# Con: Delamanid is a Group C Drug for MDR-TB

전남대학교병원
권용수

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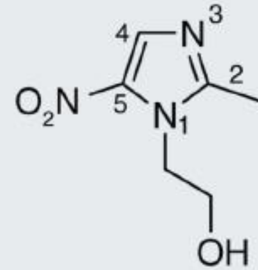
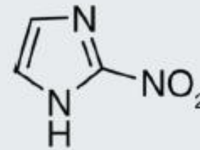
- Preclinical stage and clinical trial phase 1 and 2a
- Clinical trial phase 2b and 3
- Cohort studies

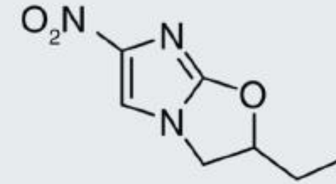
# Nitroimidazole



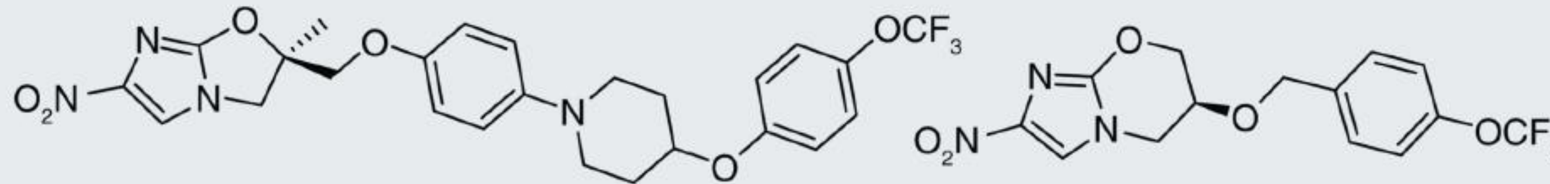
**1**: Metronidazole



**2**: Azomycin



**3**: CGI-17341



**4**: OPC-67683

**5**: PA-824

CGI-17341: **bicyclic nitroimidazoles,** active against drug-susceptible as well as MDR Mtb. However, further development was abandoned due to its **mutagenicity**
A few years prior to the discovery of OPC-67683, PathoGenesis (now Novartis) came out with their lead compound PA-824 from a series of over 300 nitroimidazooxazines, which showed increased activity against Mtb with potential to decrease the duration of therapy

Mukherjee, et al. Future Med Chem 2011;3:1427

# Delamanid (OPC-67683)

- The mutagenic potential: OPC-67683 did not show mutagenicity
- Susceptibility testing
  - The MICs against standard strains: 0.006 to 0.012 ug/ml

| | RFP | INH | EB | SM | CGI-17341 | PA-824 |
|---|---|---|---|---|---|---|
| MIC of OPC-67683 | 4-64 | 2-32 | 128-256 | 64-512 | 8-16 | 4-16 |
| $MIC_{90}$ of OPC-67683 | 24 | 8 | 303 | 244 | | |

Matsumoto M et al. PLOS Med 2006;3:e466

# Mechanism of action

**Table 5.** $IC_{50}$ of OPC-67683 and INH against Mycolic Acid Synthesis

| Compound | Subclass Mycolic Acid and Fatty Acid | IC50 (μg/ml) | 95% Confidence Interval (μg/ml) |
|---|---|---|---|
| OPC- | | | |
| | | | |
| INH | | | |
| | | | |

| | |
|---|---|
| Fatty acid | >0.25 |
| α-Mycolic acid | >0.25 |
| Methoxy-mycolic acid | 0.036 |
| Keto-mycolic acid | 0.021 |

The $IC_{50}$ (concentration required to inhibit activity by 50%) of OPC-67683 against mycolic acid synthesis in *M. bovis* BCG was determined and compared with that of INH, a well-known inhibitor of mycolic acid synthesis. $^{14}C$-labeled acetic acid was incorporated to mycolic acid by incubation with *M. bovis* BCG cell cultures in the presence of OPC-67683 or INH as a reference. $^{14}C$-labeled fatty acid and mycolic acid subclasses were detected using thin-layer chromatography (TLC, $n = 3$), and analyzed by BAS-2500 (Fujifilm). The radioactivity of each fatty acid and mycolic acid subclasses was calculated using photo-stimulated luminescence, expressed as the percentage of incorporation in untreated controls, and statistical analysis was conducted by linear regression analysis to calculate $IC_{50}$ values and 95% confidence intervals (significance level: 5%).

doi:10.1371/journal.pmed.0030466.t005

Matsumoto M et al. PLOS Med 2006;3:e466

# Activity against Intracellular Mycobacteria in Human Macrophages

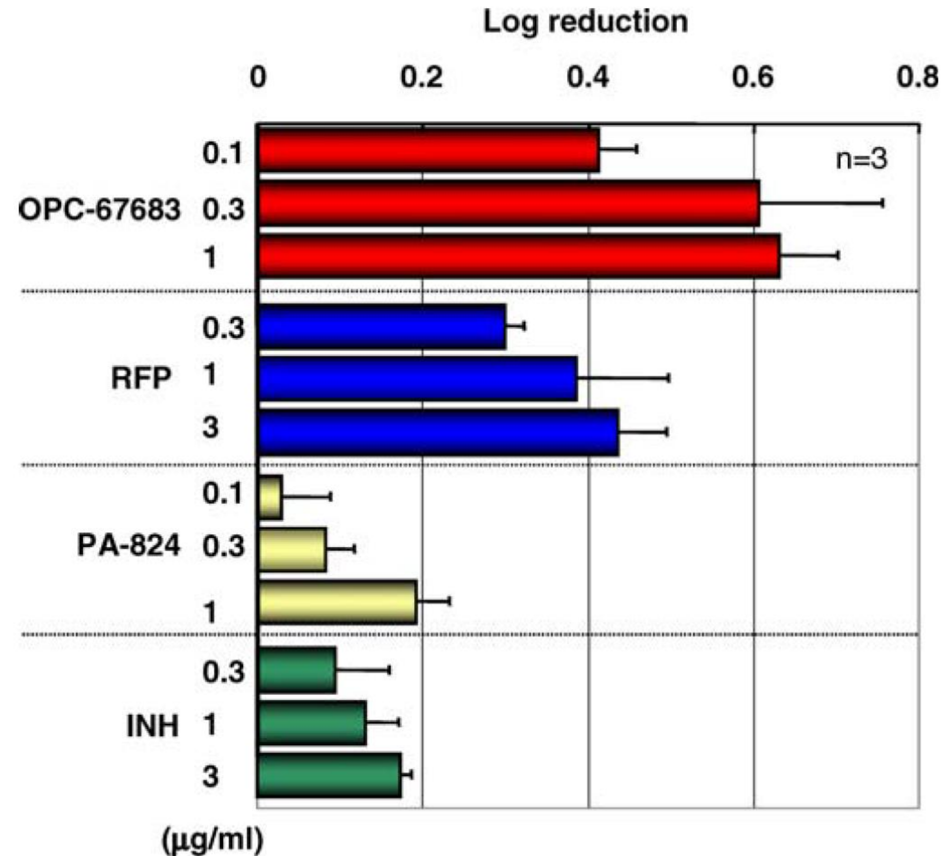



**Figure 3.** Effect of Pulsed Exposures to OPC-67683, RFP, INH, and PA-824 on the Intracellular Growth of *M. tuberculosis* H37Rv within THP-1 Cells

Infected cells were incubated with the test compound for 4 h, washed, cultured until 68 h at 37 °C, plated on 7H11 agar, and counted for colonies after 16 d of growth at 37 °C. Values represent mean ± S.D ($n = 3$).

doi:10.1371/journal.pmed.0030466.g003

Matsumoto M, et al. PLOS Med 2006;3:e466

**Table 7.** Plasma Concentration of OPC-67683, RFP, INH, EB, and PZA after Oral Administration in Mice Infected with *M. tuberculosis* Kurono

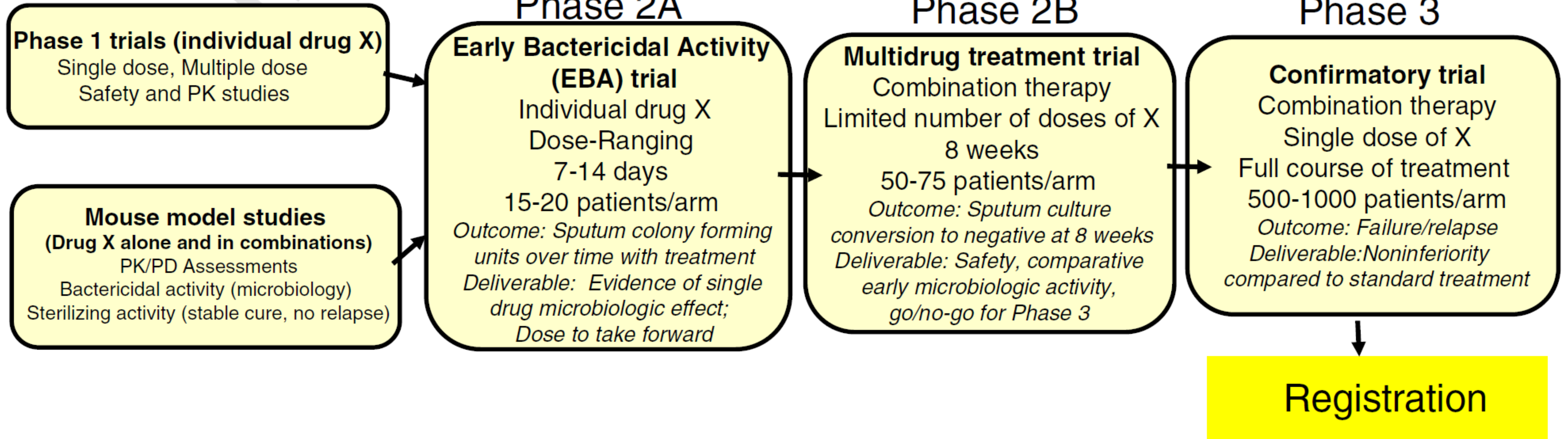
| Compound (Dose; mg/kg) | Concentration (µg/ml) | | | | | | | | | | | $C_{max}$ (µg/ml) | $AUC_t$ (µg · h/ml) | $t_{max}$ (h) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.083 h | 0.25 h | 0.5 h | 1 h | 2 h | 4 h | 6 h | 8 h | 12 h | 16 h | 24 h | | | | |
| OPC-67683 (2.5) | N.T. | N.T. | N.T. | 0.133 ±0.030 | 0.193 ±0.040 | 0.220 ±0.020 | 0.297 ±0.083 | 0.167 ±0.028 | 0.166 ±0.049 | N.T. | 0.049 ±0.012 | 0.297 | 4.13 | 6 | 7.6 |
| RFP (5) | N.T. | N.T. | 3.33 ±0.87 | 4.49 ±1.04 | 4.52 ±1.90 | 3.82 ±0.70 | 5.10 ±1.63 | 3.18 ±0.68 | N.T. | 0.660 ±0.260 | N.T. | 5.10 | 48.2 | 6 | 3.4 |
| INH (10) | 2.17 ±0.435 | 3.06 ±0.779 | 2.28 ±0.390 | 1.92 ±0.478 | 0.740 ±0.202 | 0.253 ±0.057 | N.T. | N.D. | N.T. | N.T. | N.T. | 3.06 | 4.55 | 0.25 | 1.0 |
| EB (100) | 0.055 ±0.049 | 1.30 ±0.939 | 3.17 ±0.392 | 3.51 ±1.13 | 2.51 ±1.01 | 1.02 ±0.202 | N.T. | 0.612 ±0.325 | N.T. | N.T. | N.T. | 3.51 | 12.2 | 1 | 2.8 |
| PZA (100) | 49.6 ±11.2 | 59.1 ±14.1 | 63.2 ±28.9 | 60.2 ±18.7 | 35.5 ±6.45 | 18.4 ±3.09 | N.T. | 0.815 ±0.580 | N.T. | N.T. | N.T. | 63.2 | 197 | 0.5 | 1.1 |

