Delamanid is a Group C Drug for MDR-TB: Pro

국립마산병원
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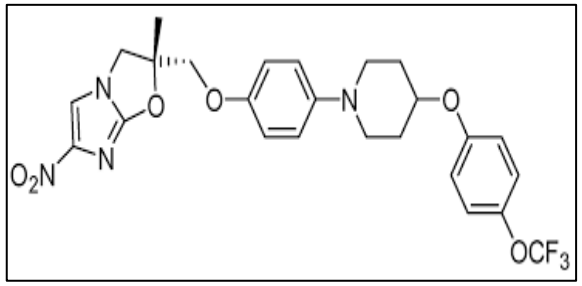
2021 4. 10.
131차 대한결핵및호흡기학회 춘계학술대회

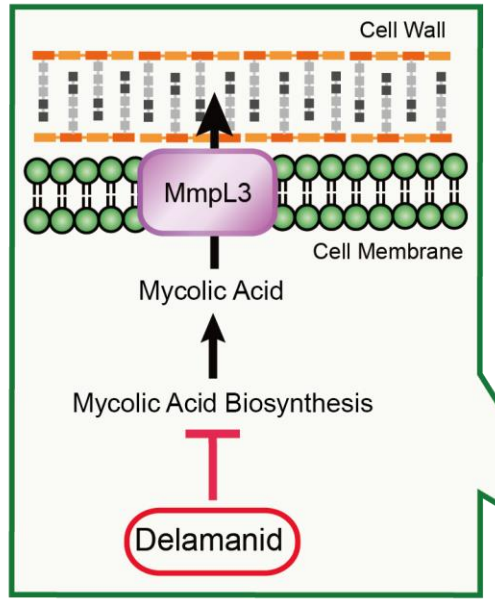
Delamanid : Otsuka pharmaceuticals

nitro-dihydro-imidazooxazole derivative

inhibiting mycolic acids synthesis

delamanid
DELTYBA®





https://www.pharmacodia.com

M. tuberculosis

OPC-67683, a nitro-dihydroimidazooxazole derivative with promising action against tuberculosis in vitro and in mice. PLoS Med 2006;3(11):e466.

Novel agents in the management of Mycobacterium tuberculosis disease. Curr Med Chem 2007;14:2000-8.

Early bactericidal activity of delamanid (OPC-67683) in smear-positive pulmonary tuberculosis patients. Int J Tuberc Lung Dis 2011;15:949-54.

Delamanid Kills Dormant Mycobacteria *In Vitro* and in a Guinea Pig Model of Tuberculosis. Antimicrob Agents Chemother 2017 May 24;61(6):e02402-16.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 7, 2012 VOL. 366 NO. 23

