New drugs for the treatment of Tuberculosis

CHIANG Chen-Yuan, MD, MPH, DrPhilos
Mechanisms of action of tuberculosis drugs (in preclinical development)

**Multiple targets: nitroimidazoles**
- Inhibit cell wall synthesis and cell respiration
  - Delamanid
  - PA-824
  - TBA-354

**Multiple targets: pyrazinamide**
- Inhibit DNA synthesis including intracellular acidification, disrupts plasma membrane
  - Pyrazinamide

**Multiple targets: riminophenazines**
- Targeting the outer membrane and possibly bacterial respiratory chain and ion transporters
  - Clofazimine
  - TBI-166

**Arabinosyl transferase: ethambutol**
- Inhibit cell wall synthesis
  - Ethambutol

**InhA: isoniazid**
- Inhibit cell wall synthesis
  - Isoniazid

**DprE1: benzothiazinone**
- Inhibit cell wall synthesis
  - BTZ-043
  - PBTZ-169

**Transpeptidase + β-lactamase-carbapenems + clavulanic acid**
- Inhibit cell wall synthesis
  - Faropenem

**Cell wall synthesis: dimethylamine**
- Inhibit cell wall synthesis (transport and processing)
  - SQ109

**ATP-synthase: diarylquinolines**
- Inhibit ATP synthesis
  - Bedaquiline

**Cytochrome bc complex: imidazopyridines**
- Essential for proton gradient and ATP synthesis
  - Q203

**Ribosome: oxazolidinones**
- Inhibit protein synthesis
  - Linezolid
  - Sutezolid
  - AZD-5847
  - Radezolid
  - Tedizolid

TMC-207 (R207910)

- A diarylquinoline drug: structurally and mechanistically different from both fluoroquinolones and other quinoline classes, including mefloquine
- did not inhibit *M. tuberculosis* purified DNA gyrase
- inhibits the proton pump of *M. tuberculosis* adenosine triphosphate (ATP) synthase
- Target based resistance: mutation in the subunit c of ATP synthase encoded by the *atpE* gene
- the proportion of resistant mutants that emerged was $5 \times 10^{-7}$ at 4 times MIC, and $5 \times 10^{-8}$ at 8 times MIC, for *M. tuberculosis*
- non-target based resistance to BDQ (ross-resistance to clofazimine): mutations in Rv0678, a transcriptional repressor of the genes encoding the MmpS5-MmpL5 efflux pump.

Table 1. MICs of R207910 that inhibited 99% of the growth of different mycobacterial species.

<table>
<thead>
<tr>
<th>Mycobacterial species</th>
<th>Number of strains</th>
<th>Range of MICs for multiple strains (µg/ml)</th>
<th>Median MIC (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. tuberculosis</em>, H37Rv</td>
<td>1</td>
<td>—</td>
<td>0.030</td>
</tr>
<tr>
<td><em>M. tuberculosis</em>, fully susceptible clinical isolates</td>
<td>6</td>
<td>0.030–0.120</td>
<td>0.060</td>
</tr>
<tr>
<td><em>M. tuberculosis</em> resistant to isoniazid</td>
<td>7</td>
<td>0.003–0.060</td>
<td>0.010</td>
</tr>
<tr>
<td><em>M. tuberculosis</em> resistant to rifampin</td>
<td>1</td>
<td>—</td>
<td>0.030</td>
</tr>
<tr>
<td><em>M. tuberculosis</em> resistant to isoniazid and rifampin</td>
<td>2</td>
<td>0.030–0.030</td>
<td>0.030</td>
</tr>
<tr>
<td><em>M. tuberculosis</em> resistant to isoniazid and streptomycin</td>
<td>1</td>
<td>—</td>
<td>0.010</td>
</tr>
<tr>
<td><em>M. tuberculosis</em> resistant to ethambutol</td>
<td>1</td>
<td>—</td>
<td>0.010</td>
</tr>
<tr>
<td><em>M. tuberculosis</em> resistant to pyrazinamide</td>
<td>1</td>
<td>—</td>
<td>0.030</td>
</tr>
<tr>
<td><em>M. tuberculosis</em> resistant to fluoroquinolone</td>
<td>2</td>
<td>0.060–0.120</td>
<td>0.090</td>
</tr>
<tr>
<td><em>M. bovis</em></td>
<td>1</td>
<td>—</td>
<td>0.003</td>
</tr>
<tr>
<td><em>M. avium/M. intracellulare</em> (MAC)</td>
<td>7</td>
<td>0.007–0.010</td>
<td>0.010</td>
</tr>
<tr>
<td><em>M. kansasii</em></td>
<td>1</td>
<td>—</td>
<td>0.003</td>
</tr>
<tr>
<td><em>M. marinum</em></td>
<td>1</td>
<td>—</td>
<td>0.003</td>
</tr>
<tr>
<td><em>M. fortuitum</em></td>
<td>5</td>
<td>0.007–0.010</td>
<td>0.010</td>
</tr>
<tr>
<td><em>M. abscessus</em></td>
<td>1</td>
<td>—</td>
<td>0.250</td>
</tr>
<tr>
<td><em>M. smegmatis</em></td>
<td>7</td>
<td>0.003–0.010</td>
<td>0.007</td>
</tr>
<tr>
<td><em>M. ulcerans</em></td>
<td>1</td>
<td>—</td>
<td>0.500</td>
</tr>
</tbody>
</table>