Each value represents mean ± SD ($n = 3$).
Each pharmacokinetic parameter was calculated by WINNONLIN (Version 4.1).
N.D., not detected (<0.05 µg/ml for INH); N.T., not tested.
doi:10.1371/journal.pmed.0030466.t007

Matsumoto M, et al. PLOS Med 2006;3:e466

Preclinical assessment
Clinical PK-safety

Clinical Efficacy & Safety




K.E. Dooley et al. Advanced Drug Delivery Reviews. 2016 Jul 1;102:116

# Delamanid: Phase IIa study

**Table 1** Mean sputum counts and fall in $\log_{10}$ cfu/ml sputum over time

| | Delamanid | | | | | |
|---|---|---|---|---|---|---|
| | 100 mg ($n$ = 11) mean (SD) | 200 mg ($n$ = 10) mean (SD) | 300 mg ($n$ = 10) mean (SD) | 400 mg ($n$ = 11) mean (SD) | All ($n$ = 42) mean (SD) | HRZE ($n$ = 6) mean (SD) |
| Sputum counts ($\log_{10}$ cfu/ml) | | | | | | |
| Baseline | | | | | 7) | 6.36 (0.61) |
| Day 2 | | | | | 1)† | 5.25 (0.82) |
| Day 14 | | | | | 8) | 4.78 (1.58)‡ |
| Mean fall $\log_{10}$ cfu/ml | | | | | | |
| Day 0–2 | | | | | 8) | 1.11 (0.76) |
| | | | | | ) | 0.64 (1.44) |
| | | | | | ) | 1.67 (1.84) |
| | | | | | 08) | 0.553 (0.379) |
| | | | | | 62) | 0.100 (0.156) |
| Day 0–14 | 0.026 (0.042) | 0.052 (0.045) | 0.065 (0.089) | 0.020 (0.027) | 0.040 (0.056) | 0.147 (0.164) |

*$n$ = 9.
†$n$ = 41.
‡$n$ = 5.
SD= standard deviation; H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol; cfu = colony forming units; EBA = early bactericidal activity.

| | Delamanid | | | |
|---|---|---|---|---|
| | 100 mg ($n$ = 11) mean (SD) | 200 mg ($n$ = 10) mean (SD) | 300 mg ($n$ = 10) mean (SD) | 400 mg ($n$ = 11) mean (SD) |
| EBA: mean fall $\log_{10}$ cfu/ml per day | | | | |
| Day 0–2 | 0.066 (0.165) | 0.138 (0.271) | 0.023 (0.193) | 0.049 (0.205) |
| Day 2–14 | 0.026 (0.044) | 0.038 (0.060) | 0.063 (0.096) | 0.018 (0.033) |
| Day 0–14 | 0.026 (0.042) | 0.052 (0.045) | 0.065 (0.089) | 0.020 (0.027) |

Diacon AH, et al. Int J Tuberc Lung Dis 2011;15:949

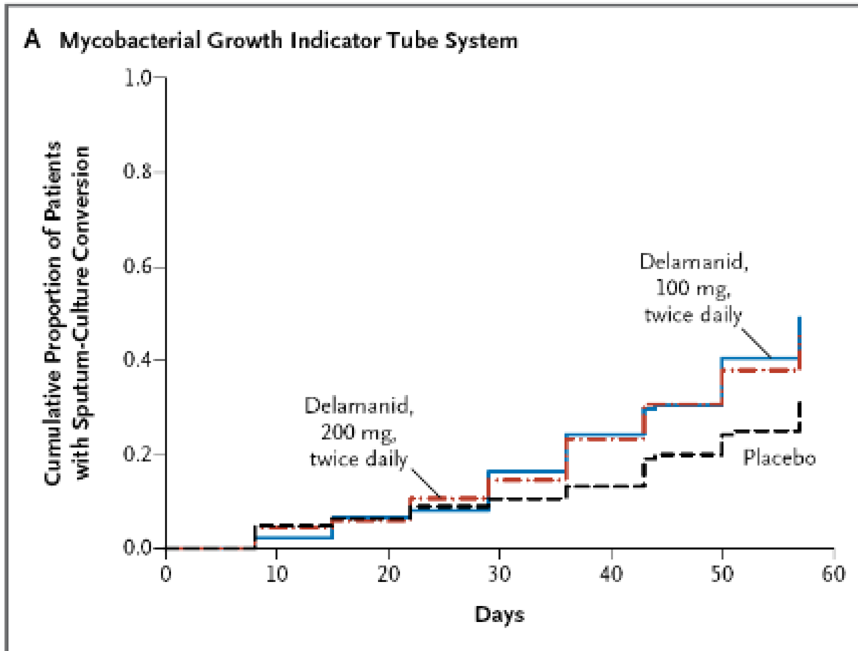
# Delamanid

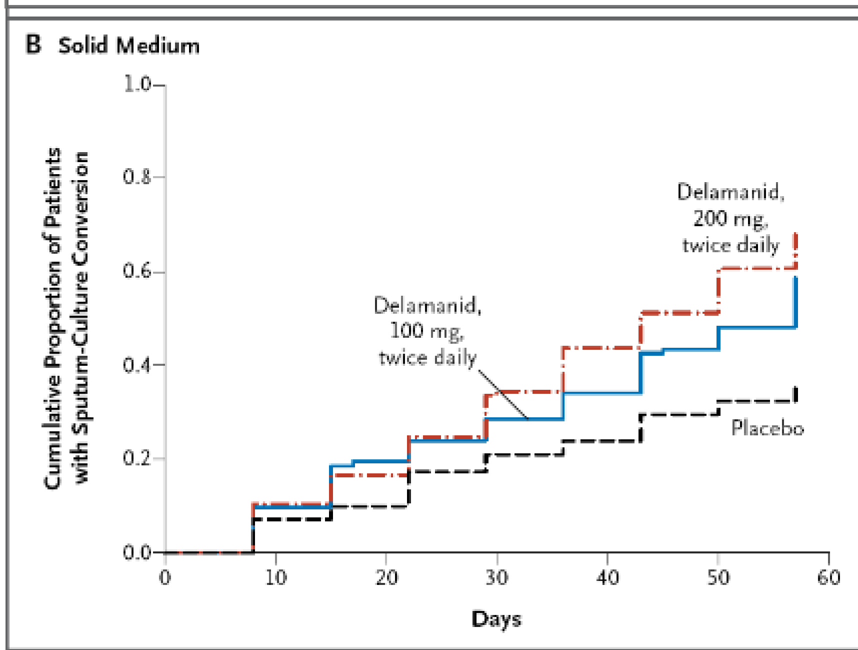
- Phase 2b RCT (Trial 204)
- 2 months of treatment (100 and 200 mg twice daily) in combination with a standard MDR-TB regimen
- Culture conversion at 2 months

  **45%** in the 100-mg group vs.

  42% in the 200-mg group vs.

  **29%** in the placebo group




Gler MT, et al. N Engl J Med 2012;366:2151

# Bedaquiline

- •A potent new drug that targets the proton pump of ATP synthesis
- •Phase 2 RCT (C208 (stage 1)
- •47 MDR-TB
- •TMC207 (400mg/day 2wks → 200mg 3times/week with standard 5 drug second line regimen
- •Primary: 8weeks culture conversion

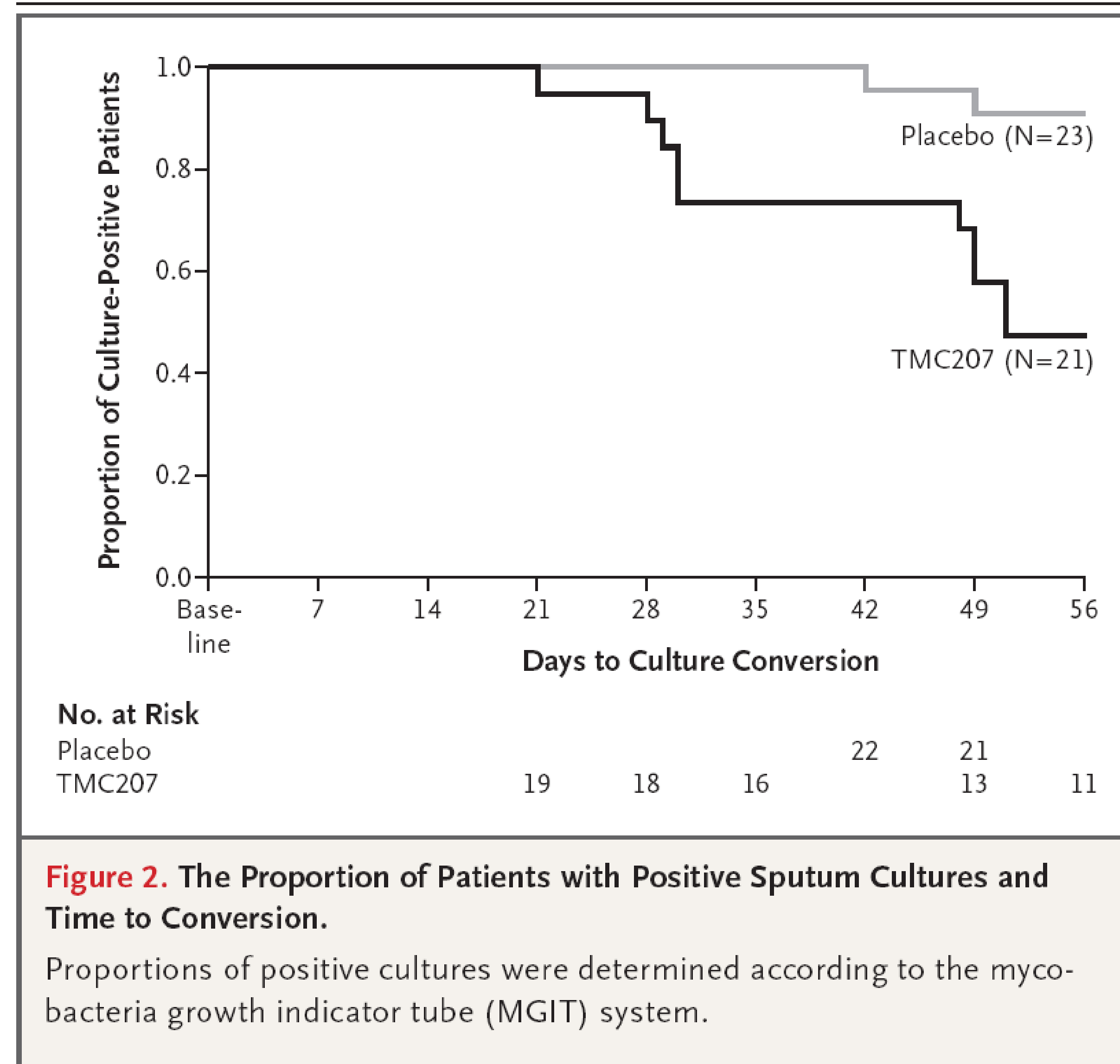



**Figure 2. The Proportion of Patients with Positive Sputum Cultures and Time to Conversion.**

Proportions of positive cultures were determined according to the mycobacteria growth indicator tube (MGIT) system.