Delamanid for Multidrug-Resistant Pulmonary Tuberculosis

multinational, randomized, double-blind, placebo-controlled trial

161 Were assigned to receive 100 mg of delamanid twice daily

160 Were assigned to receive 200 mg of delamanid twice daily

160 Were assigned to receive placebo

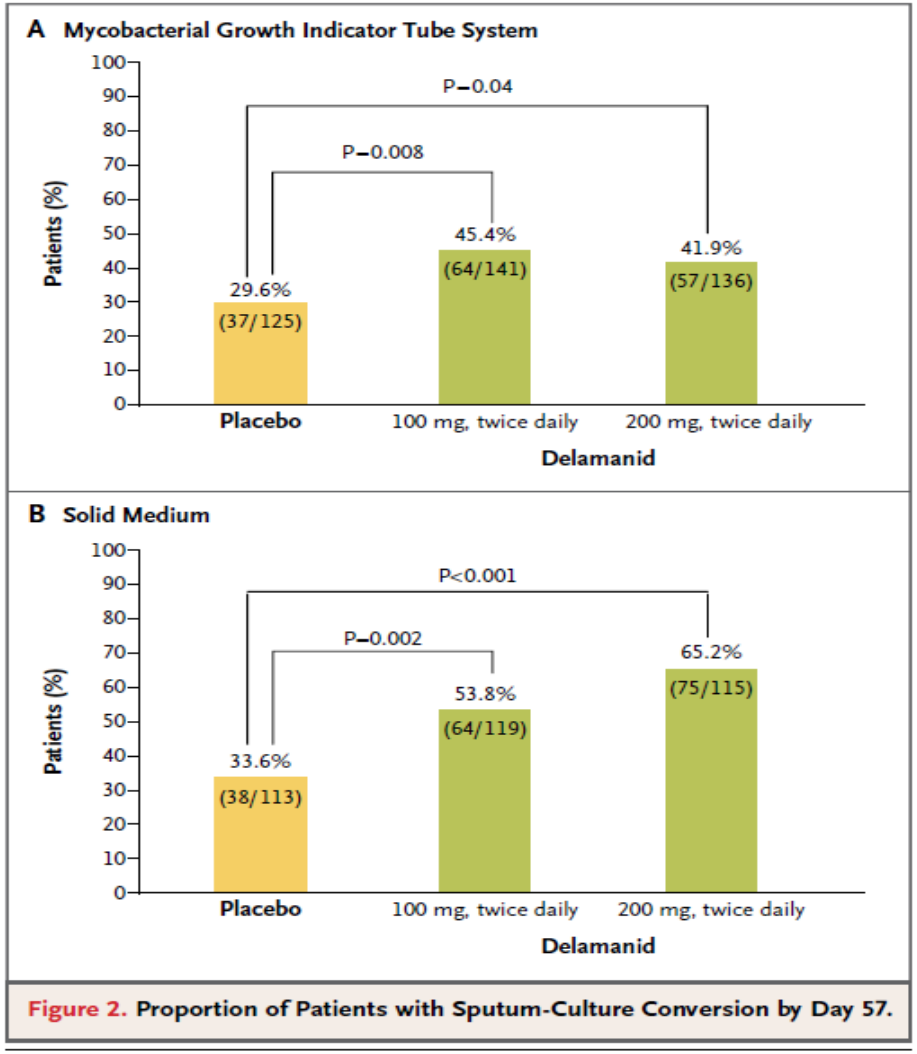


Figure 2. Proportion of Patients with Sputum-Culture Conversion by Day 57.

Eur Respir J 2013; 41: 1393–1400
DOI: 10.1183/09031936.00125812

ERJ Open

Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis

Vija Skripconoka*, Manfred Danilovits#, Lea Pehme#, Tarmo Tomson¶, Girts Skenders*, Tiina Kummik#, Andra Cirule*, Vaira Leimane*, Anu Kurve¶, Klavdia Levina¶, Lawrence J. Geiter+, Davide Manissero§ and Charles D. Wells+

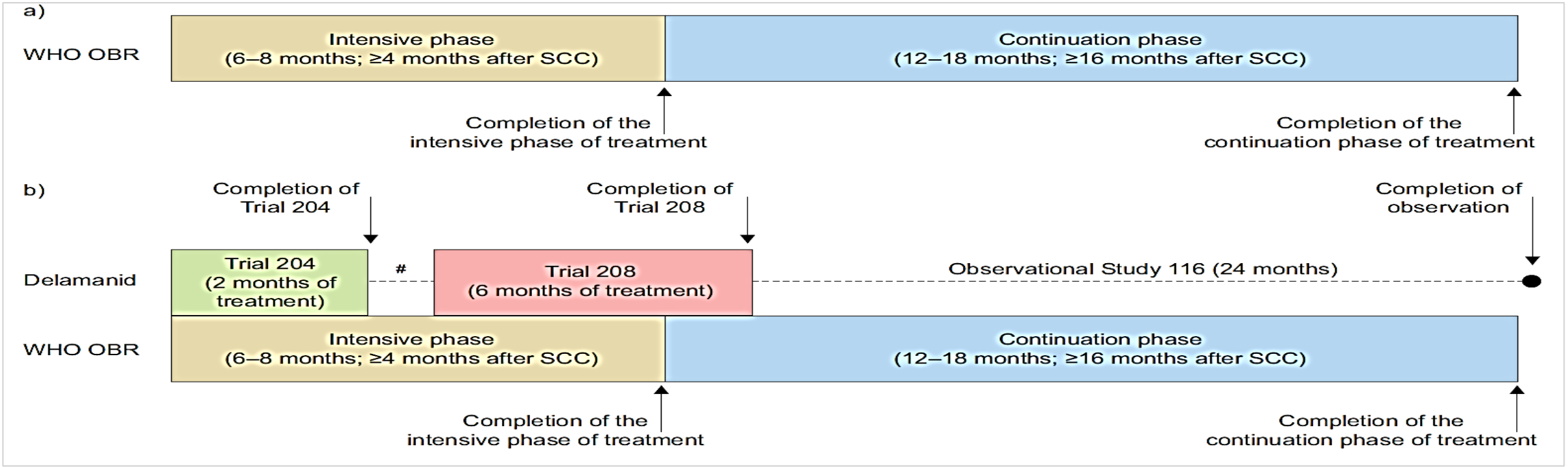


TABLE 2 Long-term (24 month) treatment outcomes after treatment with delamanid in combination with an optimised background treatment regimen: MDR- and XDR-TB patients

Treatment outcome	Long-term treatment[#]	Short-term treatment[¶]	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 ($p \geqslant 0.05$).

