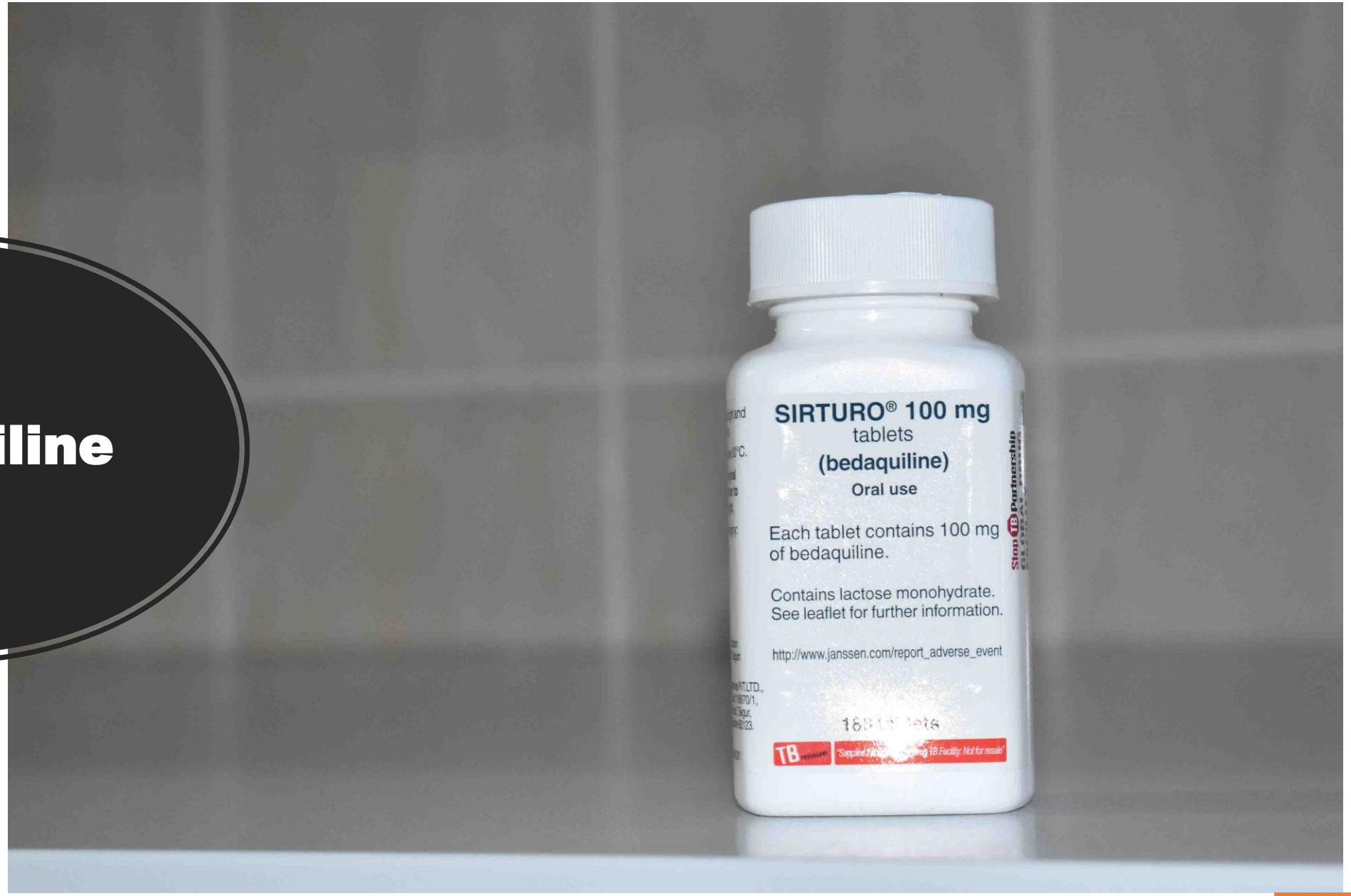
- Historically, the treatment of TB in children has lagged behind that of adults, due to a lack of research
- The duration of TB treatment in children was based on the adult studies, mandating a 6-month combination of daily medications.
- A recent study has recommended that the treatment duration for children with drug susceptible (DS) TB be shortened from 6 months to 4 months

- WHO has updated the dosage recommendations for TB, including MDR/RR TB in children which are based on body weight and age.
- These recommendations include the use of bedaquiline in shorter or longer regimens for treating MDR/RR TB in children of all ages,
- But the use of delamanid in longer regimens for treating MDR/RR-TB in children of all ages
- Children are generally expected to respond to TB treatment as well as or better than adults

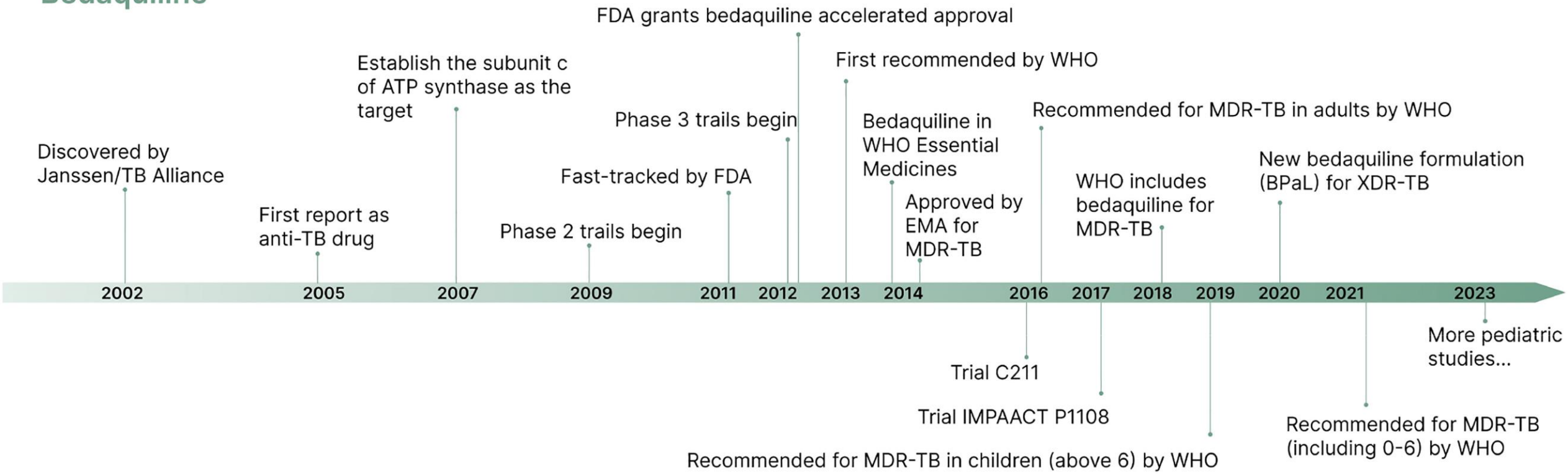
Table 1. The World Health Organization (WHO) groups of multidrug-resistant TB drug.