Diacon AH. N Engl J Med 2009;360:2397-2405

# Phase 2b studies for 8weeks culture conversion

| | Dlm (100mg Bid) | D-placebo | Bdq | B-placebo |
|---|---|---|---|---|
| Study period | 2008.5~2010.6 | | 2007.6~2008.1 | |
| n | 161 | 160 | 23 | 24 |
| Age | 36 | 35 | 33 | 33 |
| BMI | 19.8 | 19.5 | 18.3 | 18.5 |
| Male | 57% | 56% | 78% | 71% |
| HIV | Almost no | Almost no | 57% | 54% |
| Cavity | 60% | 54% | 87% | 83% |
| FQ resistance | | | 4% | 8% |
| XDR | Yes | Yes | No | No |
| Use of injectable drugs | 68% | 70% | 100% | 100% |
| Use of FQ | 99% | 99% | 100% | 96% |
| Use of Lzd | No | No | No | No |
| Culture conversion at 8weeks | | | | |
| Total | 45% | 29% | 48% | 9% |
| XDR | 17% | 7% | | |

Gler MT, et al. N Engl J Med 2012;366:2151

Diacon AH. N Engl J Med 2009;360:2397-2405

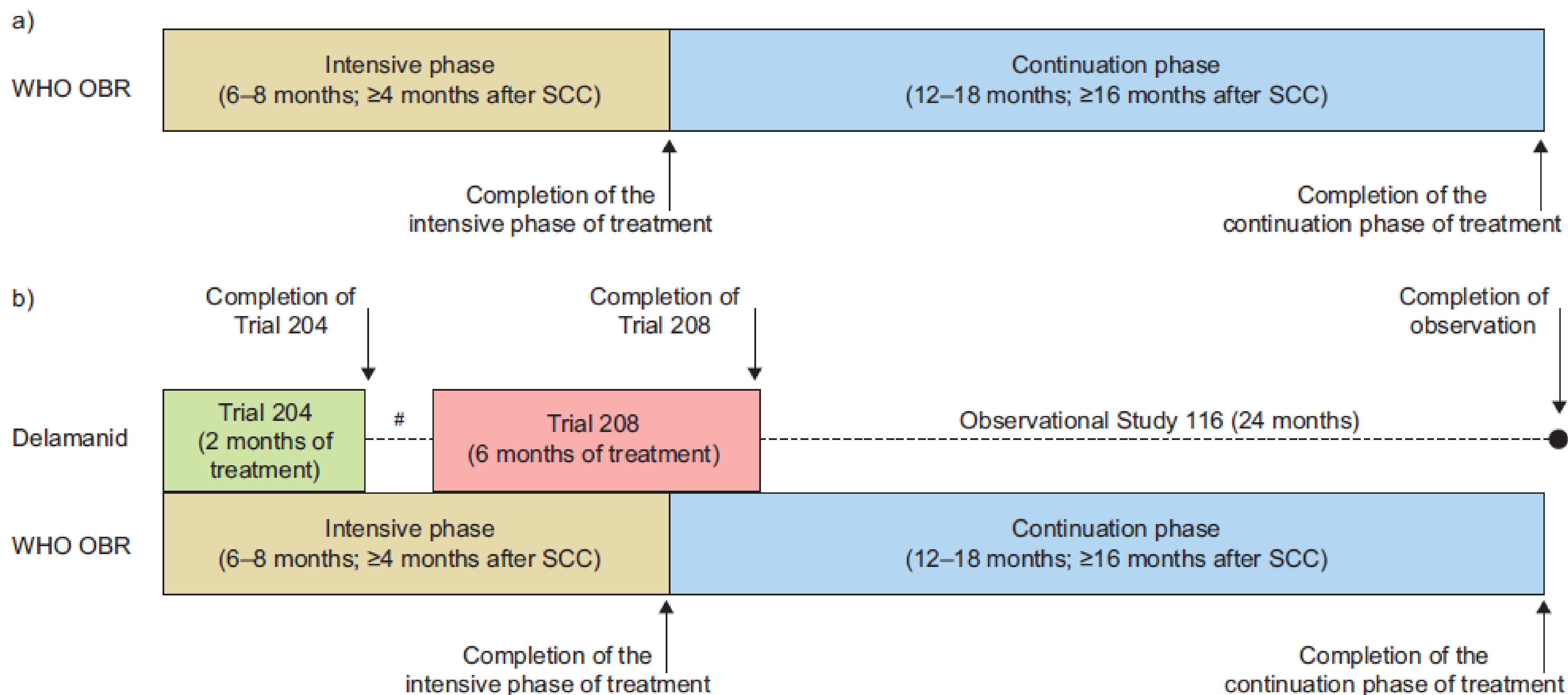



**FIGURE 1.** World Health Organization (WHO) recommended treatment for multidrug-resistant tuberculosis (MDR-TB) and the design of delamanid Trial 204, Trial 208 and Study 116. a) WHO optimised background treatment regimen (OBR) recommendations for the treatment of MDR-TB [19]. b) Otsuka (Otsuka, Tokyo, Japan) design for Trial 204, Trial 208 and Study 116 (delamanid trials/study). SCC: sputum culture conversion. [#]: time varied between the completion of Trial 204 and the initiation of Trial 208 based on local approval processes.

# Phase 2b, Dlm for MDR and XDR-TB

**TABLE 2** Long-term (24 month) treatment outcomes after treatment with delamanid in combination with an optimised background treatment regimen: MDR- and XDR-TB patients

| Treatment outcome | Long-term treatment[#] >6 m | Short-term treatment[¶] <2 m | All patients[+] |
|---|---|---|---|
| Favourable | 143 (74.5; 67.7–80.5)[§] | 126 (55.0; 48.3–61.6)[§] | 269 (63.9; 59.1–68.5) |
| Cured | 110 (57.3; 50.0–64.4) | 111 (48.5; 41.8–55.1) | 221 (52.5; 47.6–57.4) |
| Completed | 33 (17.2; 12.1–23.3)[§] | 15 (6.6; 3.7–10.6)[§] | 48 (11.4; 8.5–14.8) |
| Unfavourable | 49 (25.5; 19.5–32.3)[§] | 103 (45.0; 38.4–51.7)[§] | 152 (36.1; 31.5–40.9) |
| Died | 2 (1.0; 0.1–3.7)[§] | 19 (8.3; 5.1–12.7)[§] | 21 (5.0; 3.1–7.5) |
| Failed | 32 (16.7; 11.7–22.7) | 26 (11.4; 7.6–16.2) | 58 (13.8; 10.6–17.4) |
| Defaulted | 15 (7.8; 4.4–12.6)[§] | 58 (25.3; 19.8–31.5)[§] | 73 (17.3; 13.8–21.3) |

Data are presented as n (%; 95% CI). MDR: multidrug-resistant; TB: tuberculosis; XDR: extensively drug-resistant. #: 192 patients received delamanid (100 mg and/or 200 mg twice a day) for at least 6 months; ¶: 229 patients received delamanid (100 mg or 200 mg twice a day) or placebo for 2 months; +: n=421; §: differences between the long-term and the short-term treatment groups for the corresponding treatment outcome were statistically significant ($p<0.001$), all other differences did not reach statistical significance ($p \geq 0.05$).

- the mortality rates in patients receiving delamanid for ≥6 months and ≤2 months were 1% and 8.3%

Skripconoka V et al. Eur Respir J 2013;41:1393

C208 stage 2

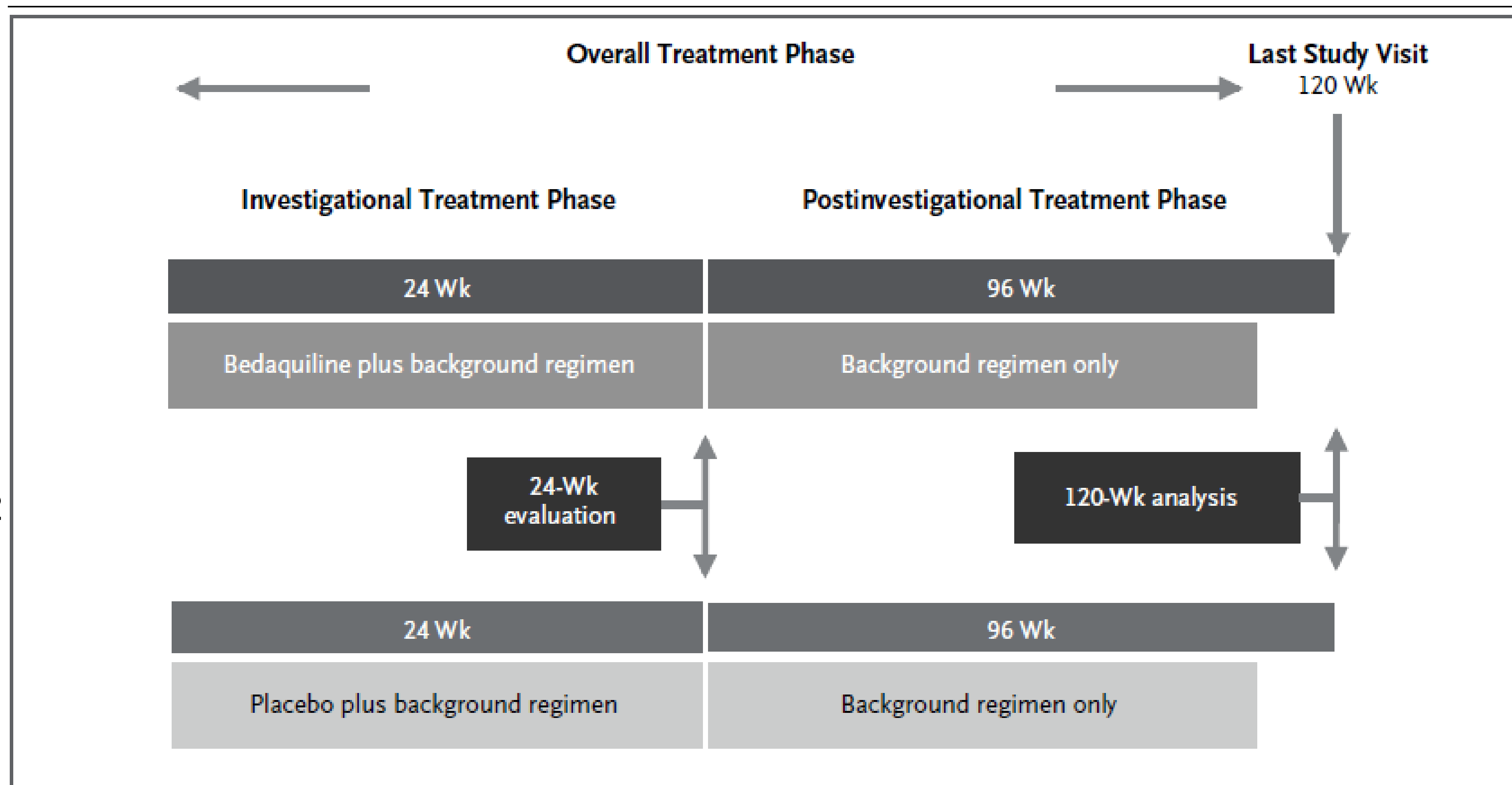
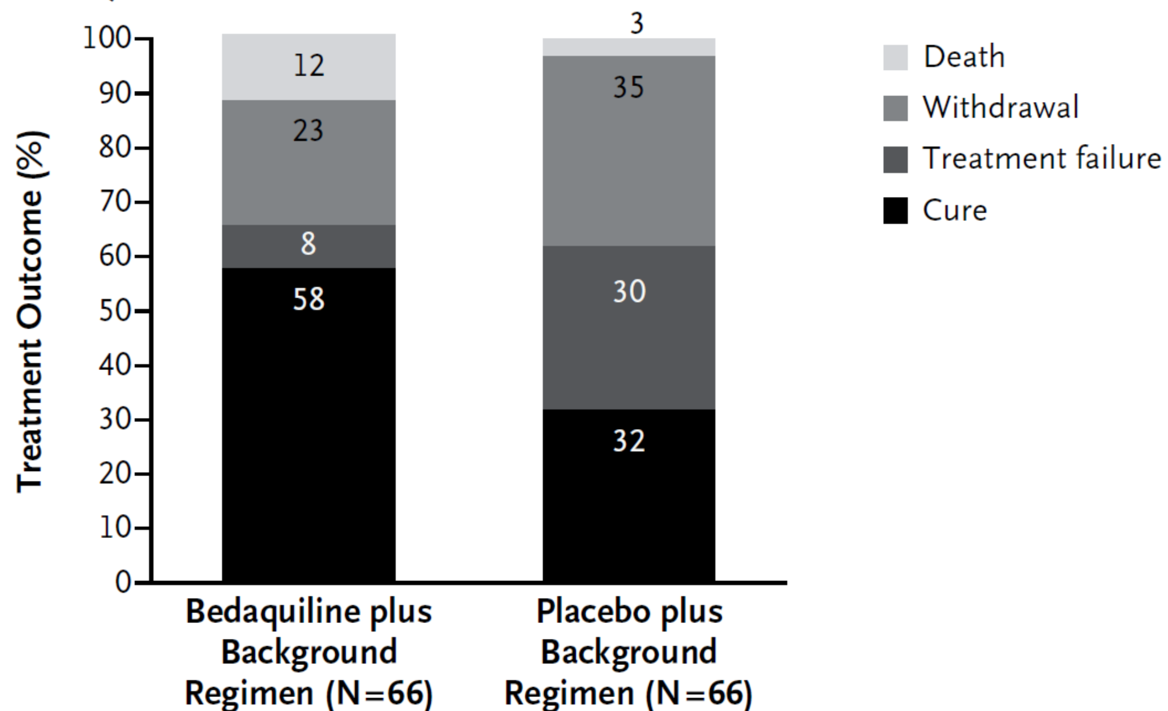