This analysis suggests that treatment with delamanid for 6 months in combination with an optimised background regimen can improve outcomes and reduce mortality among patients with both multidrug-resistant and extensively drug-resistant TB.

Eur Respir J. 2013 Jun;41(6):1393-400.

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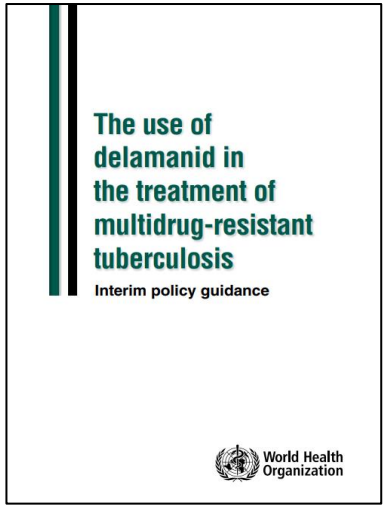
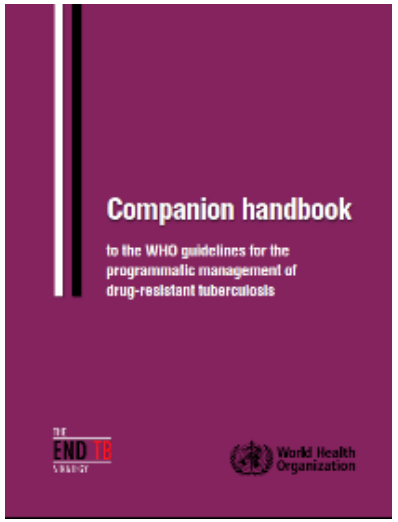


2014

- 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).



GROUP NAME	ANTI-TB AGENT	ABBREVIATION
Group 5. Anti-TB drugs with limited data on efficacy and/or long term safety in the treatment of drug-resistant TB (This group includes new anti-TB agents)	Bedaquiline	Bdq
	Delamanid	Dlm
	Linezolid	Lzd
	Clofazimine	Cfz
	Amoxicillin/ clavulanate	Amx/Clv
	Imipenem/cilastatin[f]	Ipm/Cln
	Meropenem[f]	Mpm
	High-dose isoniazid	High dose H
	Thioacetazone[g]	T
	Clarithromycin[g]	Clr

Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis, 2014, WHO

2018
Rapid Communication: Key changes to Tx of MDR TB

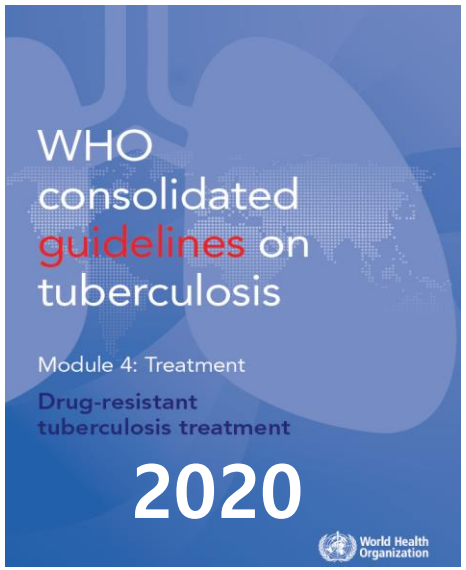


Table 1. Grouping of medicines recommended for use in longer MDR-TB regimens

GROUP	MEDICINE	Abbreviation
Group A: Include all three medicines (unless they cannot be used)	Levofloxacin OR Moxifloxacin	Lfx Mfx
	Bedaquiline[1,4]	Bdq
	Linezolid[2]	Lzd
Group B: Add both medicines (unless they cannot be used)	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[3,4]	Dlm
	Pyrazinamide[5]	Z
	Imipenem-cilastatin OR Meropenem[6]	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)[7]	Am (S)
	Ethionamide OR Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