Andries K et al. Science 2005;307:223-7
<table>
<thead>
<tr>
<th>Strain</th>
<th>Description</th>
<th>Mutation in Rv0678</th>
<th>BDQ MIC (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DNA</td>
<td>Protein</td>
</tr>
<tr>
<td>H37Rv</td>
<td>wild type <em>M. tuberculosis</em> strain</td>
<td>wt</td>
<td>wt</td>
</tr>
<tr>
<td>BCLA 2</td>
<td>BDQ-R mutant, H37Rv-derived, no <em>atpE</em> mutations</td>
<td>A413G</td>
<td>E138G</td>
</tr>
<tr>
<td>BCA 4</td>
<td>BDQ-R mutant, H37Rv-derived, no <em>atpE</em> mutations</td>
<td>G281A</td>
<td>R94Q</td>
</tr>
<tr>
<td>BCA 8</td>
<td>BDQ-R mutant, H37Rv-derived, no <em>atpE</em> mutations</td>
<td>G281A</td>
<td>R94Q</td>
</tr>
<tr>
<td>BK12</td>
<td>BDQ-R mutant, H37Rv-derived, <em>atpE</em> mutation [2]</td>
<td>no mutation</td>
<td>no mutation</td>
</tr>
<tr>
<td>LV13</td>
<td>BDQ-R mutant, H37Rv-derived, <em>atpE</em> mutation [24]</td>
<td>Ins G 192–193</td>
<td>frameshift</td>
</tr>
<tr>
<td>EH 3.0</td>
<td>MDR <em>M. tuberculosis</em> strain [3]</td>
<td>wt</td>
<td>wt</td>
</tr>
<tr>
<td>EH 3.2</td>
<td>BDQ-R mutant, EH 3.0-derived, no <em>atpE</em> mutations [3]</td>
<td>A202G</td>
<td>S68G</td>
</tr>
<tr>
<td>EH 3.6</td>
<td>BDQ-R mutant, EH 3.0-derived, no <em>atpE</em> mutations [3]</td>
<td>I56110 nt 272</td>
<td>disruption</td>
</tr>
<tr>
<td>EH 3.3</td>
<td>BDQ-R mutant, EH 3.0-derived, no <em>atpE</em> mutations [3]</td>
<td>Ins A 38–39</td>
<td>frameshift</td>
</tr>
</tbody>
</table>

The MICs of BDQ-R preclinical strains derived from either the drug susceptible H37Rv or the MDR EH3.0 parent strains are shown. Fold-changes between brackets represent the difference between resistant and wild-type MICs. <i>wt</i>: wild-type; <i>Ins</i>: insertion; <i>nt</i>: nucleotide; BDQ: bedaquiline; BDQ-R: bedaquiline-resistant.
doi:10.1371/journal.pone.0102135.t001
Mechanism of bedaquiline and clofazimine resistance in Rv0678 mutants