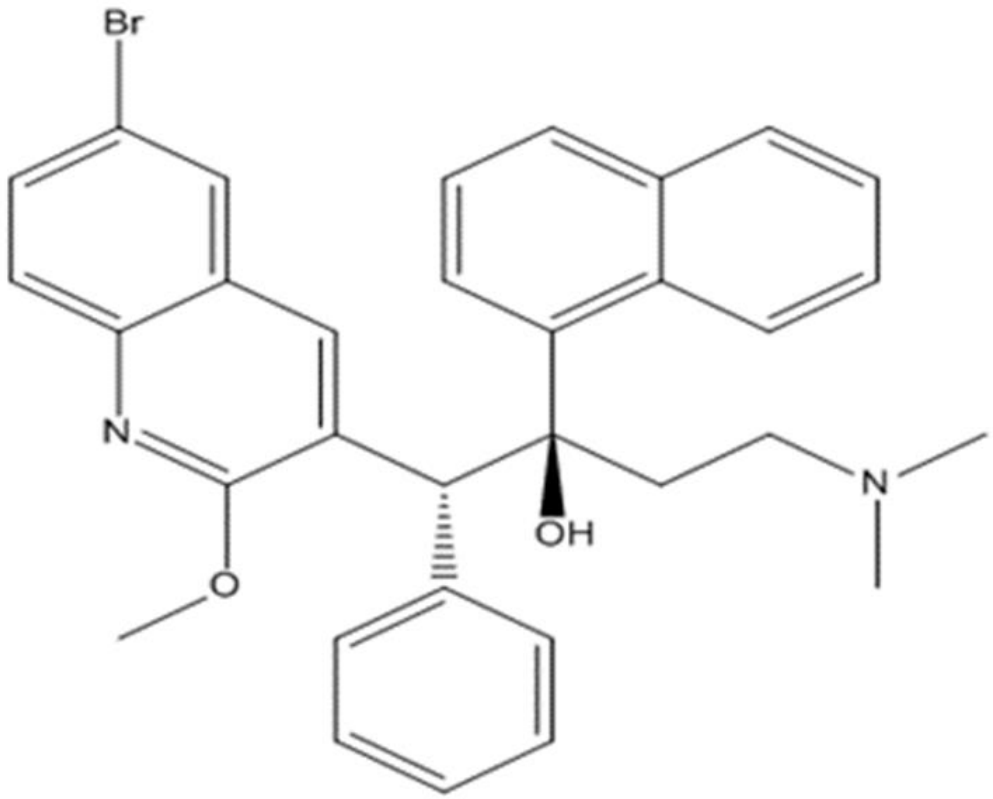
Groups and Steps	Medicine	Abbreviation
Group A: Include all three medicines	Levofloxacin or moxifloxacin	Lfx Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B: Add one or both medicines	Clofazimine	Cfz
	Cycloserine or terizidone	Cs Trd
Group C: Add to complete the regimen, and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin or meropenem	Ipm-Cln Mpm
	Amikacin (or streptomycin)	Am (S)
	Ethionamide or prothionamide	Eto Pto
	P-aminosalicylic acidi	PAS

Bedaquiline



Bedaquiline





Bedaquiline (TMC207)

- Bedaquiline is a diarylquinoline having alcohol and amine groups on its side chains.
- Its antimycobacterial effect is due to these two side chains.
- It has a quinolinic central heterocyclic nucleus
- Molecular formula: C33H31BrN2O2.
- Molecular weight: 555.504 g/mol.

Bedaquiline, was approved for use in adults with MDR-TB in 2013 by FDA

Since the accelerated approval of bedaquiline for MDR-TB treatment in 2012, >2500 patients had already received this drug in 50 countries by the end of 2015.

Its discovery dates back to 2002, when Andries et al. investigated the inhibitory effect of various chemicals on the growth of *M. smegmatis.*

Table 1. In Vitro Activity of Bedaquiline[a] Against *Mycobacterium tuberculosis*.[18,19]

Organism	Isolates, n	Range of MICs (µg/mL)
M tuberculosis		
Drug susceptible[b,c]	41	0.002-0.12
Multidrug resistant[b,c]	44	0.004-0.13

[a]Susceptibility to bedaquiline was determined using an agar dilution method.

[b]MIC_{50} = minimum inhibitory concentration for 50% of tested isolates = 0.03 µg/mL.

[c]MIC_{90} = minimum inhibitory concentration for 90% of tested isolates = 0.06 µg/mL.

Bedaquiline is the first new drug approved for the treatment of MDR-TB since rifampin in 1971.

Although bedaquiline has many advantages as a promising new adult TB drug, more research is required to understand how young children are affected by bedaquiline and what dose to use for them.

Mechanisms of action

It inhibits mycobacterial adenosine triphosphate (ATP) synthase's proton pump.

Prokaryotic as well as eukaryotic cells require the production of ATP for cell life.

Bedaquiline inhibits the generation of ATP.

It binds to mycobacterial ATP synthase at subunit c which is oligomeric and proteolipid. As a result, it causes bacterial death.

- Bedaquiline binds to mycobacterial ATP synthase with more than 20,000 times more affinity than it binds to human mitochondrial ATP synthase.
- It is the reason for specific action in mycobacterium only and minimum host cell damage

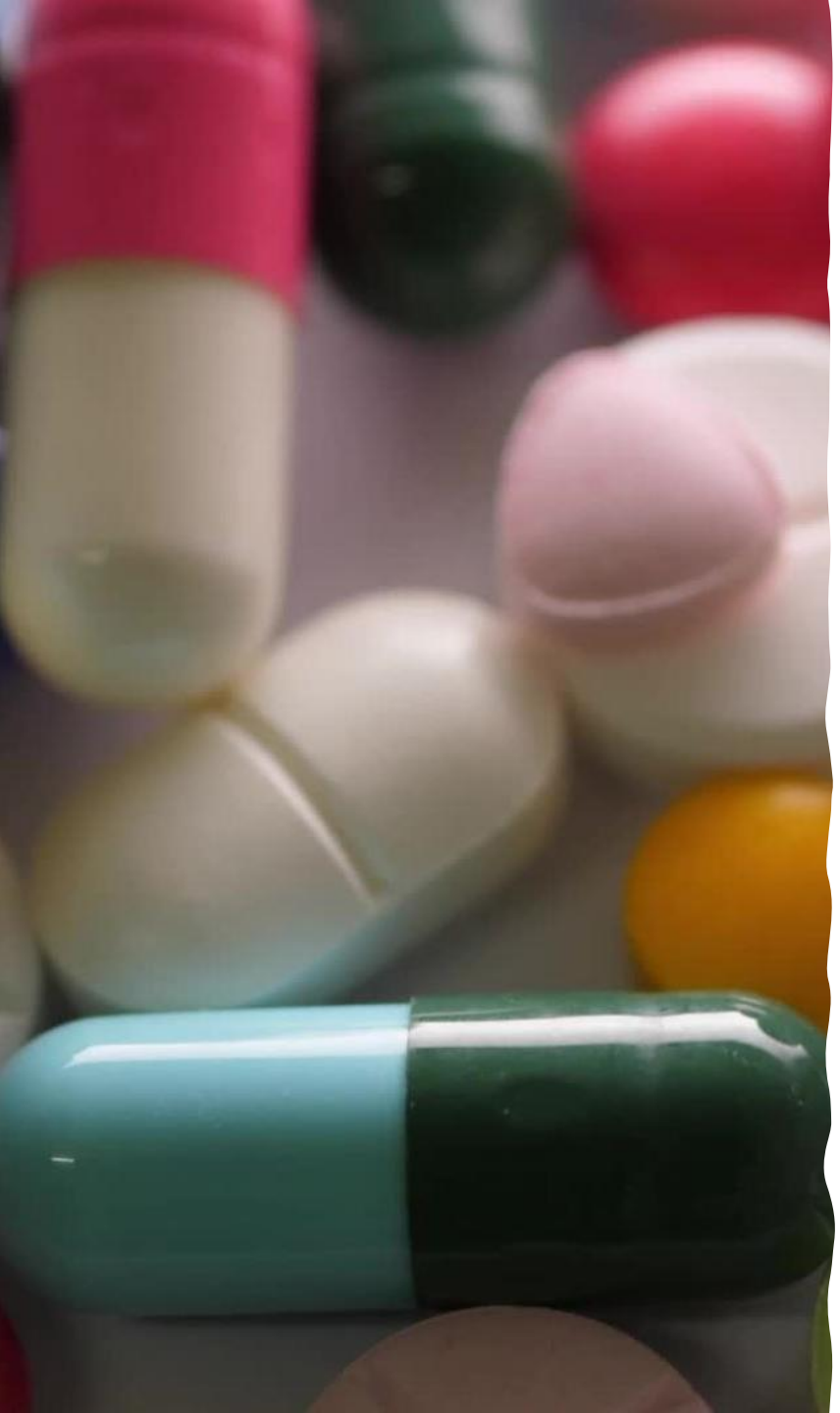
- Studies have shown that bedaquiline exhibits superior in vitro antibacterial activity when compared to other antibiotics.
- This highlights ATP synthase as a promising target for the treatment of TB, as it offers a new mode of action against TB.
- This differs from traditional antibiotics such as quinolones, which block DNA gyrase