**Figure 1. Study Design and Drug Regimens.**

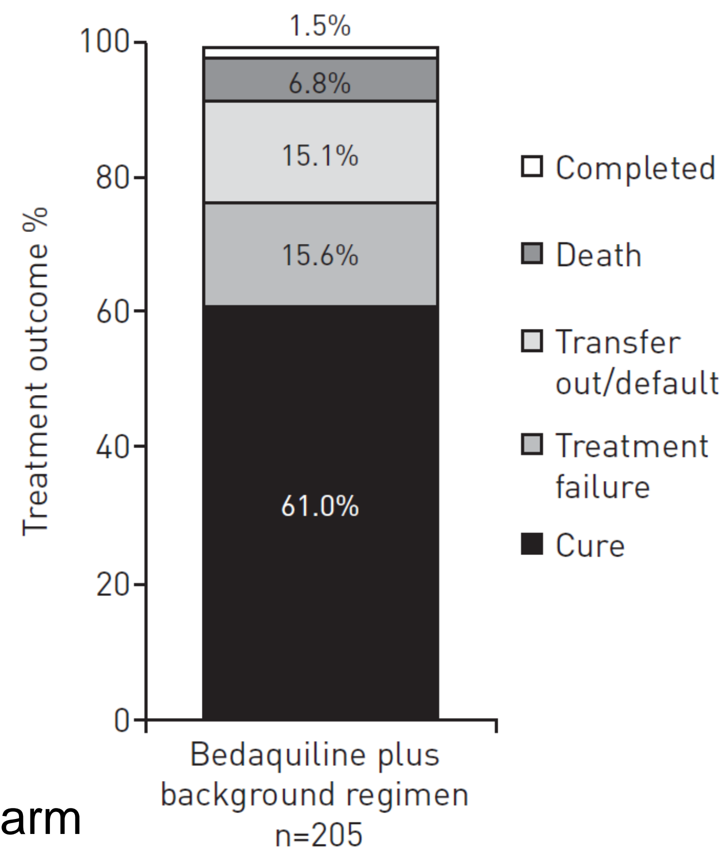
Patients with multidrug-resistant tuberculosis were assigned in a 1:1 ratio to receive either bedaquiline (400 mg once daily for 2 weeks, followed by 200 mg three times a week for 22 weeks) or placebo, plus a preferred five-drug, second-line antituberculosis background regimen. The total treatment period 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.

# Phase 2b, Bdq for MDR and XDR-TB




C208 stage 2

Diacon A et al. NEJM 2014;371:723




C209 Single-arm

Pym AS. et al. Eur Rerspir J 2016;47:394

# Phase 2b studies for final outcomes

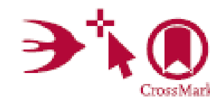
| Phase 2B | Dlm | Bdq | Bdq |
|---|---|---|---|
| | 2008.5-2012.5 | 2007.6-2008.1 | 2009.8-2010.9 |
| n | 421 | 132 | 205 |
| Age | 34 | 34 | 32 |
| Male | 65% | 64% | 64% |
| HIV | 1% | 14% | 4% |
| Cavity | 67% | 83% | 66% |
| FQ resistance | NA | 9% | 6% |
| XDR | 13% | 0% | 18% |
| Outcomes | | | |
| Cure or com plete | 75% | 58% | 61% |

Skripconoka V et al. Eur Respir J 2013;41:1393

Diacon A et al. NEJM 2014;371:723

Pym AS. et al. Eur Rerspir J 2016;47:394

# Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis




*The Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017; Nafees Ahmad, Shama D Ahuja, Onno W Akkerman, Jan-Willem C Alffenaar, Laura F Anderson, Parvaneh Baghaei, Didi Bang, Pennan M Barry, Mayara L Bastos, Digamber Behera, Andrea Benedetti, Gregory P Bisson, Martin J Boeree, Maryline Bonnet, Sarah K Brode, James C M Brust, Ying Cai, Eric Caumes, J Peter Cegielski, Rosella Centis, Pei-Chun Chan, Edward D Chan, Kwok-Chiu Chang, Macarthur Charles, Andra Cirule, Margareth Pretti Dalcolmo, Lia D'Ambrosio, Gerard de Vries, Keertan Dheda, Aliasgar Esmail, Jennifer Flood, Gregory J Fox, Mathilde Fréchet-Jachym, Geisa Fregona, Regina Gayoso, Medea Gegia, Maria Tarcela Gler, Sue Gu, Lorenzo Guglielmetti, Timothy H Holtz, Jennifer Hughes, Petros Isaakidis, Leah Jarlsberg, Russell R Kempker, Salmaan Keshavjee, Faiz Ahmad Khan, Maia Kipiani, Serena P Koenig, Won-Jung Koh, Afranio Kritski, Liga Kuksa, Charlotte L Kvasnovsky, Nakwon Kwak, Zhiyi Lan, Christoph Lange, Rafael Laniado-Laborín, Myungsun Lee, Vaira Leimane, Chi-Chiu Leung, Eric Chung-Ching Leung, Pei Zhi Li, Phil Lowenthal, Ethel L Maciel, Suzanne M Marks, Sundari Mase, Lawrence Mbuagbaw, Giovanni B Migliori, Vladimir Milanov, Ann C Miller, Carole D Mitnick, Chawangwa Modongo, Erika Mohr, Ignacio Monedero, Payam Nahid, Norbert Ndjeka, Max R O'Donnell, Nesri Padayatchi, Domingo Palmero, Jean William Pape, Laura J Podewils, Ian Reynolds, Vija Riekstina, Jérôme Robert, Maria Rodriguez, Barbara Seaworth, Kwonjune J Seung, Kathryn Schnippel, Tae Sun Shim, Rupak Singla, Sarah E Smith, Giovanni Sotgiu, Ganzaya Sukhbaatar, Payam Tabarsi, Simon Tiberi, Anete Trajman, Lisa Trieu, Zarir F Udwadia, Tjip S van der Werf, Nicolas Veziris, Piret Viiklepp, Stalz Charles Vilbrun, Kathleen Walsh, Janice Westenhouse, Wing-Wai Yew, Jae-Joon Yim, Nicola M Zetola, Matteo Zignol, Dick Menzies*

## Summary

**Background** Treatment outcomes for multidrug-resistant tuberculosis remain poor. We aimed to estimate the association of treatment success and death with the use of individual drugs, and the optimal number and duration of treatment with those drugs in patients with multidrug-resistant tuberculosis.

**Methods** In this individual patient data meta-analysis, we searched MEDLINE, Embase, and the Cochrane Library to identify potentially eligible observational and experimental studies published between Jan 1, 2009, and April 30, 2016. We also searched reference lists from all systematic reviews of treatment of multidrug-resistant tuberculosis published since 2009. To be eligible, studies had to report original results, with end of treatment outcomes (treatment completion [success], failure, or relapse) in cohorts of at least 25 adults (aged >18 years). We used anonymised individual patient data from eligible studies, provided by study investigators, regarding clinical characteristics, treatment, and outcomes. Using propensity score-matched generalised mixed effects logistic, or linear regression, we calculated adjusted odds ratios and adjusted risk differences for success or death during treatment, for specific drugs currently used to treat multidrug-resistant tuberculosis, as well as the number of drugs used and treatment duration.

*Lancet* 2018; 392: 821–34

See Comment pages 797 and 798

**Faculty of Pharmacy and Health Sciences, University of Baluchistan, Quetta, Pakistan** (N Ahmad PhD); **Bureau of Tuberculosis Control, New York City Department of Health and Mental Hygiene, NY, USA** (S D Ahuja PhD, L Trieu MPH); **Department of Pulmonary Diseases and Tuberculosis** (O W Akkerman PhD, T S van der Werf MD), **Tuberculosis Centre Beatrixoord** (O Akkerman),

(Continued from previous page)

| | Drug given (events/total) | Drug not given (events/total) | Crude OR (95% CI) | Propensity score matched multivariate regression | | | |
|---|---|---|---|---|---|---|---|
| | | | | Pairs (n) | Adjusted OR (95% CI) | $I^2$ | Adjusted RD (95% CI) |
| **Macrolides** | | | | | | | |
| No drug susceptibility testing | | | | | | | |
| Success | 560/723 | 2628/3093 | 0·6 (0·5–0·7) | 722 | 0·6 (0·5–0·8) | 10·9% | –0·08 (–0·12 to –0·03) |
| Death | 185/908 | 562/3655 | 1·4 (1·2–1·7) | 908 | 1·6 (1·2–2·0) | 75·3% | 0·06 (0·02 to 0·09) |
| **Bedaquiline** | | | | | | | |
| No drug susceptibility testing** | | | | | | | |
| Success | 431/491 | 6312/7220 | 1·0 (0·8–1·4) | 490 | 2·0 (1·4–2·9) | NC | 0·10 (0·05 to 0·14) |
| Death | 59/550 | 1569/8789 | 0·6 (0·4–0·7) | 548 | 0·4 (0·3· 0·5) | 33·5% | –0·14 (–0·19 to –0·10) |

## APPENDIX Table S2.3: Treatment received by all 12,030 PATIENTS INCLUDED IN THE IPD ANALYSES

| **Drugs used in treatment** *(% of all patients)* | N | % |
|---|---|---|
| Bedaquiline (BDQ) | 641 | 5.3 % |
| Carbapenem (& clavulanate) | 192 | 1.6 % |
| Delamanid | 29 | 0.2 % |

# Bedaquline

- A retrospective cohort study
- 25 centers in Africa, Asia, Europe, Oceania, Southern America

| Total | 428 |
|---|---|
| Age | 35 |
| Male | 62% |
| HIV | 22% |
| XDR | 46% |
| Culture conversion | 92% |
| Treatment success | 71% |
| Death | 13% |

ORIGINAL ARTICLE
TUBERCULOSIS

## Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study

Sergey E. Borisov[1,50], Keertan Dheda[2,50], Martin Enwerem[3,50], Rodolfo Romero Leyet[4,50], Lia D'Ambrosio[5,6,50], Rosella Centis[5,50], Giovanni Sotgiu[7,50], Simon Tiberi[8,9,50], Jan-Willem Alffenaar[10,50], Andrey Maryandyshev[11,50], Evgeny Belilovski[1,50], Shashank Ganatra[12,50], Alena Skrahina[13,50], Onno Akkerman[14,15], Alena Aleksa[16], Rohit Amale[12], Janina Artsukevich[16], Judith Bruchfeld[17], Jose A. Caminero[18,19], Isabel Carpena Martinez[20], Luigi Codecasa[21], Margareth Dalcolmo[22], Justin Denholm[23], Paul Douglas[24], Raquel Duarte[25], Aliasgar Esmail[26], Mohammed Fadul[26], Alexey Filippov[1], Lina Davies Forsman[17], Mina Gaga[27], Julia-Amaranta Garcia-Fuertes[28], José-María García-García[29], Gina Gualano[30], Jerker Jonsson[31], Heinke Kunst[9], Jillian S. Lau[32], Barbara Lazaro Mastrapa[33], Jorge Lazaro Teran Troya[33], Selene Manga[34], Katerina Manika[35], Pablo González Montaner[36], Jai Mullerpattan[12], Suzette Oelofse[26], Martina Ortelli[37], Domingo Juan Palmero[36], Fabrizio Palmieri[30], Antonella Papalia[38], Apostolos Papavasileiou[39], Marie-Christine Payen[40], Emanuele Pontali[41], Carlos Robalo Cordeiro[42], Laura Saderi[7], Tsetan Dorji Sadutshang[43], Tatsiana Sanukevich[16], Varvara Solodovnikova[13], Antonio Spanevello[44,45], Sonam Topgyal[43], Federica Toscanini[46], Adrian R. Tramontana[47], Zarir Farokh Udwadia[12], Pietro Viggiani[38], Veronica White[48], Alimuddin Zumla[49] and Giovanni Battista Migliori[5,50]