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)*
	Pyrazinamide	1 248	2.7 (0.7–10.9)	1 272	1.2 (0.1–15.7)
	Imipenem–cilastatin *OR* meropenem	206	0.4 (0.2–0.7)	204	0.2 (0.1–0.5)
	Amikacin	635	0.3 (0.1–0.8)	727	0.7 (0.4–1.2)
	Streptomycin	226	0.5 (0.1–2.1)	238	0.1 (0.0–0.4)
	Ethionamide *OR* prothionamide	2 582	1.6 (0.5–5.5)	2 750	2.0 (0.8–5.3)
	p-aminosalicylic acid	1 564	3.1 (1.1–8.9)	1 609	1.0 (0.6–1.6)
Other medicines	Kanamycin	2 946	1.9 (1.0–3.4)	3 269	1.1 (0.5–2.1)
	Capreomycin	777	2.0 (1.1–3.5)	826	1.4 (0.7–2.8)
	Amoxicillin–clavulanic acid	492	1.7 (1.0–3.0)	534	2.2 (1.3–3.6)

Lancet. 2018 September 08; 392(10150): 821–834. doi:10.1016/S0140-6736(18)31644-1.

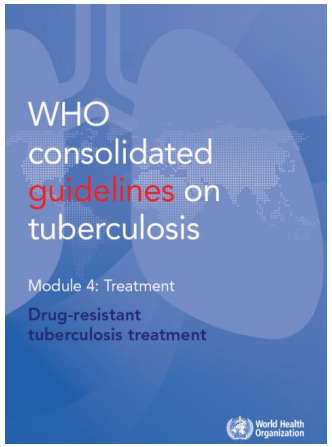
Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis

Pooled outcomes from aggregate data meta-analysis, overall and stratified by major covariate

	Treatment success (n=7346)	Failed treatment or relapsed (n=1017)	Died during treatment (n=1729)	Did not complete (patient decision, data lost, outcome unknown, or patient transferred; n=1938)
All patients	65% (59–70)	6% (5–8)	11% (8–14)	12% (10–15)

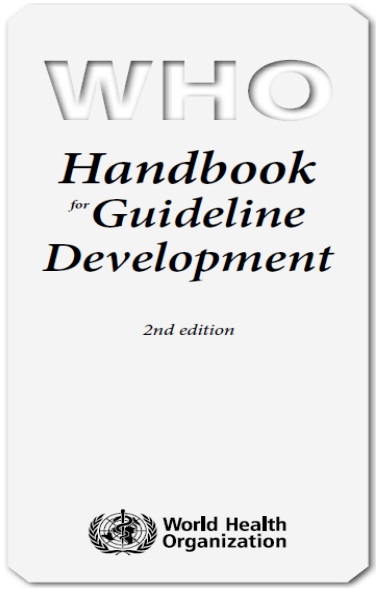
individual patient data meta-analysis,
eligible observational and experimental studies published between Jan 1, 2009, and April 30, 2016.
original results, with end of treatment outcomes (ie, success, failure or relapse, and death)
for 25 or more adults with bacteriologically confirmed pulmonary MDR-TB
12 030 patients from 25 countries in 50 studies

7346 (61%) had treatment success, 1017 (8%) had failure or relapse, and 1729 (14%) died.



· Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens (conditional recommendation, moderate certainty in the estimates of effect).

· Prothionamide or PAS may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used or if better options to compose a regimen are not possible (conditional recommendation against use, very low certainty in the estimates of effect).



- Guideline development group
- External review group

PICO questions

Population, Intervention, Comparator and Outcome

GRADE system

Grading of Recommendations Assessment, Development and Evaluation

** IPD: Individualized Patient Data

Table 10.2. Interpretation of strong and conditional recommendations for an intervention

Audience	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action; only a small proportion would not. Formal decision aides are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Most individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Adherence to the recommendation could be used as a quality criterion or performance indicator.	Different choices will be appropriate for individual patients, who will require assistance in arriving at a management decision consistent with his or her values and preferences. Decision aides may be useful in helping individuals make decisions consistent with their values and preferences.
Policy-makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

Table 9.2. Quality of evidence in GRADE

Quality level	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

GRADE: Grading of Recommendations Assessment, Development and Evaluation.