Andries K, et al.
PLoS ONE 2014
A mutation associated with clofazimine and bedaquiline cross-resistance in MDR-TB following bedaquiline treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>TB isolate</th>
<th>TB relapse isolate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MGIT 960 phenotype</td>
<td>Resistance genotype</td>
</tr>
<tr>
<td>Linezolid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg·L⁻¹</td>
<td>1.0</td>
<td>Resistant</td>
</tr>
<tr>
<td></td>
<td>4.0</td>
<td>Resistant</td>
</tr>
<tr>
<td></td>
<td>16.0</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg·L⁻¹</td>
<td>0.25</td>
<td>Resistant</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>Resistant</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>Susceptible</td>
</tr>
<tr>
<td></td>
<td>7.5</td>
<td>Not performed</td>
</tr>
<tr>
<td>Clofazimine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg·L⁻¹</td>
<td>0.5</td>
<td>Resistant</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>Susceptible</td>
</tr>
<tr>
<td></td>
<td>4.0</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Bedaquiline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not available</td>
<td>Not available</td>
<td>Rv0678 wild type</td>
</tr>
</tbody>
</table>

Critical concentrations of first- and second-line antituberculosis drugs in the MGIT 960 system are highlighted in bold.

Bactericidal Potencies of New Regimens Are Not Predictive of Their Sterilizing Potencies in a Murine Model of Tuberculosis

- Five experimental regimens with various combinations of TMC207, rifapentine (RFT), moxifloxacin (Moxi), and pyrazinamide were tested for their bactericidal and sterilizing potencies in Swiss mice intravenously inoculated with Mycobacterium tuberculosis bacilli.

- the rank order for bactericidal potencies: TMC>RFT>Moxi,
- the rank order for sterilizing potencies: RFT>TMC>Moxi.
The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis

In the first stage of a two-stage, phase 2, randomized, controlled trial,

1. TMC207 (400 mg daily for 2 weeks, followed by 200 mg three times a week for 6 weeks) (23 patients) or
2. placebo (24 patients)

– in combination with a standard five-drug, second-line anti-tuberculosis regimen.

The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis

- The primary efficacy end point was the conversion of sputum cultures

- The addition of TMC207 to standard therapy for MDR-TB reduced the time to conversion to a negative sputum culture, as compared with placebo (hazard ratio, 11.8; 95% CI, 2.3-61.3; P = 0.003 by Cox regression analysis)

The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis

Figure 2. The Proportion of Patients with Positive Sputum Cultures and Time to Conversion.
Proportions of positive cultures were determined according to the mycobacteria growth indicator tube (MGIT) system.

Figure 3. Median (±SD) Log_{10} Count of Colony-Forming Units (CFUs).
Median (±SD) log_{10} CFU counts over time are shown in the subgroup of 22 patients who provided pooled-sputum samples.

Patients with multidrug-resistant tuberculosis were assigned in a 1:1 ratio to receive either bedaquiline (400 mg once daily for 2 weeks, followed by 200 mg three times a week for 22 weeks) or placebo, plus a preferred five-drug, second-line antituberculosis background regimen. The total treatment period was 18 to 24 months, during which bedaquiline was administered for 6 months. The total trial duration was 120 weeks (30 months), which included an anticipated 6-month period after the completion of treatment.
Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline

• In this phase 2b trial, Bedaquiline
  – reduced the median time to culture conversion from 125 days to 83 days (hazard ratio 2.44 (95% CI 1.57-3.80)
  – 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).

• The overall incidence of adverse events was similar in the two groups.
• There were 10 deaths in the bedaquiline group and 2 in the placebo group, with no causal pattern evident.

Mean changes from baseline in QTcF* over time among patients treated with bedaquiline plus background regimen† (BR) versus placebo plus BR, Study C208 (Stage 2)