@ERSpublications
**Bedaquiline is safe and effective in treating MDR- and XDR-TB patients** http://ow.ly/6MWK30adHkw

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TABLE 4 Treatment outcomes of 428 culture-confirmed multidrug resistant (MDR-) and extensively drug-resistant tuberculosis (XDR-TB) patients exposed to bedaquiline-containing regimens in different settings and stratified by cohort

| | Africa | | |
|---|---|---|---|
| **Total cohort** | 113 | | |
| Success | 73 (64.6) | | |
| Cure | 73 (64.6) | | |
| Completion | | | |
| Death | 27 (23.9) | | |
| Default | 9 (8.0) | | |
| Failure | 3 (2.7) | | |
| Transfer out | 1 (0.9) | | |
| **MDR-TB** | 62 | | |
| Success | 36 (58.1) | | |
| Cure | 36 (58.1) | | |
| Completion | | 8 (20.5) | 11 (40.7) |
| Death | 17 (27.4) | 3 (7.7) | 1 (3.7) |
| Default | 7 (11.3) | 3 (7.7) | 1 (3.7) |
| Failure | 1 (1.6) | 5 (12.8) | 3 (11.1) |
| Transfer out | 1 (1.6) | | |
| **XDR-TB** | 51 | 46 | 22 |
| Success | 37 (72.6) | 37 (80.4) | 16 (72.7) |
| Cure | 37 (72.6) | 34 (73.9) | 16 (72.7) |
| Completion | | 3 (6.5) | |
| Death | 10 (19.6) | | 2 (9.1) |
| Default | 2 (3.9) | 5 (10.9) | |
| Failure | 2 (3.9) | 4 (8.7) | 4 (18.2) |
| Transfer out | | | |

Data are presented as n or n (%).

| Treatment success | |
|---|---|
| 2010-2011 | 2012-2014 |
| 56% | 79% |

# Delamanid 213 Trial – Phase 3

## Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial

*Florian von Groote-Bidlingmaier*, Ramonde Patientia*, Epifanio Sanchez, Vincent Balanag Jr, Eduardo Ticona, Patricia Segura, Elizabeth Cadena, Charles Yu, Andra Cirule, Victor Lizarbe, Edita Davidaviciene, Liliana Domente, Ebrahim Variava, Janice Caoili, Manfrid Danilovits, Virgaine Bielskiene, Suzanne Staples, Norbert Hittel, Carolyn Petersen, Charles Wells, Jeffrey Hafkin, Lawrence J Geiter, Rajesh Gupta*

Lancet Respir Med 2019;7:249–59.

- OBR + delamanid (for 6M) *vs*. OBR + placebo (for 6M)
- 17 sites in seven countries (Estonia, Latvia, Lithuania, Moldova, Peru, the Philippines, and South Africa)
- Primary outcomes
  - Time to SCC over 6 months (MGIT)
  - Difference in the distribution of time to SCC over 6 months between the two groups

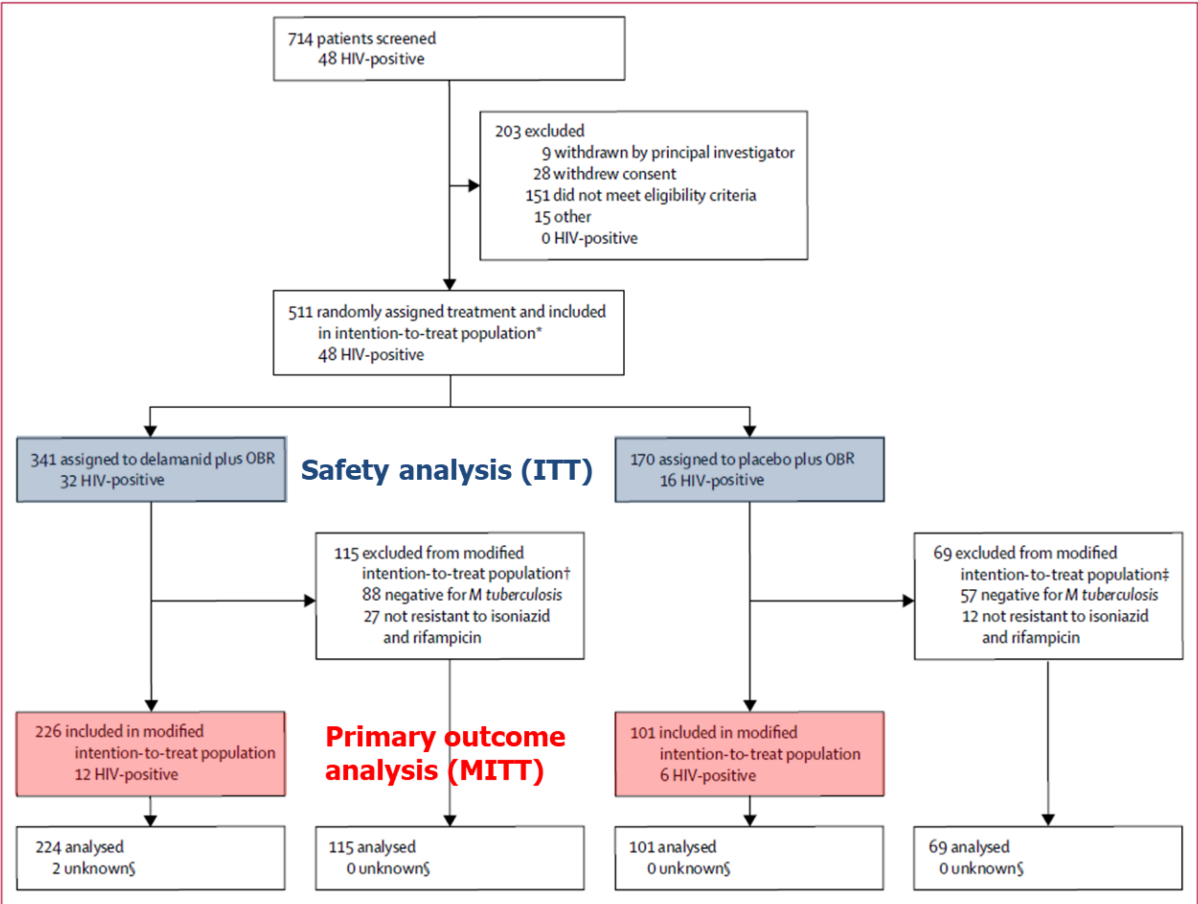



*Figure 1:* Trial profile
OBR=optimised background regimen. *Eligible for long-term outcome analyses. †24 of whom were HIV-positive. ‡10 of whom were HIV-positive. §30-month outcomes.

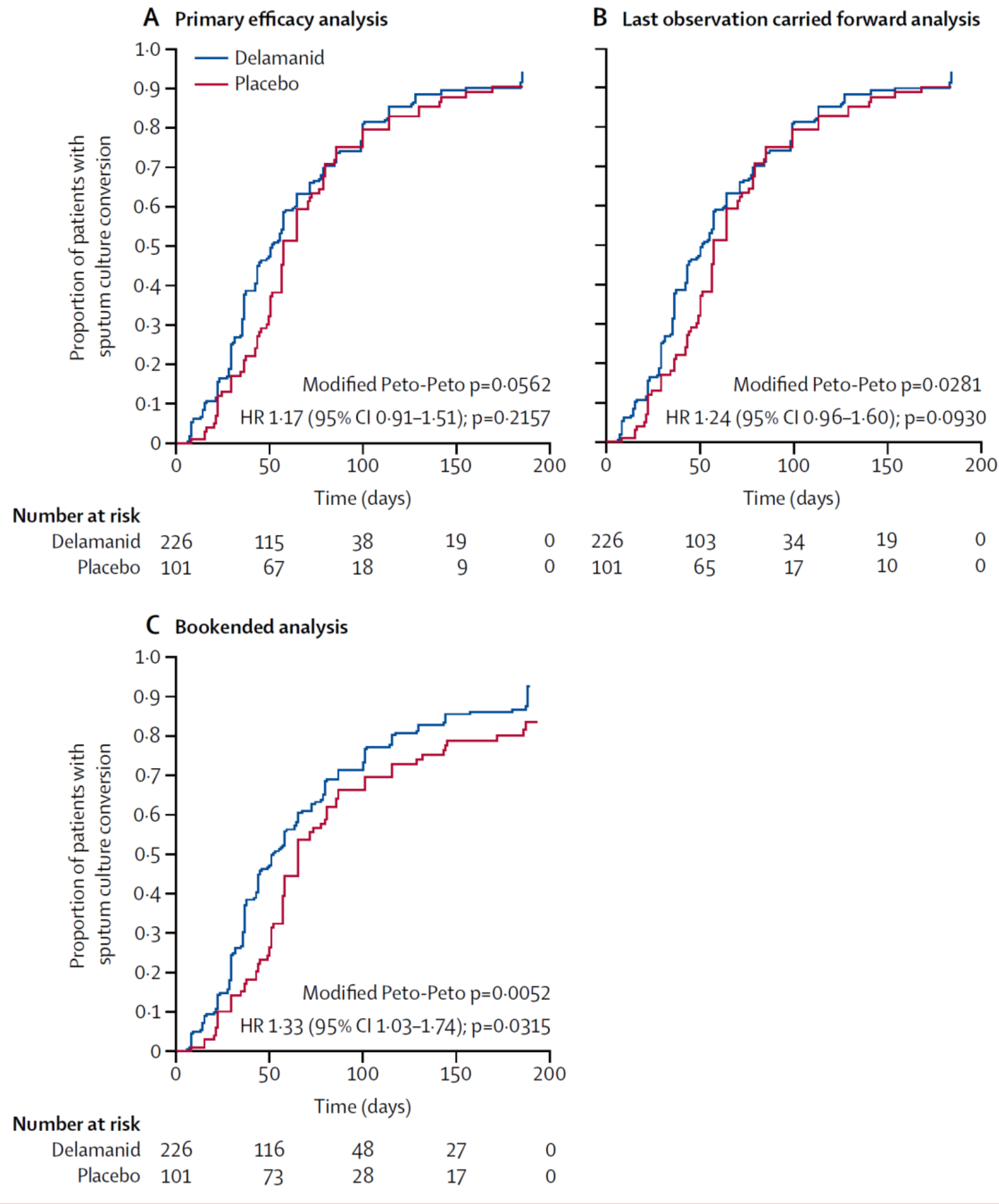



*Figure 2:* **Kaplan-Meier estimates of distribution of time to sputum culture conversion over 6 months, modified intention-to-treat population**
Delamanid and placebo groups included optimised background regimen. HR=hazard ratio.

| | Dlm | Placebo | p |
|---|---|---|---|
| 6-m culture conversion | 88% | 86% | 0.38 |
| Culture conversion at 30m | 77% | 77% | 0.90 |
| Treatment success | 77% | 77% | 0.99 |
| Death | 5% | 5% | 0.78 |

## Over-performance of the placebo group

- Cure rate: 77% (trial 213) *vs.* 55% (WHO global report)
- Late generation FQ, repurposed drugs (Lzd, Cfz), rapid diagnostic test
  (eg, Xpert MTB/RIF assay)…

## Under-performance of delamanid

- Allowance of pre-treatment up to 90 days prior to enrolment

TABLE 6 Treatment outcomes of 9036 patients with multidrug-resistant/rifampin-resistant tuberculosis