- By blocking mycobacterial ATP synthase, bedaquiline kills dormant as well as actively reproducing mycobacteria.
- It inhibits drug-resistant mycobacterium along with drug-sensitive mycobacterium
- Bedaquiline has a substantial inhibitory impact on a wide range of nontuberculous *mycobacteria* (NTM), including *Mycobacterium avium, Mycobacterium ulcerans, Mycobacterium abscessus*, and *Mycobacterium intracellulare*.

Organism	Isolates, n	Range of MIC_{99}	MIC_{50} (µg/mL)
Corynebacterium jeikeium	1		4
C urealyticum	1		4
Helicobacter pylori	20	2 to >4	4
Nocardia asteroids	1		>16
N farcinia	1		>16
Escherichia coli	1		>32
Haemophilus influenza	1		>32
Streptococcus pneumoniae	10	16-64	>32
Staphylococcus aureus	1		>32

Abbreviations: MIC_{50} = minimum inhibitory concentration for 50% of tested isolates; MIC_{99} = minimum inhibitory concentration for 99% of tested isolates.

[a]Susceptibility to bedaquiline was determined using the standard CLSI (Clinical and Laboratory Standards Institute) method of susceptibility testing.



- Bedaquiline does not cross-reaction with other anti tuberculosis drugs, making it effective against both MDR-TB strains and DR-TB strains

Bedaquiline recommended for the treatment of MDR-TB

A clinical study was conducted to evaluate the efficacy of bedaquiline, when added to the standard treatment for DR-TB.

The study found that the addition of bedaquiline significantly reduced the amount of time for patients' sputum to convert to culture when compared to a placebo.

When the patients were followed up for an additional 24 weeks, 50% of the patients in the bedaquiline group achieved culture conversion in 78 days, whereas 129 days in the placebo group

- Similarly, another clinical trial involving patients with DR-TB showed that patients who received bedaquiline had higher rates of sputum conversion compared to those who received a placebo.

- Specifically, after 24 weeks, 79% of patients in the bedaquiline group achieved sputum conversion compared to 58% in the placebo group

- Several studies have supported a significant reduction in the mortality rate of patients who received bedaquiline compared to those who received a placebo

Table 3. Principal studies on bedaquiline in children and adolescents (0–18 years old) with MDR-TB.

Authors (Year)	Type of Study	Study Population	Median Age of Patients (Range)	Therapy	Results
Aschar et al. [55] (2017)	retrospective cohort study	27 patients with confirmed or presumed MDR/XDR-TB	16 years (10–17 years)	Bedaquiline (400 mg once daily for 2 weeks, followed by 200 mg three times a week for 24 weeks), plus background regimen One 10-years-old girl (weighing 35 kg) received 300 mg daily during her loading phase	Sputum culture negative: 23/23 (100%) and No clinical signs suggestive of treatment failure 5 patients (19%) reported adverse effects caused by bedaquiline (prolongation of QTc), without correlated symptoms
Conradie et al. [56] (2020)	Open-label, single-group study	109 patients with MDR/XDR-TB	35 years (17–60 years)	Bedaquiline (400 mg once daily for 2 weeks, followed by 200 mg three times a week for 24 weeks) + Pretomanid (200 mg daily for 26 weeks) + Linezolid (1200 mg daily for 26 weeks)	Unfavourable outcome: 11 patients (10%) vs. Favourable outcome: 98 patients (90%) Serious adverse events: 19 patients (17%) No patient had a QT interval increase > 480 msec.

MDR, multidrug-resistant; TB, tuberculosis; XDR, extensively drug-resistant.

Drug resistance

- Inadequate or incomplete treatment can lead to the selection of resistant mutants.
- Further treatment eradicates drug-susceptible bacteria, allowing the drug-resistant variants to become predominant.
- If an *M. tuberculosis* strain is sensitive only to a single medication in a treatment regimen, the small number of bacteria randomly resistant to that medication will selectively propagate, eventually leading to treatment failure and relapse

Reports of the emergence of bedaquiline resistance soon after introduction are alarming.

bedaquiline resistance can be acquired by *M.tuberculosis* during long-term treatment.

The identification of bedaquiline-resistant strains in MDR-TB patients without prior exposure to bedaquiline suggests that resistance to this drug can emerge spontaneously.

Bedaquiline-resistant mutations are found in 1 out of every 10^8 organisms.

There are three mechanisms for the occurrence of mutation for bedaquiline:

atpE gene

Rv0678

pepQ

Genes	Gene Function	MIC Increase
*atp*E [4, 45]	Coding for a transmembrane protein of the ATP synthase, target of Bdq	8- to 133-fold increase in Bdq MIC
Rv0678 [16, 18]	Regulating the expression of the MmpS5-MmpL5 efflux pump	2- to 8-fold increase in Bdq MIC and 2- to 4-fold increase in clofazimine MIC
*pep*Q [24]	Unclear	4-fold increase in Bdq and clofazimine MICs