Abbreviation: 95% CI = 95% confidence interval.
Source: Food and Drug Administration primary clinical review.
* The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart’s electrical cycle. A lengthened QT interval is a biomarker for ventricular tachyarrhythmias and a risk factor for sudden death. The QT interval is dependent on the heart rate and may be corrected by calculation to improve the detection of patients at increased risk of ventricular arrhythmia. One of several calculation correction formulas focuses on the QT interval divided by cube-root of RR (QTcF), where RR is the interval from the onset of one QRS complex (the graphical deflections seen on an electrocardiogram (ECG) that correspond to the depolarization of the right and left ventricle with each heart beat) to the onset of the next QRS complex, measured in milliseconds.
† Ethionamide, kanamycin, pyrazinamide, ofloxacin, and cycloserine/terizidone.
5 Time to smear culture conversion (two consecutive cultures from sputum samples that were negative for Mycobacterium tuberculosis) in weeks.
1. the QT interval needs to be adjusted (corrected) for the heart rate
2. the Fredericia method (QTcF): dividing the QT interval by the cubed root of the interval in seconds between the peak of two successive R waves (RR)
QT interval: the time from the *start* of the QRS complex to the *end* of the T wave, representing the total duration of electrical activity (depolarization and repolarization) in the ventricles.

Basic of electrocardiography

- The recording paper speed is 25 mm per second
- The unit time per square: 0.04 second
- The unit time per space separated by thick lines on ECG paper: 0.2 second
- Heart rate: 1500/the number of square per RR

<table>
<thead>
<tr>
<th>Number of 0.20 s Spaces</th>
<th>Heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>300</td>
</tr>
<tr>
<td>2</td>
<td>150</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>43</td>
</tr>
<tr>
<td>8</td>
<td>37</td>
</tr>
<tr>
<td>9</td>
<td>33</td>
</tr>
</tbody>
</table>
QTcF

• A value greater than 440 ms is considered prolonged.
• A value greater than 480 ms (or an increase of greater than 60 ms from baseline) should trigger electrolyte testing and more frequent ECG monitoring.
• A QTcF interval of more than 500 ms is considered dangerous and stopping QT prolonging drugs is indicated.

WHO Companion Handbook 2014
**WHO Companion Handbook 2014**

**Bedaquiline**<sup>2</sup> (Bdq)

**DRUG CLASS: DIARYLQUINOLINE**

<table>
<thead>
<tr>
<th>Activity against TB, mechanism of action, and metabolism</th>
<th><strong>Bactericidal.</strong> Inhibits ATP synthesis; novel method of action; The drug has a 5.5-month half-life. CYP3A4 is the major CYP isoenzyme involved in the metabolism of bedaquiline. The metabolism leads to the formation of N-monodesmethyl metabolite (M2). M2 is not thought to contribute significantly to clinical efficacy given its lower average exposure (23–31%) in humans and lower antimycobacterial activity (4- to 6-fold lower) compared to the parent compound. M2 concentrations appeared to correlate with QT prolongation. Bedaquiline is mainly eliminated in faeces. The renal clearance of unchanged drug is insignificant.</th>
</tr>
</thead>
</table>

**Dose**

**Adults:** 400 mg once daily for 2 weeks, followed by 200 mg, 3 times per week for 22 weeks with food.

**Children:** Not yet determined.

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be taken with a light meal (better absorption of bedaquiline occurs with food)
Bedaquiline – adverse reactions

• Common: Gastrointestinal distress (nausea, vomiting, abdominal pain, loss of appetite), joint pain (arthralgia), headache.

• Less common: QT prolongation, hyperuricaemia, phospholipidosis (the accumulation of phospholipids in the body’s tissues), elevated aminotransferases. Possibly an increased risk of pancreatitis.
Bedaquiline

Do not use or discontinue bedaquiline

• Clinically significant ventricular arrhythmia.
• A QTcF interval of >500 ms (confirmed by repeat ECG).
• Severe liver disease.

Use with caution in the following:

• Use with other QT prolonging drugs
• A history of torsade de pointes
• A history of congenital long QT syndrome
• A history of hypothyroidism and bradyarrhythmias
• A history of uncompensated heart failure
• Serum calcium, magnesium or potassium levels below the lower limits of normal.

WHO Companion Handbook 2014
Bedaquiline

• Bedaquiline is metabolized by CYP3A4.
• Rifampicin (a CYP3A4 inducer) reduces bedaquiline in blood by half.
• Efavirenz appears to reduce the amount of bedaquiline though inducing CYP3A4.
• CYP3A4 inhibitors (e.g. azole anti-fungal drugs, some macrolides, protease inhibitors, and many others) can raise the level of bedaquiline
WHO recommends that bedaquiline may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB (conditional recommendation, very low confidence in estimates of effects).
Five conditions for the inclusion of bedaquiline in the adult treatment regimen of MDR-TB

- Treatment is administered under closely monitored conditions
- Proper patient inclusion
- Patient informed consent obtained
- Adherence to principles of designing a WHO-recommended MDR-TB regimen
- Pharmacovigilance and proper management of adverse drug reactions and prevention of drug–drug interactions.