2001-2003 → 2013-2015

Treatment success 46% → 72%

Treatment failure and relapse 25% → 5%

| | Period 1 2001–2003 | Period 2 2004–2006 | Period 3 2007–2009 | Period 4 2010–2012 | Period 5 2013–2015 | p-value trend over time | Total 2001–2015 |
|---|---|---|---|---|---|---|---|
| Low-/lower-middle | 16 (13) | 18 (4) | 57 (10) | 81 (10) | 5 (5) | 0.06 | 177 (10) |
| Upper-middle | 188 (31) | 38 (11) | 131 (25) | 49 (19) | 31 (5) | <0.001 | 437 (19) |
| High | 4 (4) | 47 (8) | 45 (8) | 51 (10) | 6 (3) | 0.59 | 153 (8) |
| **Loss to follow-up or transfer** | | | | | | | |
| Total | 248 (18) | 345 (18) | 459 (17) | 179 (10) | 155 (13) | <0.001 | 1386 (15) |
| Low-/lower-middle | 34 (19) | 106 (17) | 195 (23) | 81 (10) | 6 (5) | <0.001 | 422 (16) |
| Upper-middle | 196 (19) | 96 (17) | 180 (15) | 46 (14) | 116 (4) | 0.004 | 634 (16) |
| High | 18 (13) | 143 (18) | 84 (12) | 52 (9) | 33 (12) | <0.001 | 330 (13) |
| **Death** | | | | | | | |
| Total | 229 (26) | 254 (17) | 595 (30) | 170 (12) | 135 (13) | <0.001 | 1383 (21) |
| Low-/lower-middle | 21 (16) | 77 (16) | 104 (17) | 116 (17) | 17 (14) | 0.77 | 335 (17) |
| Upper-middle | 194 (31) | 119 (28) | 456 (54) | 24 (11) | 104 (16) | <0.001 | 897 (32) |
| High | 14 (12) | 58 (10) | 35 (6) | 30 (6) | 14 (6) | 0.002 | 151 (8) |

Kwak N et al. Eur Respir J 2020; 56: 2001394

# Safety

| | Delamanid plus OBR (n=341) | Placebo plus OBR (n=170) |
|---|---|---|
| **Gastrointestinal** | | |
| Dyspepsia | 33 (9·7%) | 14 (8·2%) |
| Gastritis | 77 (22·6%) | 27 (15·9%) |
| Vomiting | 92 (27·0%) | 39 (22·9%) |
| **General** | | |
| Asthenia | 28 (8·2%) | 10 (5·9%) |
| Chest pain | 22 (6·5%) | 8 (4·7%) |
| **Infections** | | |
| Gastroenteritis | 17 (5·0%) | 6 (3·5%) |
| Influenza | 21 (6·2%) | 6 (3·5%) |
| Upper respiratory tract infection | 49 (14·4%) | 21 (12·4%) |
| Urinary tract infection | 36 (10·6%) | 15 (8·8%) |
| **Metabolic and nutritional disorders** | | |
| Decreased appetite | 26 (7·6%) | 9 (5·3%) |
| Hypomagnesaemia | 21 (6·2%) | 7 (4·1%) |

| | Delamanid plus OBR (n=341) | Placebo plus OBR (n=170) |
|---|---|---|
| **Musculoskeletal and connective tissue disorders** | | |
| Musculoskeletal pain | 21 (6·2%) | 10 (5·9%) |
| Myalgia | 31 (9·1%) | 14 (8·2%) |
| **Nervous system disorders** | | |
| Dizziness | 51 (15·0%) | 23 (13·5%) |
| Headache | 104 (30·5%) | 39 (22·9%) |
| Tremors | 22 (6·5%) | 5 (2·9%) |
| **Other** | | |
| ECG, QT interval prolonged* | 18 (5·3%) | 5 (2·9%) |
| Proteinuria | 18 (5·3%) | 7 (4·1%) |
| Rash | 27 (7·9%) | 9 (5·3%) |
| Contusion | 22 (6·5%) | 10 (5·9%) |

Data are number of patients (%). The adverse events shown are those that occurred in at least 5% of the delamanid group and at a higher frequency in the delamanid group than in the placebo group. Patients could have more than one adverse event. *As determined by trial investigators.

***Table 4:*** **Incidence of treatment-emergent adverse events occurring in at least 5% of patients in the delaminid group and at a higher frequency in the delaminid group**

# WHO position statement on the use of delamanid for multidrug-resistant tuberculosis

Expedited review of the phase III clinical trial data of delamanid added to an optimised background MDR-TB regimen

January 2018

## Conclusions

- *Trial 213* is the first-ever phase III randomized controlled clinical trial for MDR-TB treatment to be completed and reported, and thus represents a much-needed scientific breakthrough to guide treatment. WHO commends the efforts of everyone involved, including those MDR-TB patients who consented to participate.

- Translating the results of *Trial 213* into definitive policy guidance on the use of delamanid in MDR-TB treatment is, however, challenging for a number of reasons:

  - *Trial 213* did not confirm the efficacy findings from the Otsuka phase IIb trials, which suggested statistically significant reductions in mortality and increased culture conversion at two months; in contrast, the safety conclusions were the same as those in the phase IIb trials, and provided reassurance of delamanid as a relatively safe drug compared to many second-line medicines;
  - *Trial 213* was not designed to indicate which MDR-TB patients would most likely benefit from delamanid, or whether delamanid can effectively replace or protect other medicines in composing MDR-TB regimens.

- The treatment success achieved in the placebo arm in *Trial 213* was much higher than that reported from earlier programmatic MDR-TB treatment cohorts. This was likely due to careful design and strong implementation of the clinical trial (e.g. careful selection of trial investigators, sites, and participants, excluding highest-risk individuals and assuring high standards of care) and probably also to improved MDR-TB management at country level over time (facilitated by earlier detection with rapid molecular diagnostics and improved treatment regimen composition);

- The favourable outcomes and high patient retention on *Trial 213* were achieved through greatly enhanced efforts to ensure that participants were engaged in their care and not lost to follow-up – an essential message for routine clinical and programmatic care of MDR-TB patients.

# WHO consolidated guidelines on drug-resistant tuberculosis treatment

THE END TB STRATEGY

World Health Organization

**Table 2.2. Relative risk for (i) treatment failure or relapse and (ii) death (versus treatment success), 2018 IPD-MA for longer MDR-TB regimens and delamanid Trial 213 (intent-to-treat population)[22]**

| Medicine | | Treatment failure or relapse versus treatment success | | Death versus treatment success | |
|---|---|---|---|---|---|
| | | Number treated | Adjusted odds ratio (95% confidence limits) | Number treated | Adjusted odds ratio (95% confidence limits) |
| **A** | Levofloxacin *OR* moxifloxacin | 3 143 | 0.3 (0.1–0.5) | 3 551 | 0.2 (0.1–0.3) |
| | Bedaquiline | 1 391 | 0.3 (0.2–0.4) | 1 480 | 0.2 (0.2–0.3) |
| | Linezolid | 1 216 | 0.3 (0.2–0.5) | 1 286 | 0.3 (0.2–0.3) |
| **B** | Clofazimine | 991 | 0.3 (0.2–0.5) | 1 096 | 0.4 (0.3–0.6) |
| | Cycloserine *OR* terizidone | 5 483 | 0.6 (0.4–0.9) | 6 160 | 0.6 (0.5–0.8) |
| **C** | Ethambutol | 1 163 | 0.4 (0.1–1.0) | 1 245 | 0.5 (0.1–1.7) |
| | Delamanid | 289 | 1.1 (0.4–2.8)* | 290 | 1.2 (0.5–3.0)* |

Clinical Infectious Diseases
MAJOR ARTICLE

IDSA Infectious Diseases Society of America
hivma hiv medicine association
OXFORD

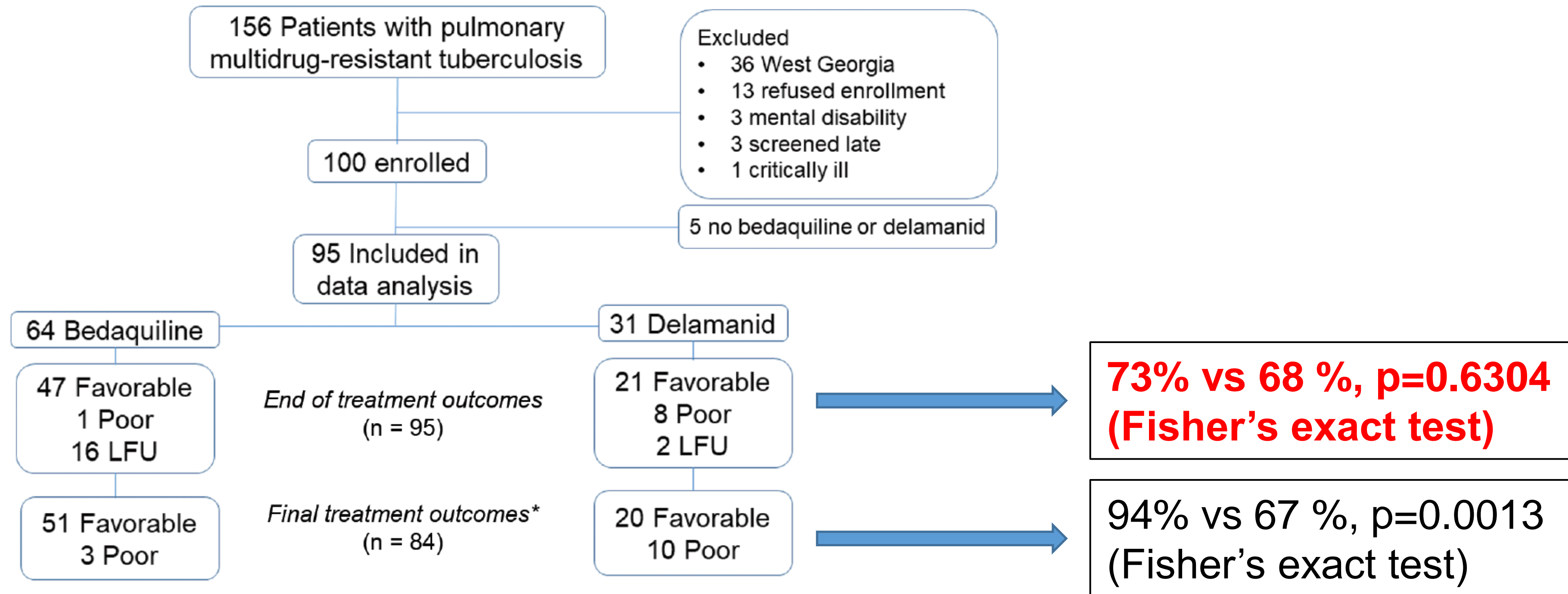
# Clinical Outcomes Among Patients With Drug-resistant Tuberculosis Receiving Bedaquiline- or Delamanid-Containing Regimens

R. R. Kempker,[1,] L. Mikiashvili,[2] Y. Zhao,[3] D. Benkeser,[3] K. Barbakadze,[2] N. Bablishvili,[2] Z. Avaliani,[2] C. A. Peloquin,[4] H. M. Blumberg,[1,5] and M. Kipiani[2]

[1]Department of Medicine, Division of Infectious Disease, Emory University School of Medicine, Atlanta, Georgia, USA, [2]National Center for Tuberculosis and Lung Disease, Tbilisi, Georgia, [3]Department of Biostatistics and Bioinformatics, Emory Rollins School of Public Health, Atlanta, Georgia, USA, [4]Department of Pharmacy, University of Florida, Gainesville, Florida, USA, and [5]Departments of Epidemiology and Global Health, Rollins School of Public Health, Emory University, Atlanta, Georgia, USA

- Not randomized → selection bias
- No protocol → different treatment
- Excluded LFU in final treatment outcome
  → more favorable in Bdq

R R Kempker et al. Clin Infect Dis 2020; 71: 2336




**73% vs 68 %, p=0.6304 (Fisher's exact test)**

94% vs 67 %, p=0.0013 (Fisher's exact test)

# Bedaquiline- and delamanid-containing regimens achieve excellent interim treatment response without safety concerns

## endTB interim analysis

July 2018

*Table 11. Culture conversion in endTB and other cohorts*

| Cohort | Number of patients | Culture conversion |
|---|---|---|
| Delamanid Phase III trial (unpublished) | 226 | 88% |
| endTB interim analysis | 174 | 79% |
| Compassionate use[8] | 78 | 80% |
| MSF[9] | 53 | 68% |
| South Korea[10] | 32 | 94% |

[7] Lee M, Lee J, Carroll MW, Choi H, Min S et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. *N Engl J Med* 2012; 367(16): 1508-18.