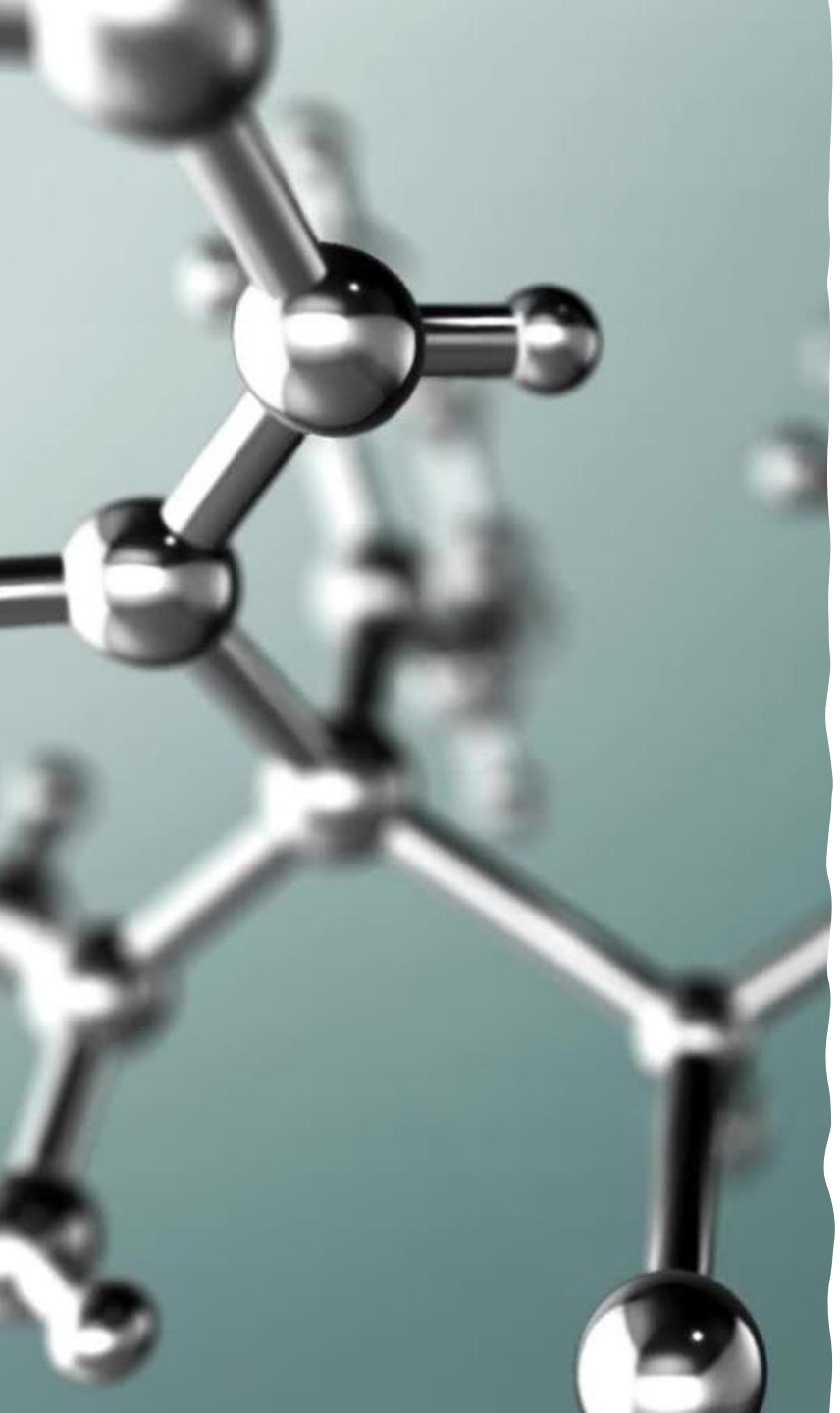
The amino acid sequence of the *atpE* gene is highly conserved.

Mutations in the *atpE* gene at position 63 and position 66 can prevent bedaquiline from binding to the C subunit, thus resulting in resistance to bedaquiline

Mutations in *Rv0678* induced the expression of the MmpS5 and MmpL5 efflux pumps

Expression of efflux pump leads to drug efflux enhancement which is the mechanism behind bedaquiline resistance.

Mutation in *Rv0678* is also bedaquiline resistance and cross-resistance with clofazimine (CFZ) and Linezolid



- *pepQ* have also been shown to cause low-level resistance to bedaquiline and clofazimine
- The gene function of *pepQ* in MTB and how the gene mutation may cause a reduction in susceptibility to bedaquiline and clofazimine remain unclear
- Similar to *Rv0678* mutations

- 2015-2019
- 11 countries
- 5.036 MDR-TB

10%

- Co-resistance to bedaquiline and Linezolid 0.1%
- Co-resistance to Clofazimine and Linezolid 0.3%
- Simultaneous resistance to bedaquiline, Clofaximine, and Linezolid was seen in 3/5,036 isolates (0.06%), all from South Africa

2020, China

- Ten (1.93%) bedaquiline-resistant strains were isolated from 518 MDR – TB
- The resistance rate of bedaquiline was not correlated to sex, age, treatment history, region, or genotype.
- Five bedaquiline-resistant isolates were found to carry *Rv0678* mutations; six mutation types were identified, including G5T, A263G, C185T, G19 deletion, C265T, and T323C.
- No mutations within the *atpE* and *pepQ* genes were observed.

2021, China

339 – 88 MDR-TB

Delamanid - 4.5% (4/88)

Bedaquiline 2.3% (2/88)

2024 – China

1877 MTB-

263 MDR-TB

Table 2
Drug resistance profile of strains enrolled in our study.

Drug resistance profiles	Total percentage, %*
Pan-susceptible	72.5 (1360/1877)
MDR	14.0 (263/1877)
Pre-XDR	7.5 (141/1877)
XDR	0.4 (7/1877)
Resistance to	
INH	21.0 (394/1877)
RIF	15.5 (290/1877)
EMB	4.4 (82/1877)
LFX	12.9 (242/1877)
MOX	13.2 (247/1877)
BDQ	0.2 (4/1877)
LZD	0.8 (15/1877)

MDR, multidrug-resistance; Pre-XDR, pre-extensive drug-resistance; XDR, extensively drug-resistance; INH, isoniazid; RIF, rifampicin; EMB, ethambutol; LFX, levofloxacin; MOX, moxifloxacin; BDQ, bedaquiline; LZD, linezolid. * , the data were shown as percentage, % (no. of isolates/ total no. of isolates).

- The drug resistance rates of BDQ and LZD in MDR-TB were 1.5% (4/263) and 2.2% (6/263)

  - Two strains had mutations at *Rv0678* and *pepQ*,
  - one had an insertion C at condon 156 of the *Rv0678* gene,
  - The other had a substitution of Gly→ Phe at codon 97 of the *pepQ* gene.

- The WHO has issued a caution regarding the potential acceleration of resistance with the inappropriate utilization of Bedaquiline.

- Recently, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) formally approved a cutoff value of ≤0.25 µg/mL as the breakpoint for the application of Bedaquiline.

- Bedaquiline showed bactericidal activity against *M. leprae* in a murine leprosy model.

Three species of nontuberculous *mycobacteria* were found to be intrinsically resistant to bedaquiline:

M. novocastrense (MIC of 8.0 µg/mL)

M. shimoidei (MIC of 8.0 µg/mL)

M. xenopi (MIC 4.0-8.0 µg/mL)

Pharmacokinetics

- **Absorption**:
- Bedaquiline is well absorbed in humans after single and several doses of oral administration.

❖A standard diet containing approximately 22 g of fat has been found to improve bedaquiline bioavailability by a factor of 2 compared to fasting

- Bedaquiline has a linear relationship between dose and maximum plasma concentration (Cmax), and peak concentration is reached on average 5-6 hours after treatment, and an effective half-life of 24 hours on average

- Bedaquiline is mainly metabolized by cytochrome P-450 3A4 (CYP3A4) and is converted to the relatively inactive N-desmethyl metabolite N-monodesmethyl (M2)

AUC
Adults: 25,863 ng·hr/mL
Age 14-18 years: 26,300 ng·hr/mL
Distribution
Protein Bound: >99.9%
Vd: 164 L

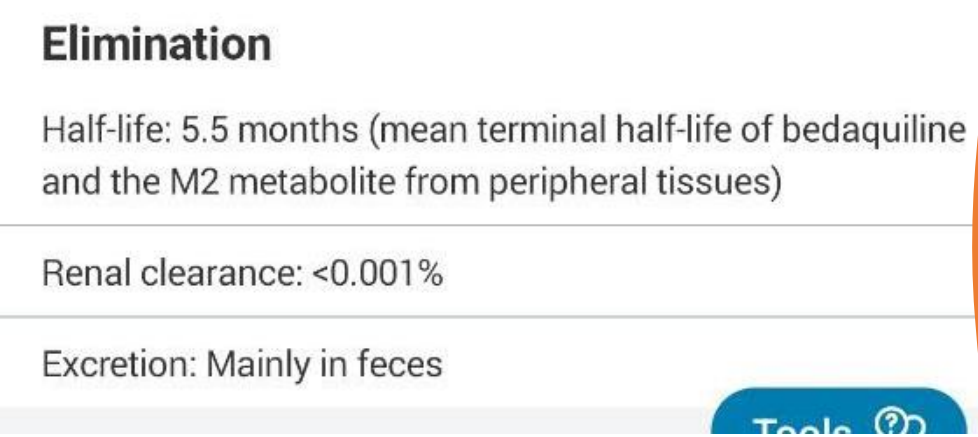
- **Distribution**:

➢ Bedaquiline has a plasma protein binding rate of >99.9%.