WHO Interim policy guidance 2013
STREAM trial

• **Regimen C:** a 40-week all-oral regimen consisting of bedaquiline, clofazimine, ethambutol, levofloxacin, and pyrazinamide given for 40 weeks supplemented by isoniazid and prothionamide for the first 16 weeks (intensive phase).

• **Regimen D:** a 28-week regimen consisting of bedaquiline, clofazimine, levofloxacin, and pyrazinamide given for 28 weeks supplemented by isoniazid and kanamycin for the first 8 weeks (intensive phase).
Treatment phases of investigational regimens

- **Regimen A**: Locally used WHO-approved MDR-TB regimen
- **Regimen B**: KM + INH + PTO + MFX + CFZ + EMB + PZA
  - Week 0 to Week 16: KM + INH + PTO + MFX + CFZ + EMB + PZA
  - Week 16 to Week 28: MFX + CFZ + EMB + PZA
- **Regimen C**: INH + PTO + BDQ + LFX + CFZ + EMB + PZA
  - Week 0 to Week 16: INH + PTO + BDQ + LFX + CFZ + EMB + PZA
  - Week 16 to Week 28: BDQ + LFX + CFZ + EMB + PZA
- **Regimen D**: KM + INH + BDQ + LFX + CFZ + PZA
  - Week 0 to Week 16: KM + INH + BDQ + LFX + CFZ + PZA
  - Week 16 to Week 28: BDQ + LFX + CFZ + PZA

Time:
- Week 0: First dose
- Week 8
- Week 16
- Week 28
- Week 40: Follow-up

- **Intensive phase**
- **Continuation phase**
- Locally used WHO-approved MDR-TB regimen (treatment phases may vary)

International Union Against Tuberculosis and Lung Disease
Long-term outcome and safety of prolonged bedaquiline treatment for multidrug-resistant tuberculosis

45 MDR-TB patients (53% XDR-TB):
• median bedaquiline treatment duration 361 days
• 33 patients (73%) received prolonged (>190 days) bedaquiline treatment.
• 36 patients (80%) had favourable outcome
• Severe and serious adverse events were recorded in 60% and 18% of patients
• Values of Fridericia-corrected QT interval (QTcF) >500 ms were recorded in 11% of patients,
• neither arrhythmias nor symptomatic cardiac side-effects occurred

Guglielmetti L. Eur Respir J 2017; 49: 1601799
Long-term outcome and safety of prolonged bedaquiline treatment for multidrug-resistant tuberculosis

## TABLE 4 Treatment safety in the whole cohort and comparison between patients receiving standard (≤190 days) or prolonged (>190 days) bedaquiline treatment

<table>
<thead>
<tr>
<th></th>
<th>Whole cohort</th>
<th>Standard bedaquiline treatment</th>
<th>Prolonged bedaquiline treatment</th>
<th>p-value#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>45</td>
<td>12</td>
<td>33</td>
<td>1.000</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>44 (97.8)</td>
<td>12 (100)</td>
<td>32 (97.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Any severe adverse event</td>
<td>28 (62.2)</td>
<td>5 (41.7)</td>
<td>23 (69.7)</td>
<td>0.163</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>7 (15.6)</td>
<td>1 (8.3)</td>
<td>6 (18.2)</td>
<td>0.655</td>
</tr>
<tr>
<td>At least one drug stopped due to adverse events</td>
<td>37 (82.2)</td>
<td>8 (66.7)</td>
<td>29 (87.9)</td>
<td>0.181</td>
</tr>
<tr>
<td>Bedaquiline stopped due to adverse events</td>
<td>3 (6.7)</td>
<td>1 (8.3)</td>
<td>2 (6.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Liver enzyme elevation</td>
<td>17 (37.8)</td>
<td>6 (50.0)</td>
<td>11 (33.3)</td>
<td>0.325</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1 (2.2)</td>
<td>1 (8.3)</td>
<td>0</td>
<td>0.267</td>
</tr>
<tr>
<td>QTcF &gt;500 ms</td>
<td>5 (11.1)</td>
<td>0</td>
<td>5 (15.2)</td>
<td>0.303</td>
</tr>
<tr>
<td>QTcF &gt;60 ms increase</td>
<td>13 (28.9)</td>
<td>4 (33.3)</td>
<td>9 (27.3)</td>
<td>0.721</td>
</tr>
<tr>
<td>Maximum QTcF increase during treatment</td>
<td>36.2 [17.9–68.5]</td>
<td>31.9 [16.0–73.3]</td>
<td>41.6 [19.7–63.7]</td>
<td>0.437</td>
</tr>
</tbody>
</table>