[8] Hafkin J, Hittel N, Martin A, Gupta R. Early outcomes in MDR-TB and XDR-TB patients treated with delamanid under compassionate use. *Eur Respir J* 2017; 50(1).

[9] Hewison C, Ferlazzo G, Avaliani Z, Hayrapetyan A, Jonckheere S, et al. Six-month response to delamanid treatment in MDR TB patients. *Emerg Infect Dis* 2017; 23(10).

[10] Mok J, Kang H, Hwang SH, Park JS, Kang B, et al. Interim outcomes of delamanid for the treatment of MDR- and XDR-TB in South Korea. *J Antimicrob Chemother* 2018; 73(2): 503-508.

*Clinical Infectious Diseases*

BRIEF REPORT

# Culture Conversion at 6 Months in Patients Receiving Delamanid-containing Regimens for the Treatment of Multidrug-resistant Tuberculosis

**Kwonjune J. Seung,[1,a] Palwasha Khan,[2,a] Molly F. Franke,[3] Saman Ahmed,[2] Stalbek Aiylchiev,[4] Manzur Alam,[5] Fauziah Asnely Putri,[6] Mathieu Bastard,[7] Wisny Docteur,[8] Gary Gottlieb,[1] Catherine Hewison,[9] Shirajul Islam,[5] Naira Khachatryan,[10] Tinatin Kotrikadze,[11] Uzma Khan,[12] Andargachew Kumsa,[13] Leonid Lecca,[14] Yoseph Melaku Tassew,[15] Nara Melikyan,[15] Ye Yint Naing,[16] Lawrence Oyewusi,[17] Michael Rich,[1] Stephen Wanjala,[18] Askar Yedilbayev,[1] Helena Huerga,[7,b] and Carole D. Mitnick[3,b]; for the endTB Study Group**

[1]Partners In Health, Boston, Massachusetts, USA, [2]Interactive Research and Development, Karachi, Pakistan, [3]Department of Global Health and Social Medicine, Harvard Medical School and Partners In Health, Boston, Massachusetts, USA, [4]Médecins Sans Frontières, Kyrgyzstan, [5]Interactive Research and Development, Dhaka, Bangladesh, [6]Interactive Research and Development, Indonesia, [7]Field Epidemiology Department, Epicentre, Paris, France, [8]Zanmi Lasante, Port-Au-Prince, Haiti, [9]Medical Department, Médecins Sans Frontières, Paris, France, [10]Médecins Sans Frontières, Armenia, [11]Médecins Sans Frontières, Georgia, [12]Interactive Research and Development, Dubai, United Arab Emirates, [13]Partners In Health, Addis Ababa, Ethiopia, [14]Socios En Salud, Lima, Peru, [15]Médecins Sans Frontières, Belarus, [16]Médecins Sans Frontières, Myanmar, [17]Partners In Health, Maseru, Lesotho, and [18]Médecins Sans Frontières, Kenya

Delamanid should be effective against highly resistant strains of *Mycobacterium tuberculosis*, but uptake has been slow globally. In the endTB (expand new drug markets for TB) Observational Study, which enrolled a large, heterogeneous cohorts of patients receiving delamanid as part of a multidrug regimen, 80% of participants experienced sputum culture conversion within 6 months.

**Clinical Trials Registration.** NCT02754765.

**Keywords:** multidrug-resistant tuberculosis; extensively drug-resistant tuberculosis; antitubercular agents; delamanid.

- The endTB Observational Study
- Bdq- or Dlm-containing regimen for RR/MDR-TB at sites in 17 countries
- 631 initiated a Dlm-containing regimen, and 325 had a positive baseline culture and were eligible for analysis.
- **80% culture conversion** within 6 months

KJ Seung et al. Clin Infect Dis 2020;71:415

J Antimicrob Chemother 2018; **73**: 503–508
doi:10.1093/jac/dkx373 Advance Access publication 23 October 2017

Journal of Antimicrobial Chemotherapy

# Interim outcomes of delamanid for the treatment of MDR- and XDR-TB in South Korea

Jeongha Mok[1], Hyungseok Kang[2], Soo Hee Hwang[2], Jin Su Park[2], Bohyoung Kang[3], Taehoon Lee[4], Won-Jung Koh[5], Jae-Joon Yim[6] and Doosoo Jeon[7]*

Efficacy (culture conversion)

| Weeks | Solid medium | Liquid medium |
|---|---|---|
| 8 | 72% | 50% |
| 24 | 94% | 93% |

Safety

| ADR | |
|---|---|
| Grade 3/4 (QT prolongation) | 6% / 0% |
| **Nausea vomiting** | **19%** |
| Dyspepsia | 17% |
| Temporary discontinuation | 4% |

Mok J et al. J Antimicrob Chemothera 2018; 73: 503

AGORA
RESEARCH LETTER

# Final treatment outcomes of delamanid-containing regimens in patients with MDR-/XDR-TB in South Korea

Jeongha Mok[1], Hyungseok Kang[2], Won-Jung Koh[3], Byung Woo Jhun[3], Jae-Joon Yim[4], Nakwon Kwak[4], Taehoon Lee[5], Bohyoung Kang[6] and Doosoo Jeon[7]

Mok J et al. Eur Respir J. 2019;54:1900811

| | Total | MDR | preXDR_slid | preXDR_fq | XDR |
|---|---|---|---|---|---|
| n | 49 | 14 | 7 | 20 | 8 |
| Tx success | 82% | 86% | 86% | 75% | 88% |

QTcF interval of >500 msec (n=3): 4 weeks (n=1) and 12 weeks (n=2).
One patient continued delamanid, while two patients transiently discontinued delamanid.

ORIGINAL ARTICLE
TUBERCULOSIS

# Bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis: a multicentre cohort study in Korea

Cheon Tae Kim[1], Tae-Ok Kim[2], Hong-Joon Shin[2], Young Chun Ko[3], Yeong Hun Choe[4], Hak-Ryul Kim[5] and Yong-Soo Kwon[2]

**Affiliations**: [1]Mokpo National TB Hospital, Mokpo, Republic of Korea. [2]Dept of Internal Medicine, Chonnam National University Hospital, Gwangju, Republic of Korea. [3]Dept of Internal Medicine, Kwangju Christian Hospital, Gwangju, Republic of Korea. [4]Division of Respiratory Medicine and Allergy, Dept of Internal Medicine, Chonbuk National University Medical School, Jeonju, Republic of Korea. [5]Dept of Internal Medicine, Institute of Wonkwang Medical Science, Wonkwang University School of Medicine, Iksan, Republic of Korea.

**Correspondence**: Yong-Soo Kwon, Dept of Internal Medicine, Chonnam National University Hospital, 42 Jebongro, Donggu, Gwangju 61469, Republic of Korea. E-mail: yskwon@jnu.ac.kr

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**Bedaquiline and delamanid are effective and safe for MDR-TB treatment when combined with @WHO recommended regimens** http://ow.ly/Xw8O30iqa0j

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Kim CT et al. Eur Respir J. 2018;51:1702467

# Culture conversion

| Variables | Total(n=61) | Dlm (n=11) | Bdq (n=39) | Both (n=11) | p |
|---|---|---|---|---|---|
| Culture conversion | 71% | 100% | 68% | 64% | 0.16 |
| Time to culture conversion, days | 119 (53-199) | 122 (53-145) | 84 (36-174) | 308 (235-347) | <0.01 |

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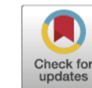



# Interim treatment outcomes in multidrug-resistant tuberculosis using bedaquiline and/or delamanid in South Korea

Hyungseok Kang [a], Kyung-Wook Jo [b], Doosoo Jeon [c], Jae-Joon Yim [d], Tae Sun Shim [b,*]

[a] *Department of Chest Medicine, Masan National Tuberculosis Hospital, Masan, South Korea*
[b] *Division of Pulmonary and Critical Care Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea*
[c] *Department of Internal Medicine, Pusan National University Yangsan Hospital, Yangsan, South Korea*
[d] *Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea*

Kang H et al. Respiratory Medicine 2020; 167: 105956

A R T I C L E  I N F O

*Keywords:*
Multidrug-resistant tuberculosis
Bedaquiline
Delamanid
South Korea

A B S T R A C T

*Purpose:* The Korea Centers for Disease Control & Prevention has implemented a review process for the approval of new drugs used to treat patients with multidrug-resistant tuberculosis (MDR-TB) since September 2016. Therefore, this study aimed to evaluate the efficacy and safety of these new drugs bedaquiline (Bdq) and delamanid (Dlm).

*Methods:* A total of 318 patients with MDR-TB were reviewed by the committee from September 2016 to February 2018; 282 (88.7%) of them were treated with the new drugs (Bdq, 107 patients; Dlm, 108 patients; and both concurrently or sequentially, 67 patients) and retrospectively evaluated. Culture conversion rates, interim treatment outcomes at 12 months, and predictors of unfavorable outcomes were analyzed. Treatment efficacy was also compared between Bdq and Dlm.

*Results:* The mean age of the patients was 49.3 years, and 197 (69.9%) were male. Three patients were HIV seropositive and 151 (53.5%) were quinolone resistant. The culture conversion rates at 2 and 6 months were 57.4% (81/141) and 89.4% (126/141), respectively. A favorable outcome at 12 months was achieved in 84.8% of patients (239/282). Differences in the culture conversion rate or interim treatment outcomes were not statistically significant among the drug susceptibility test patterns or new drugs used. Multivariable analysis showed that age >60 years and body mass index of $<18.5\ kg/m^2$ were significant risk factors for unfavorable outcomes at 12 months.

*Conclusions:* The use of new drugs resulted in satisfactory interim treatment results, without significant differences between them.

**Table 4**

Interim treatment outcome at 12 months according to new drug groups.

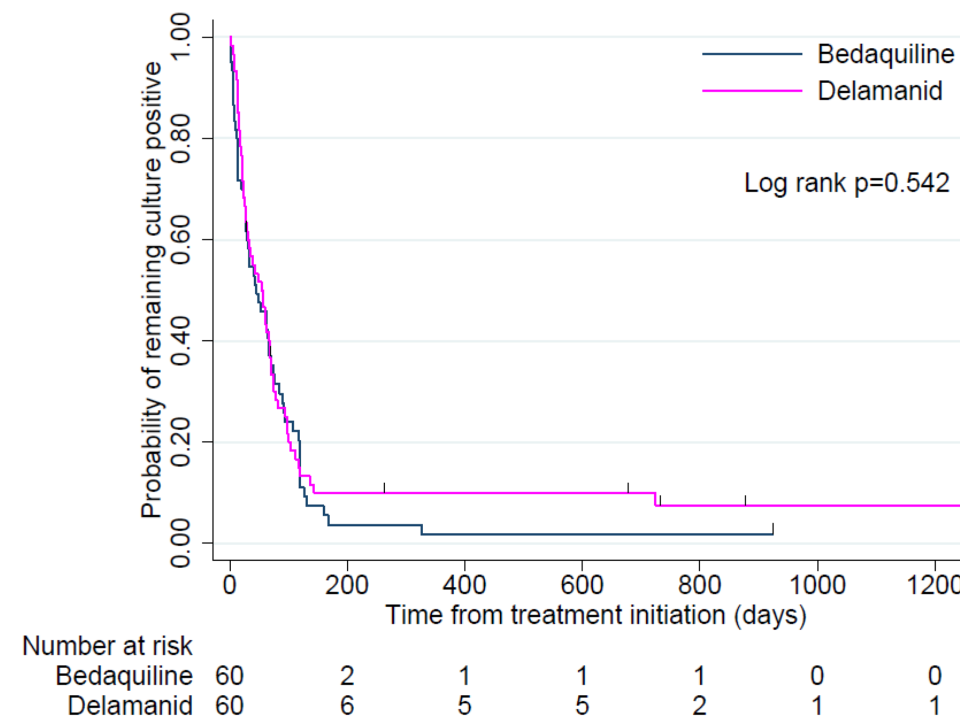
| | Total | Bedaquiline | Delamanid | Both drugs | p-value |
|---|---|---|---|---|---|
| | 282 | 107 | 108 | 67 | |
| **Favorable** | **239 (84.8)** | **86 (80.4)** | **95 (88.0)** | **58 (86.6)** | **0.270** |
| **Unfavorable** | **43 (15.2)** | **21 (19.6)** | **13 (12.0)** | **9 (13.4)** | |
| Death | 23 | 12 | 8 | 3 | |
| LTFU | 15 | 8 | 4 | 3 | |
| Failure | 5 | 1 | 1 | 3 | |

Note: Data are expressed as number (%) of patients.
LTFU, lost to follow-up.