❖ Bedaquiline has concentration-dependent bactericidal activity.

Metabolism

- Bedaquiline undergoes phase I metabolism in humans. It undergoes N-methylation in the liver. It is processed by CYP3A4, CYP2C8, and CYP2C19.
- A major role is of CYP3A4.
- The final product is N-monodesmethyl metabolite, M2



Excretion:

Bedaquiline is primarily eliminated by feces.

In feces, 75-85% is eliminated in unchanged form and 3.7-7.2% is M2.

Elimination of unchanged form in the urine is less than 0.001% of the administered dose.

How should this medicine be used?

- It is taken with food once a day for 2 weeks and then three times a week for 24 weeks.
- When taking bedaquiline three times a week, allow at least 48 hours between doses.
- Co-treatment with lopinavir/ritonavir
- Can be used safely in malnourished children

- For the first two weeks, 400 mg (four tablets of 100 mg) of bedaquiline is prescribed which is needed to be taken once daily.
- From weeks 3 to 24, 200 mg (two tablets of 100 mg) of bedaquiline need to be administered three times per week with at least 48 hours between two consecutive doses.

Table 5. Bedaquiline recommended dosing.

Bedaquiline	≥15 Years	< 15 Years	
		16–30 kg	>30 kg
100 mg tab	4 tabs qd for first 2 weeks; then 2 tabs qd M/W/F for 22 weeks	2 tabs qd for 2 weeks; then 1 tab qd M/W/F for 22 weeks	4 tabs qd for 2 weeks; then 2 tabs qd M/W/F for 22 weeks
20 mg dt		10 dts qd for 2 weeks; then 5 dts od M/W/F for 22 weeks	20 dts qd for 2 weeks; then 10 dts od M/W/F for 22 weeks

Dt, dispersible tablet; qd, once daily; M/W/F, Monday, Wednesday, Friday; tab, tablet.4.

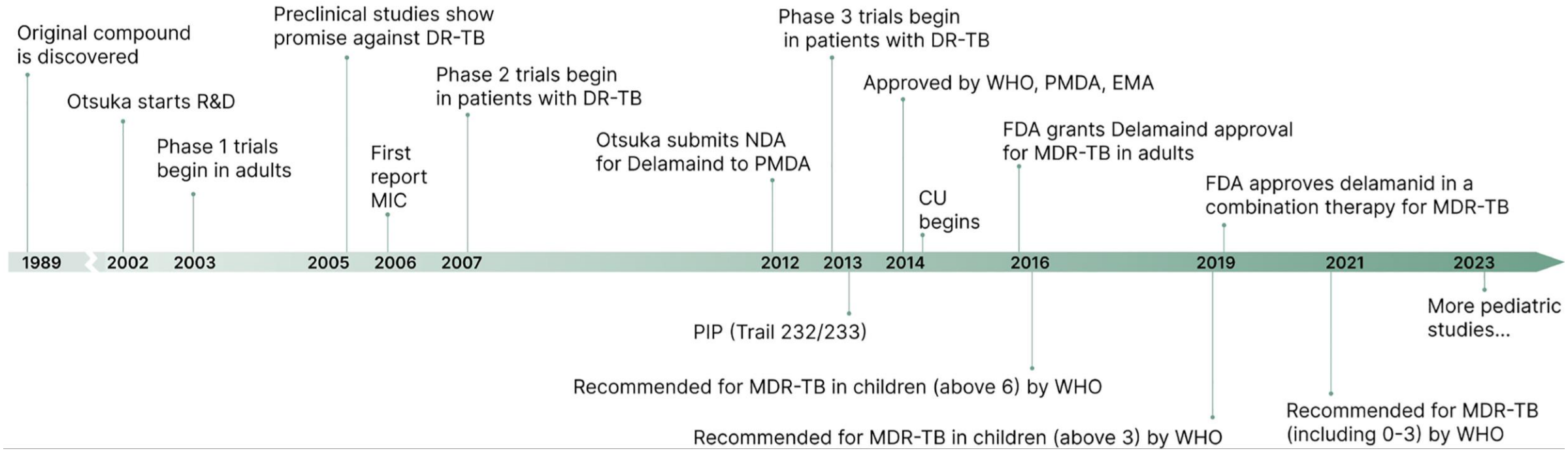
Side effects of bedaquiline

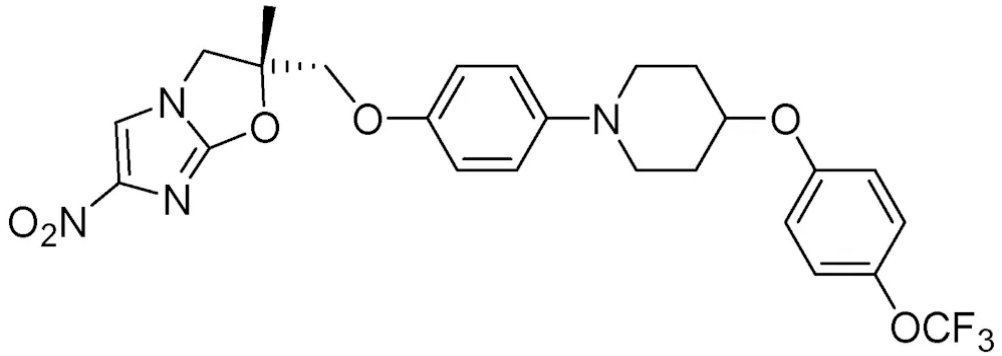
- Nausea, vomiting, diarrhea
- Pain abdomen, limb pain, arthralgia
- Back pain, headache, dizziness, rash,
- Pruritus, acne, hemoptysis, pleuritic pain
- Pharyngolaryngeal pain, deafness, hyperuricemia,
- QT interval prolongation,
- Elevated transaminases

Delamanid


DELTYBA®
delamanid
film-coated tablets
50mg
Each film-coated tablet contains: 50 mg delamanid.
Contains lactose. See leaflet for further information
Box, 6 Blisters @ 10 film-coated tablets
Manufactured by:
Otsuka Pharmaceutical Co., Ltd.
Tokushima Itano Factory
13 Minami, Shishitoki
Matsutani, Itano-cho, Itano-gun
Tokushima, 779-0195, Japan
Imported and Repacked by:
PT. Otsuka Indonesia
Jl. Sumber Waras No. 25
Lawang, Malang 65216, Indonesia
Under License of
Otsuka Pharmaceutical Co., Ltd., Japan
Otsuka

Delamanid


Original compound is discovered
Otsuka starts R&D
Phase 1 trials begin in adults
Preclinical studies show promise against DR-TB
First report MIC
Phase 2 trials begin in patients with DR-TB
Otsuka submits NDA for Delamaind to PMDA
Phase 3 trials begin in patients with DR-TB
Approved by WHO, PMDA, EMA
CU begins
FDA grants Delamaind approval for MDR-TB in adults
FDA approves delamanid in a combination therapy for MDR-TB
More pediatric studies...
1989
2002
2003
2005
2006
2007
2012
2013
2014
2016
2019
2021
2023
PIP (Trail 232/233)
Recommended for MDR-TB in children (above 6) by WHO
Recommended for MDR-TB in children (above 3) by WHO
Recommended for MDR-TB (including 0-3) by WHO



- Delamanid (OPC-67683), a bicyclic nitroimidazole, is a new TB drug developed by Otsuka that has demonstrated potent TB activity in vitro and in vivo
- It was originally discovered in 1989, and improvements have been made to eliminate mutagenicity while increasing its anti-TB effects

- Delamanid, was approved by the WHO, PMDA and EMA in 2014 but has not been approved by the FDA.