Data are presented as n, n (%) or median (interquartile range), unless otherwise stated. QTcF: Fridericia-corrected QT interval. #: comparison between patients with standard and prolonged bedaquiline treatment, calculated with Wilcoxon’s test for continuous variables and Fisher’s exact test for categorical variables.
Remodelling the existing antibacterial drug classes

<table>
<thead>
<tr>
<th>Antibiotic class</th>
<th>Parent scaffold</th>
<th>Derivatized scaffolds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones</td>
<td>Nalidixic acid</td>
<td>Gatifloxacin, Moxifloxacin</td>
</tr>
<tr>
<td>Nitroimidazoles</td>
<td>Metronidazole</td>
<td>PA-824, OPC-67683</td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>Linezolid</td>
<td>PNU-100480</td>
</tr>
<tr>
<td>1,2-ethylene diamine</td>
<td>Ethambutol</td>
<td>SQ109</td>
</tr>
</tbody>
</table>

doi:10.1038/nature09657
OPC-67683 (Delamanid)

- a nitro-dihydro-imidazooxazole derivative

- a mycolic acid biosynthesis inhibitor

- requires metabolic activation by M. tuberculosis in order for the anti-TB activity to be exerted

- minimum inhibitory concentration (MIC) 0.006–0.024 ug/ml in vitro

Delamanid (Dlm)\textsuperscript{5}

**DRUG CLASS:** NITRODIHYDRO-IMIDAZO-OXAZOLE.

- a pro-drug that must be reduced by the deazaflavin-dependent nitroreductase to its des-nitro metabolite to be active
- QTc prolongation is very closely correlated with the major delamanid metabolite DM-6705
- **Dose:** Adults: 100 mg twice daily for 24 weeks. It is recommended to administer with water and to be taken with, or just after a meal
- **Common adverse reactions:** nausea (38.3%), vomiting (33%), and dizziness (30.2%)
Delamanid

- no cross-resistance to rifampicin, isoniazid, ethambutol, or streptomycin, and no antagonistic activity to these drugs.
- highly (>97%) protein bound
- no effect on human cytochrome p450 enzymes CYP1A1/2, CYP2A6, CYP2B6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4
- require activation by mycobacterial F420-dependent deazaflavin-dependent nitroreductase (Ddn) coenzymes. Mutation in one of five coenzyme F420 genes, fgd, Rv3547, fbiA, fbiB, and fbiC has been proposed as the mechanism of resistance of delamanid

Therapeutics and Clinical Risk Management 2015:11 779–791
Delamanid

- delamanid exposure is increased by food, in particular by a high-fat meal. Exposure is approximately three times greater in a fed as opposed to fasted state.
- eliminated directly from plasma with a half-life of 30–38 hours. It is not excreted in the urine.
- It is thought to be metabolized largely by plasma albumin
- strong CYP3A4 inducer rifampicin reduces the exposure to delamanid by 47% in healthy volunteers
- the European Medicines Agency (EMA) recommends that coadministration of delamanid with strong CYP3A4 enzyme inducers is contraindicated
Early bactericidal activity of delamanid (OPC-67683) in smear-positive pulmonary tuberculosis patients

Figure 2  Fall of mean sputum counts over time. Single data points represent mean values of individual treatment groups. All delamanid dosages follow a monophasic decline. The fall of log$_{10}$ cfu in sputum over time increases from the 100 mg to the 200 mg dosage and plateaus at the 300 mg dosage. The activity of delamanid 400 mg is lower again indicating reduced drug exposure in this group. Shown is a fitted linear regression line for all delamanid treatment groups, with 95% CIs represented by dotted lines. The horizontal lines are the mean baseline count (top) with lower 95%CI (bottom). A significant decrease is found from day 3 onwards, indicated by CIs no longer including baseline. Standard anti-tuberculosis treatment (HRZE) as the positive control shows the expected biphasic pattern with a steep initial decline. cfu = colony forming units; H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol; CI = confidence interval.