Kang H et al. Respiratory Medicine 2020; 167: 105956

# Final outcomes of Bdq or Dlm in Korea

| | Total | Bedaquiline | Delamanid | p-value |
|---|---|---|---|---|
| Number of patients | 260 | 119 | 141 | |
| Culture conversion (n = 120) | 93% | 93% | 92% | 1.000 |
| Median time to culture conversion, days (95% CI) (n = 120) | 48.0 (27.0–69.0) | 45.0 (17.8–72.2) | 54.0 (27.4–80.6) | 0.542 |
| Final outcomes | | | | |
| Cured | 172 (66.2) | 75 (63.0) | 97 (68.8) | 0.327 |
| Completed | 35 (13.5) | 15 (12.6) | 20 (14.2) | 0.710 |
| Failure | 6 (2.3) | 2 (1.7) | 4 (2.8) | 0.691 |
| Died | 31 (11.9) | 18 (15.1) | 13 (9.2) | 0.143 |
| Tuberculosis-related | 12 (4.6) | 7 (5.9) | 5 (3.5) | |
| Not related to tuberculosis | 13 (5.0) | 10 (8.4) | 3 (2.1) | |
| Unknown | 6 (2.3) | 1 (0.8) | 5 (3.5) | |
| Loss to follow-up | 16 (6.2) | 9 (7.6) | 7 (5.0) | 0.385 |
| Treatment success | 79% | 76% | 82% | 0.189 |




- Initiation of bedaquiline rather than delamanid was not associated with treatment success (aOR = 0.671, 95% CI = 0.350–1.285).
- Frequencies of adverse events were not significantly different between the two groups.

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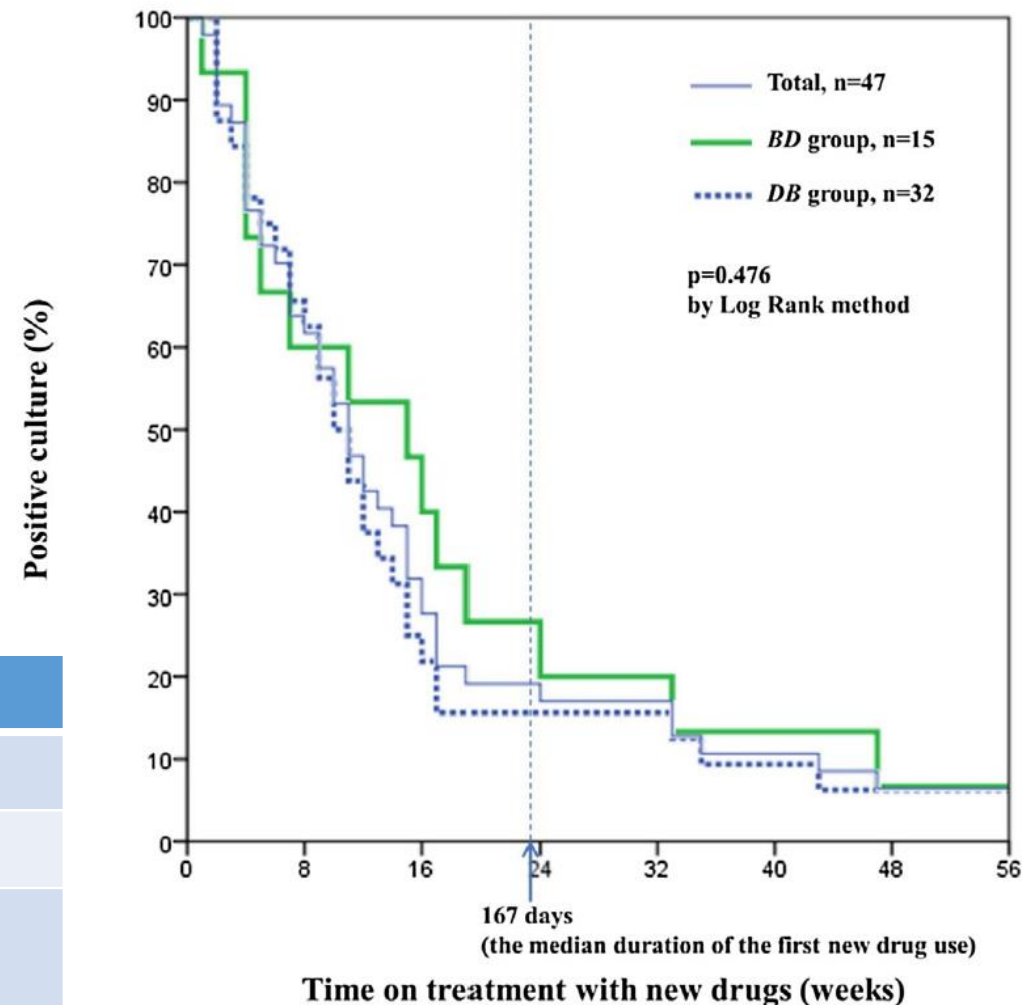
# Interim treatment outcomes in multidrug-resistant tuberculosis patients treated sequentially with bedaquiline and delamanid

Hoon Hee Lee[a], Kyung-Wook Jo[a], Jae-Joon Yim[b], Doosoo Jeon[c], Hyungseok Kang[d], Tae Sun Shim[a,*]

| | Total (n=74) | BD (n=22) | DB (n=52) |
|---|---|---|---|
| Culture conversion | 94% | 93% | 94% |
| Favorable outcome | 92% | 96% | 90% |
| Discontinuation due to QTcF prolongation | 1% | 0% | 2% |

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MDRTB 컨소시엄 교육자료

STATE OF THE ART

# The devil we know: is the use of injectable agents for the treatment of MDR-TB justified?

A. Reuter,* P. Tisile,† D. von Delft,† H. Cox,‡ V. Cox,§ L. Ditiu,¶ A. Garcia-Prats,# S. Koenig,** E. Lessem,†† R. Nathavitharana,‡‡ J. A. Seddon,§§ J. Stillo,¶¶ A. von Delft,†§ J. Furin**

We conclude that there is limited evidence of the efficacy of IAs, clear evidence of the risks of these drugs, and that persons living with MDR-TB should be informed about these risks and provided with access to alternative therapeutic options.

**=> Injectable-free regimen**

* aDSM: active TB drug safety monitoring and management

# RR/MDR-TB 치료 약제(WHO, 2019)

| Groups & steps | Medicine | |
|---|---|---|
| **Group A:**<br>Include all three medicines | levofloxacin *OR*<br>moxifloxacin | Lfx<br>Mfx |
| | bedaquiline[2,3] | Bdq |
| | linezolid[4] | Lzd |
| **Group B:**<br>Add one or both medicines | clofazimine | Cfz |
| | cycloserine *OR*<br>terizidone | Cs<br>Trd |
| **Group C:**<br>Add to complete the regimen and when medicines from Groups A and B cannot be used | ethambutol | E |
| | delamanid[3,5] | Dlm |
| | pyrazinamide[6] | Z |
| | imipenem–cilastatin *OR*<br>meropenem[7] | Ipm–Cln<br>Mpm |
| | amikacin<br>(*OR* streptomycin)[8] | Am<br>(S) |
| | ethionamide *OR*<br>prothionamide[9] | Eto<br>Pto |
| | *p*-aminosalicylic acid[9] | PAS |

# How about Lzd?

## Drug-associated adverse events in the treatment of multidrug-resistant tuberculosis: an individual patient data meta-analysis

ea Benedetti, Sarah K Brode, James C M Brust, Jonathon R Campbell,
saakidis, Russell R Kempker, Maia Kipiani, Liga Kuksa, Christoph Lange,
ngla, Zarir F Udwadia, Dick Menzies, and The Collaborative Group for the
)17*

llosis requires long-term therapy with a combination of multiple
ımerous adverse events that can cause severe morbidity, such as

Lancet Respir Med 2020; 8: 383–94

| | Cohorts using the drug* | Adverse events†/ patients using the drug | Pooled incidence of adverse events, random effect‡ (95% CI) | Pooled incidence of adverse events, fixed effect (95% CI) | Heterogeneity $I^2$ statistics |
|---|---|---|---|---|---|
| Ciprofloxacin | 8 | 4/723 | 0·6% (0·2–1·5) | 0·6% (0·2–1·5) | 0·0% |
| Ofloxacin | 22 | 71/6062 | 0·9% (0·4–2·1) | 1·2% (0·9–1·5) | 85·9% |
| Levofloxacin | 20 | 22/1012 | 1·3% (0·3–5·0) | 2·2% (1·4–3·3) | 81·6% |
| Clofazimine | 13 | 12/1712 | 1·6% (0·5–5·3) | 0·7% (0·4–1·2) | 69·4% |
| Bedaquiline | 14§ | 9/464 | 1·7% (0·7–4·2) | 1·9% (1·0–3·7) | 25·7% |
| Ethambutol | 33 | 124/6089 | 1·8% (1·0–3·3) | 2·0% (1·7–2·4) | 84·0% |
| Streptomycin | 17 | 34/1208 | 2·9% (1·3–6·2) | 2·8% (2·0–3·9) | 71·1% |
| Moxifloxacin | 27 | 30/904 | 2·9% (1·6–5·0) | 3·3% (2·3–4·7) | 38·0% |
| Amoxicillin–clavulanate | 23 | 21/695 | 2·9% (1·7–4·8) | 3·0% (2·0–4·6) | 11·5% |
| Clarithromycin | 16 | 18/457 | 3·3% (1·5–7·0) | 3·9% (2·5–6·2) | 47·2% |
| Imipenem and meropenem | 7§ | 9/158 | 4·9% (1·0–20·5) | 5·7% (3·0–10·6) | 14·4% |
| Pyrazinamide | 35 | 410/5141 | 5·1% (3·1–8·4) | 8·0% (7·3–8·7) | 93·4% |
| Cycloserine and terizidone | 40 | 337/7547 | 5·7% (4·1–7·8) | 4·5% (4·0–5·0) | 83·8% |
| Ethionamide and protionamide | 39 | 376/4627 | 6·5% (4·1–10·1) | 8·1% (7·4–8·9) | 92·9% |
| Kanamycin | 25 | 268/1995 | 7·5% (4·6–11·9) | 13·4% (12·0–15·0) | 86·8% |
| Ca | | | | | |
| Ar | | | | | |
| Ar | | | | | |
| Li | | | | | |
| Thioacetazone | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] |

| Lzd | All ADRs (14.1%) | Peripheral neuropathy (22%) | Myelosuppression (22%) | Optic neuritis (5%) | Gastrointestinal (2%) | Rash (2%) |
|---|---|---|---|---|---|---|

*A study done in a single country was considered as one cohort; a study done in multiple countries was divided into separate cohorts by country. †Adverse events were defined as those that resulted in permanent discontinuation of a drug. ‡Generalised linear mixed model was used to pool the incidence of adverse events. §If a study or cohort only reported adverse events for specific drugs, the cohort was used in the meta-analyses for those drugs.

*Table 2:* Pooled incidence of adverse events for each drug using generalised linear mixed model

Lan Z et al. Lancet Respir Med 2020;8:383

# Summary

- Delamanid is a new nitro-hydro-imidazooxazole derivative, inhibits mycolic acid synthesis.
- It has a potent activity against DS- and DR-*M.tb* in both *in vitro* and *in vivo* studies.
- Delamanid demonstrated clinical evidence of increased sputum culture conversion and improved treatment outcomes and decreased mortality in combination with OBR over a 6-month treatment period for MDR-TB, although it did not be reproduced in a phase 3 trial.
- It can have GI side effects and QTcF prolongation, but relatively safe drug compared to other second line TB drugs.

# Conclusion

- Delamanid is an effective and safe drug for treating MDR-TB.
- It can be a core drug for treating MDR-TB.