- It was estimated that 1,429 patients had received delamanid by March 2018.

- Compared to bedaquiline, the investigation into the clinical effectiveness of delamanid, while promising, is still in its early stages.

Delamanid recommended for the treatment of MDR-TB

- In 2014, Otsuka launched the first compassionate use (CU) program, which aimed to provide free-of-cost delamanid to patients with limited treatment options.

- This program also allowed the combination of delamanid and bedaquiline under certain circumstances.

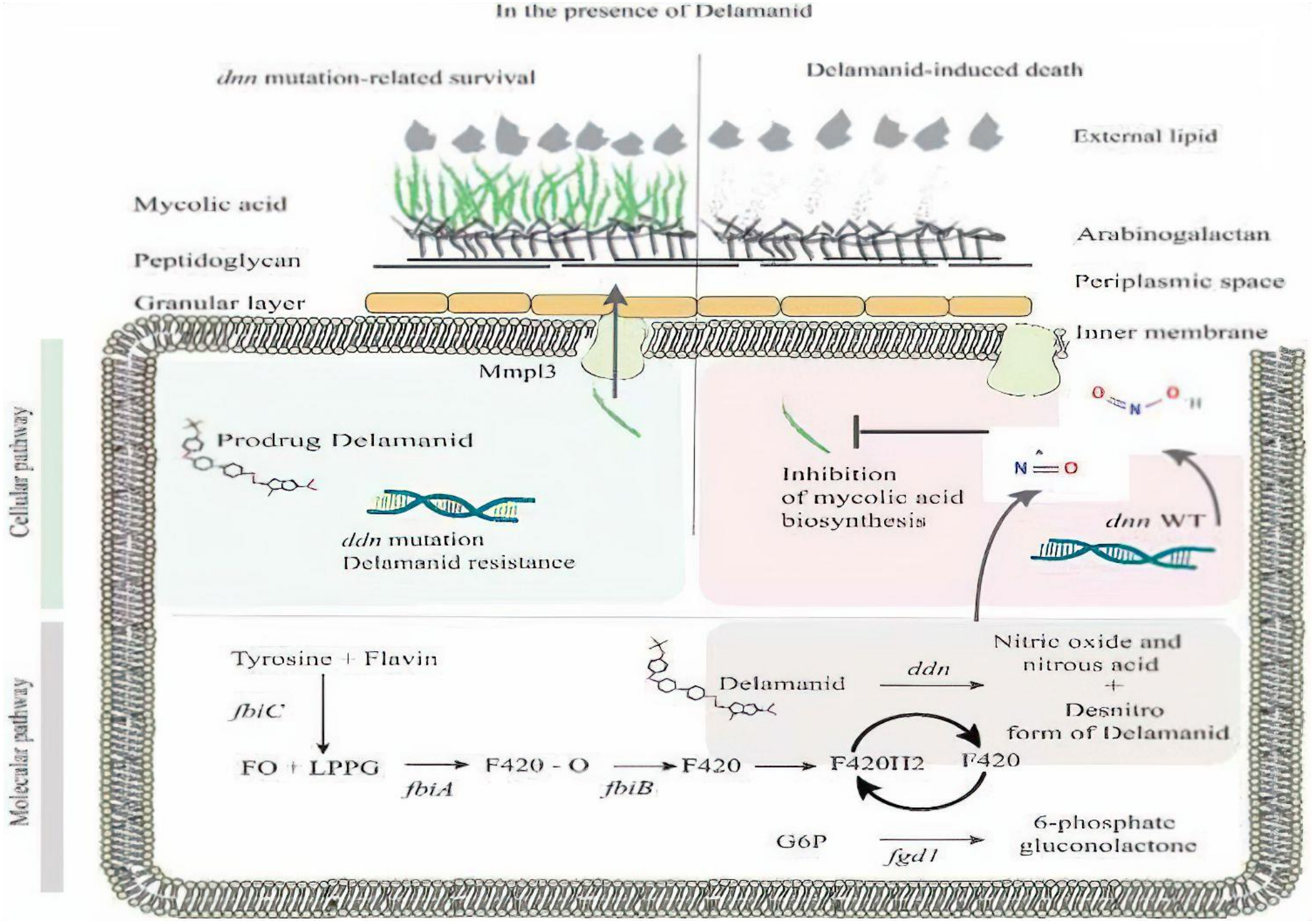
- Studies have shown that 79% of patients treated with delamanid achieved culture conversion, which is a better outcome than those treated with the combination of bedaquiline and delamanid

- Delamanid has the potential to be used as a treatment for TB because it does not show cross-reaction or antagonistic activities with other existing drugs such as isoniazid and rifampicin

- It has been recommended by the WHO for use in longer regimens for the treatment of MDR-TB in children.

Mechanisms of action

- ✓A mycolic acid biosynthesis inhibitor
- ✓Specifically methoxy-mycolic acid and keto-mycolic acid
- ✓Leading to depletion of mycobacterial cell wall components and destruction of the mycobacteria, with bactericidal activity.


In the presence of Delamanid
dnn mutation-related survival
Delamanid-induced death
External lipid
Mycolic acid
Arabinogalactan
Peptidoglycan
Periplasmic space
Granular layer
Inner membrane
Mmpl3
Prodrug Delamanid
ddn mutation
Delamanid resistance
Inhibition
of mycolic acid
biosynthesis
dnn WT
Cellular pathway
Molecular pathway
Tyrosine + Flavin
fbiC
FO + LPPG
fbiA
F420 - O
fbiB
F420
F420H2
F420
Delamanid
ddn
Nitric oxide and
nitrous acid
+
Desnitro
form of Delamanid
G6P
fgd1
6-phosphate
gluconolactone

- These free radicals such as nitric oxide (NO) are essential in mammalian defense mechanisms against mycobacterial infections, making delamanid more effective in treating such infections

By limiting the amount of mycolic acid produced, *M. tuberculosis* reproduction is inhibited, and the abnormal cell wall allows the drug to penetrate the cell.

This makes delamanid more effective in treating mycobacterial infection because mycolic acids are found in the cell walls of *mycobacteria*

- In a phase II study, Gler et al. investigated the efficacy of delamanid for the treatment of pulmonary MDR-TB in 481 patients.
- The treatment regimen was supplemented with 100 mg or 200 mg of delamanid or placebo twice daily for 8 weeks.
- The experimental group receiving delamanid had a higher rate of sputum transformation than the control group, indicating the potential as an effective therapy for MDR-TB

- The studies also indicate that delamanid is safe for long-term use.

- Delamanid should be considered as a potential treatment option for patients with MDR-TB who are unresponsive to conventional drugs or have limited alternatives.

Table 7. Principal studies on delamanid in children and adolescents (0–18 years) with MDR-TB.