Delamanid for Multidrug-Resistant Pulmonary Tuberculosis

Proportion of Patients with Sputum-Culture Conversion by Day 57

A Mycobacterial Growth Indicator Tube System

- Placebo: 29.6% (37/125)
- 100 mg, twice daily: 45.4% (64/141)
- 200 mg, twice daily: 41.9% (57/136)

P = 0.04
P = 0.008

B Solid Medium

- Placebo: 33.6% (38/113)
- 100 mg, twice daily: 53.8% (64/119)
- 200 mg, twice daily: 65.2% (75/115)

P < 0.001
P = 0.002

Delamanid for Multidrug-Resistant Pulmonary Tuberculosis

Survival Analysis of Days to Sputum-Culture Conversion, According to Culture Medium Type

A  Mycobacterial Growth Indicator Tube System

B  Solid Medium

Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis

• Favourable outcomes were observed in 143 (74.5%) out of 192 patients who received delamanid for 6 or more months, compared to 126 (55%) out of 229 patients who received delamanid for 2 or less months.
Long-term (24 month) treatment outcomes after treatment with delamanid in combination with an optimised background treatment regimen: MDR- and XDR-TB patients

<table>
<thead>
<tr>
<th>Treatment outcome</th>
<th>Long-term treatment</th>
<th>Short-term treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favourable</td>
<td>143 (74.5; 67.7–80.5)$</td>
<td>126 (55.0; 48.3–61.6)$</td>
</tr>
<tr>
<td>Cured</td>
<td>110 (57.3; 50.0–64.4)</td>
<td>111 (48.5; 41.8–55.1)</td>
</tr>
<tr>
<td>Completed</td>
<td>33 (17.2; 12.1–23.3)$</td>
<td>15 (6.6; 3.7–10.6)$</td>
</tr>
<tr>
<td>Unfavourable</td>
<td>49 (25.5; 19.5–32.3)$</td>
<td>103 (45.0; 38.4–51.7)$</td>
</tr>
<tr>
<td>Died</td>
<td>2 (1.0; 0.1–3.7)$</td>
<td>19 (8.3; 5.1–12.7)$</td>
</tr>
<tr>
<td>Failed</td>
<td>32 (16.7; 11.7–22.7)</td>
<td>26 (11.4; 7.6–16.2)</td>
</tr>
<tr>
<td>Defaulted</td>
<td>15 (7.8; 4.4–12.6)$</td>
<td>58 (25.3; 19.8–31.5)$</td>
</tr>
</tbody>
</table>

Eur Respir J 2013; 41: 1393–1400
Long-term mortality assessment of MDR-TB patients treated with delamanid

<table>
<thead>
<tr>
<th>TABLE 1 Mortality among multidrug-resistant tuberculosis patients participating in the delamanid clinical development programme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>2-month sputum culture conversion</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Delamanid treatment duration</td>
</tr>
<tr>
<td>≥6 months</td>
</tr>
<tr>
<td>≤2 months</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Data are presented as n or n (%), unless otherwise stated. *: p=0.002; **: p=0.001.
WHO recommends that delamanid may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB (conditional recommendation; very low confidence in estimates of effect)
Conditions for the use of Delamanid

• Proper patient inclusion
• Adherence to the principles of designing a WHO-recommended MDR-TB regimen
• Treatment is closely monitored
• Active pharmacovigilance and proper management of adverse drug reactions and prevention of drug–drug interactions
• Patient informed consent obtained
Delamanid may be added to the WHO-recommended longer regimen in children and adolescents (aged 6–17 years) with multidrug- or rifampicin-resistant TB (MDR/RR-TB) who are not eligible for the shorter MDR-TB regimen, under specific conditions (conditional recommendation; very low confidence in estimates of effect):