Authors (Year)	Type of Study	Study Population	Median Age of Patients (Range)	Therapy	Results
Esposito S et al. [79] (2016)	Case report	1 patient with confirmed pulmonary XDR-TB	12 years	Delamanid 100 mg td for 24 months + BR	Gastric aspirate culture negative after 1 week, the patient was considered cured at the end of the treatment. No adverse events were reported, normal corrected QT interval.
Tadolini M et al. [74] (2016)	Case series	16 patients with confirmed pulmonary MDR/XDR-TB (2 also had extrapulmonary TB)	15 years (8–14 years)	Delamanid 100 mg td for 24 weeks + BR (except one who received 50 mg td)	81.2% culture-negative; no or mild adverse events except one patient who experienced severe vomiting, renal impairment, hypokalaemia, hypomagnesaemia and QT interval prolongation
Kuksa L et al. [81] (2017)	Case series	2 patients with PreXDR/XDR-TB	12 years (11–13 years)	Delamanid for 24 weeks (dosage not reported) + BR	Both patients were considered cured at the end of the treatment. No adverse events were reported, normal corrected QT interval.

BR, background regimen; MDR, multidrug-resistant; qd, once daily; TB, tuberculosis; td, twice daily; XDR, extensively drug-resistant.

Pharmacokinetics

DLM is recognized as highly protein bound (> 97%), and its metabolism is mainly mediated by plasma albumin.

Delamanid pharmakinitic was not affected by the co-administration of bedaquiline

In humans, delamanid absorption was almost two-fold higher when administrated with meals as opposed to in a fasted state

- Delamanid has nonlinear and low water solubility, which can impede its absorption into the body.

- Plasma concentration peaks at around 4–8 h after oral dosing with a half-life of 30–38 h.

- The absolute oral bioavailability in humans is estimated to range from 25 to 47%.

- Although the full metabolic profile of Delamanid is unknown

  - This drug is seemingly converted to its primary metabolite, DM-6705, following the reaction of amino groups in serum albumin to this agent.

  ➢ The DM-6705 is broken down by hydrolysis and CYP3A4 and converted to some other metabolites, which concentration raises to steady state during 6– 10 weeks.

- It is excreted primarily in the stool, with approximately 6% excretion in the urine.

- Animal studies have indicated that delamanid can pass brain and placental blood barriers and is also excreted in breast milk

Table 9. Delamanid recommended dosing.

Delamanid		
Age (Weight Band)	**Dose**	**50 mg Tablet**
3–5 yrs (<24 kg)	25 mg twice daily	- [a]
6–11 yrs (24–34 kg)	50 mg twice daily	1 tablet twice daily
12–17 yrs (>35 kg)	100 mg twice daily	2 tablets twice daily

[a] Giving half a 50 mg adult tablet in these children does not result in the same blood levels observed in trials using the special 25 mg paediatric tablet. Bioavailability may further be altered when the 50 mg tablet is split, crushed or dissolved.

- To improve the effectiveness, it may be necessary to increase food intake or employ other measures such as liposomal formulations or co-administration with other drugs to ensure its effective delivery and absorption into the body.

- Preclinical studies have shown that delamanid is well tolerated, and likely has no genotoxicity or carcinogenicity

Drug resistance

- ✓0.64% (1/156) of MDR-TB were resistant to DLM in Shanghai, China- 2021
- ✓4.5% (4/88) reported in southwest China-2021
- ✓2.9% (3/102) reported in Beijing, China-2022
- ✓8.8% (15/170) reported in Korea-2023

- ❖It has been reported that over 25% of RR-TB isolates displayed resistance to delamanid despite no prior exposure.

TABLE 1 | Epidemiology of delamanid resistance.

References	Country	Published time	No. of MTB isolates	No. of DLM resistant isolates	MIC (μg/ml)	Mechanism of resistance	Resistance rate
Bloemberg et al., 2015	Switzerland	2015	1 (pre-XDR-MTB strain)	1	NM	Mutations in *fbiA* and *fgd1* genes	–
Hoffmann et al., 2016	Germany	2016	1 (XDR-MTB strain)	1	> 2.0	Mutations in *fbiA* gene	–
Schena et al., 2016	Italy	2016	19 (MTB clinical strains)	5	3 strains with > 32 and 2 strains with ≥ 1	Mutations in *ddn* and *fbiA* genes	21%
Stinson et al., 2016	United States	2016	460 (MDR-and XDR-MTB strains)	2 (MDR TB)	1 strain with 1 strain and 1 strain with > 8	Mutations in *ddn* gene	0.43%
Pang et al., 2017	China	2017	90 (all XDR-MTB strains)	4	1 strain with 0.5 and 3 strains with 32	Mutation in *fbiC* gene	4.4%
Yang et al., 2018	Korea	2018	420 (171 MDR, 139 Pre-XDR, and 110 XDR-MTB strains)	41 (15 MDR-, 17 Pre-XDR, and 9 XDR-MTB strains)	0.2	Mutations in *fbiA* or *ddn* (Gly81Ser and Gly81Asp) genes	10%
Polsfuss et al., 2019	Germany	2019	1 (XDR-MTB strain)	1	0.25	Mutation in *ddn*	–
von Groote-Bidlingmaier et al., 2019	Multicenter	2019	511 (Pulmonary MDR-MTB strains)	6 (Baseline resistance was reported in 2 of 511 and 4 of 341 participants during treatment (for 6 months)	NM	NM	At baseline 0.39% (2/511) and during treatment 1.17% (4/341)
Yu et al., 2019	China	2019	52 (33 RGM and 19 SGM NTM strains)	31 RGM and 8 SGM strains	> 0.25	Mutation in *ddn* gene	94% of RGM and 42% of SGM
Jing et al., 2019	China	2019	220 (110 MDR- and 110 XDR-MTB strains)	7 (4 MDR and 3 XDR-TB)	0.2	Mutation in *fbiA* (Glu249Lys) and *fgd1* (Phe320Phe) genes	3.18%
Battaglia et al., 2020	Multi-center	2020	124	39 (26 were resistant and 13 were low level of resistance)	≥ 0.12	Mutation in *ddn*, *fgd*, *fbiA*, *fbiB*, and *fbiC* genes	31.5% (21% resistant and 10.5% low-level resistance)
Kardan-Yamchi et al., 2020	Iran	2020	35 (all MDR-MTB strains)	9	> 0.125	Mutation in *ddn*, *fbiA*, and *fbiC* genes	25.7%

Side effects

- Delamanid can cause QTc prolongation, anorexia, gastritis, malaise, anemia, and psychiatric disorders.
- In children, it may result in liver damage and low white blood cell counts.
- Monitoring for these side effects is necessary to ensure the safe use of delamanid

Combination the new drugs bedaquiline and/or delamanid with other drugs

- The findings suggest that the combination of bedaquiline and delamanid is still an effective regimen for the treatment of MDR-TB, with a low incidence of clinically significant cardiotoxicity.
- The expanded use of this drug combination could be particularly beneficial for unique cohorts, such as TB patients with AIDS.

ClinicalTrials.gov Identifier	Conditions or disease	Age	Enrollment	Intervention/treatment	Phase	Trial Status	Start Date	Completion Date	the source of the clinical trial details information
NCT03828201	**TB, MDR-TB**	**≥12**	**220**	**DLM, LVX, BDQ, CFZ, LNZ**	**II**	**Recruiting**	**Jun 2022**	**Estimated Jul 2025**	https://clinicaltrials.gov/ct2/show/NCT03828201
NCT03896685	**Pulmonary TB, MDR-TB**	**≥15**	**324**	**BDQ, DLM, LNZ, CFZ**	**III**	**Recruiting**	**Apr 2020**	**Estimated Nov 2024**	https://clinicaltrials.gov/ct2/show/NCT03896685
NCT03959566	Pulmonary TB	18-65	75	BDQ, DLM, MXF, SZD	II	Completed	May 2021	Sep 2022	https://clinicaltrials.gov/ct2/show/NCT03959566
NCT04062201	**Pulmonary TB, MDR-TB, XDR-TB, Pre-XDR-TB, RR-TB**	**≥6**	**402**	**BDQ, DLM, LNZ, LVX, CFZ, INH, EMB, PZA**	**III**	**Active, not recruiting**	**Aug 2019**	**Estimated Jun 2023**	https://clinicaltrials.gov/ct2/show/NCT04062201
NCT04081077	Pulmonary TB, MDR-TB, XDR-TB	≥18	240	BDQ, PMD, MXF, LNZ, CFZ	II/III	Active, not recruiting	Aug 2019	Estimated Sep 2022	https://clinicaltrials.gov/ct2/show/NCT04081077
NCT04207112	Pulmonary TB, MDR-TB, XDR-TB	≥18	200	BDQ, PMD, MXF, LNZ, CFZ	II/III	Recruiting	Oct 2020	Estimated Jul 2022	https://clinicaltrials.gov/ct2/show/NCT04207112
NCT04545788	RR-TB	18-65	200	LNZ, BDQ, CS	/	Recruiting	Aug 2020	Estimated Dec 2022	https://clinicaltrials.gov/ct2/show/NCT04545788
NCT04550832	Pulmonary TB	18-65	76	DZD, BDQ, DLM, MXF	II	Active, not recruiting	Oct 2021	Estimated Mar 2024	https://clinicaltrials.gov/ct2/show/NCT04550832
NCT04629378	TB	18-65	22	MPM, co-amoxiclav, PZA, BDQ, EMB	II	Completed	Aug 2020	Jun 2021	https://clinicaltrials.gov/ct2/show/NCT04629378

Conclusion

TB is still one of the most difficult infectious diseases to treat, and the second most frequent cause of death due to infectious disease throughout the world.

The number of cases of MDR-/XDR-TB, which are characterized by high mortality rates, is increasing.

Up to now, resistance to both of the drugs has been reported in vitro, but standardized drug susceptibility testing has not been developed and agreed upon.

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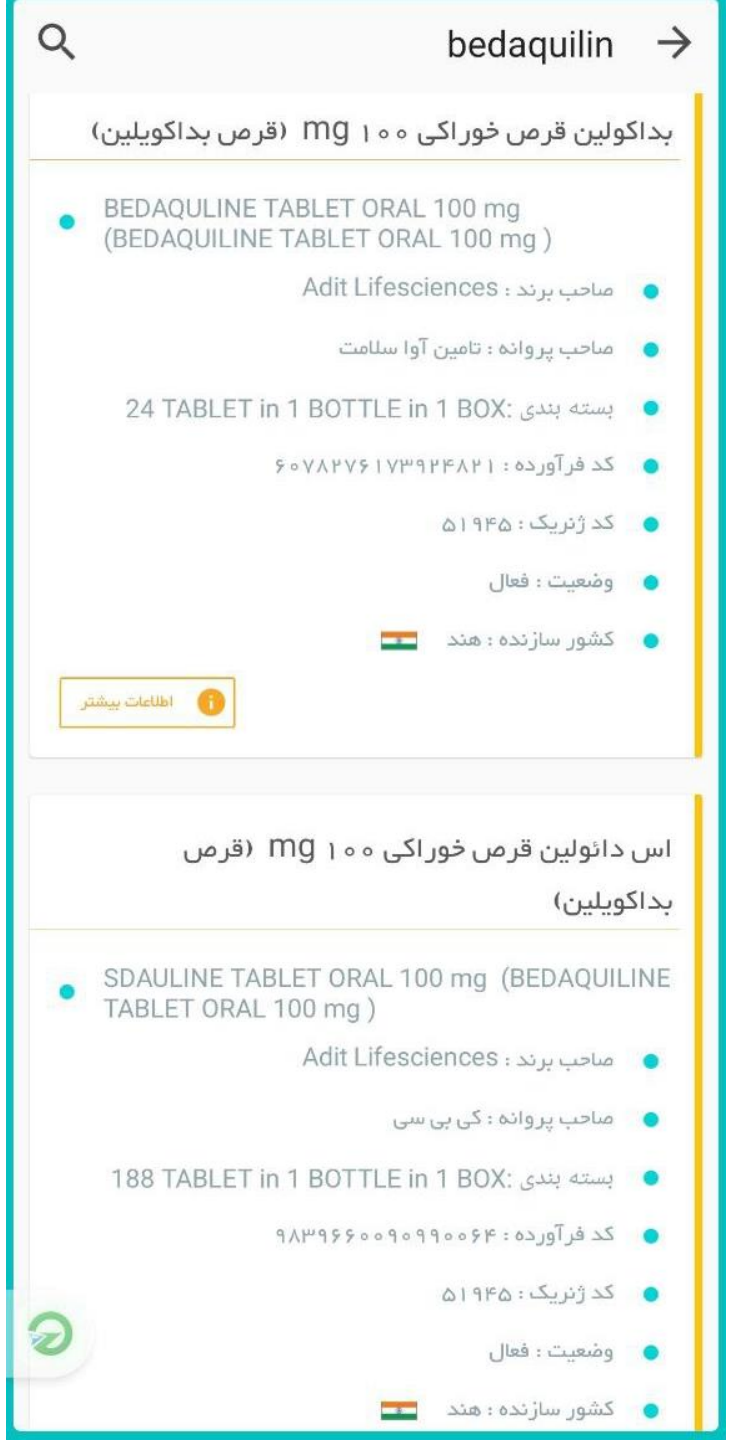
Thank you for your attention

Yours truly,

Sina


bedaquilin
SDAULINE TABLET ORAL 100 mg (BEDAQUILINE TABLET ORAL 100 mg)
صاحب برند : Adit Lifesciences
صاحب پروانه : بازرگانی سها کیش
بسته بندی :24 TABLET in 1 CAN in 1 BOX
کد فرآورده : ۲۷۱۳۷۹۵۹۹۸۳۲۹۳۵۶
کد ژنریک : ۵۱۹۴۵
وضعیت : فعال
کشور سازنده : هند
اطلاعات بیشتر
اس دائولین قرص خوراکی ۱۰۰ mg (قرص بداکویلین)
SDAULINE TABLET ORAL 100 mg (BEDAQUILINE TABLET ORAL 100 mg)
صاحب برند : Adit Lifesciences
صاحب پروانه : ماه داروی حکیم
بسته بندی :24 TABLET in 1 BOTTLE in 1 BOX
کد فرآورده : ۲۳۳۹۸۹۷۵۶۰۸۵۴۷۱۵
کد ژنریک : ۵۱۹۴۵
وضعیت : فعال
کشور سازنده : هند
اطلاعات بیشتر


bedaquilin
بداکولین قرص خوراکی ۱۰۰ mg (قرص بداکویلین)
BEDAQULINE TABLET ORAL 100 mg (BEDAQUILINE TABLET ORAL 100 mg)
صاحب برند : Adit Lifesciences
صاحب پروانه : تامین آوا سلامت
بسته بندی :24 TABLET in 1 BOTTLE in 1 BOX
کد فرآورده : ۶۰۷۸۲۷۶۱۷۳۹۲۴۸۲۱
کد ژنریک : ۵۱۹۴۵
وضعیت : فعال
کشور سازنده : هند
اطلاعات بیشتر
اس دائولین قرص خوراکی ۱۰۰ mg (قرص بداکویلین)
SDAULINE TABLET ORAL 100 mg (BEDAQUILINE TABLET ORAL 100 mg)
صاحب برند : Adit Lifesciences
صاحب پروانه : کی بی سی
بسته بندی :188 TABLET in 1 BOTTLE in 1 BOX
کد فرآورده : ۹۸۳۹۶۶۰۰۹۰۹۹۰۰۶۴
کد ژنریک : ۵۱۹۴۵
وضعیت : فعال
کشور سازنده : هند