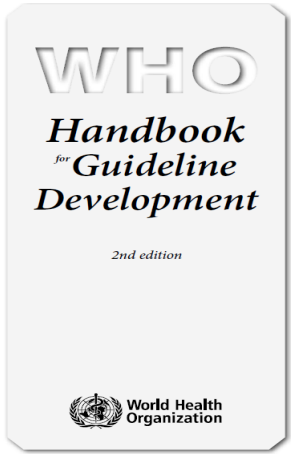


Fig. 9.1. The GRADE approach to rating quality of evidence for each outcome

1 Establish initial level of quality or confidence		2 Consider lowering or raising level of quality or confidence		3 Final level of quality (confidence rating)
Study design	*Initial confidence in an estimate of effect*	*Reasons for considering lowering or raising confidence*		*Confidence in an estimate of effect across all considerations*
		↓ Lower if	↑ Higher if [a]	
Randomized controlled trials →	High confidence	Risk of bias Inconsistency Indirectness Imprecision Publication bias	Large effect Dose response All plausible confounding and bias • would reduce a demonstrated effect or • would suggest a spurious effect if no effect was observed	High ⊕⊕⊕⊕
				Moderate ⊕⊕⊕◯
Observational studies →	Low confidence			Low ⊕⊕◯◯
				Very low ⊕◯◯◯

GRADE: Grading of Recommendations Assessment, Development and Evaluation.

[a] Criteria for upgrading the quality are only applicable to observational studies without any reason for downgrading.

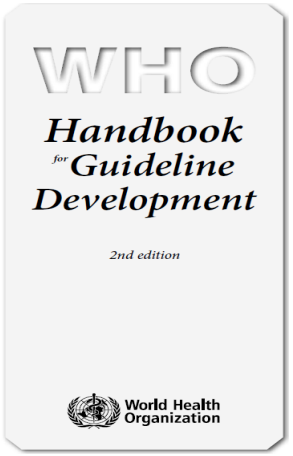
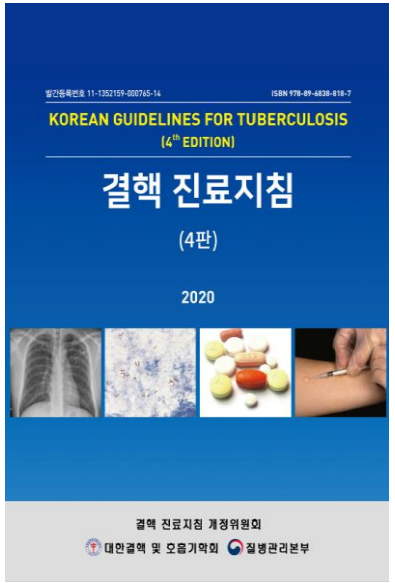


Table 10.1. Factors that determine the direction and strength of a recommendation

Factor	How the factor influences the direction and strength of a recommendation
Quality of the evidence	The quality of the evidence across outcomes critical to decision-making will inform the strength of the recommendation. The higher the quality of the evidence, the greater the likelihood of a strong recommendation.
Values and preferences	This describes the relative importance assigned to health outcomes by those affected by them; how such importance varies within and across populations; and whether this importance or variability is surrounded by uncertainty. The less uncertainty or variability there is about the values and preferences of people experiencing the critical or important outcomes, the greater the likelihood of a strong recommendation.
Balance of benefits and harms	This requires an evaluation of the absolute effects of both benefits and harms (or downsides) of the intervention and their importance. The greater the net benefit or net harm associated with an intervention or exposure, the greater the likelihood of a strong recommendation in favour or against the intervention.
Resource implications	This pertains to how resource-intense an intervention is, whether it is cost—effective and whether it offers any incremental benefit. The more advantageous or clearly disadvantageous the resource implications are, the greater the likelihood of a strong recommendation either for or against the intervention.
Priority of the problem	The problem's priority is determined by its importance and frequency (i.e. burden of disease, disease prevalence or baseline risk). The greater the importance of the problem, the greater the likelihood of a strong recommendation.
Equity and human rights	The greater the likelihood that the intervention will reduce inequities, improve equity or contribute to the realization of one or several human rights as defined under the international legal framework, the greater the likelihood of a strong recommendation.
Acceptability	The greater the acceptability of an option to all or most stakeholders, the greater the likelihood of a strong recommendation.
Feasibility	The greater the feasibility of an option from the standpoint of all or most stakeholders, the greater the likelihood of a strong recommendation. Feasibility overlaps with values and preferences, resource considerations, existing infrastructures, equity, cultural norms, legal frameworks, and many other considerations.



Group		Medicine
Group A		Levofloxacin or Moxifloxacin
		Bedaquiline[1]
		Linezolid
Group B		Cycloserine
		Clofazimine
Group C	C1[2]	Amikacin (or streptomycin)[3] Km
		Ethambutol
		Imipenem or meropenem[4]
		p-aminosalicylic acid
		Prothionamide
		Pyrazinamide
	C2	Delamanid[5]

· 좀더 근거가 축적되기까지 델라마니드를 C2군으로 구분하여 분류하고, 베다퀼린을 대체하여 사용할 수 있도록 권고한다.

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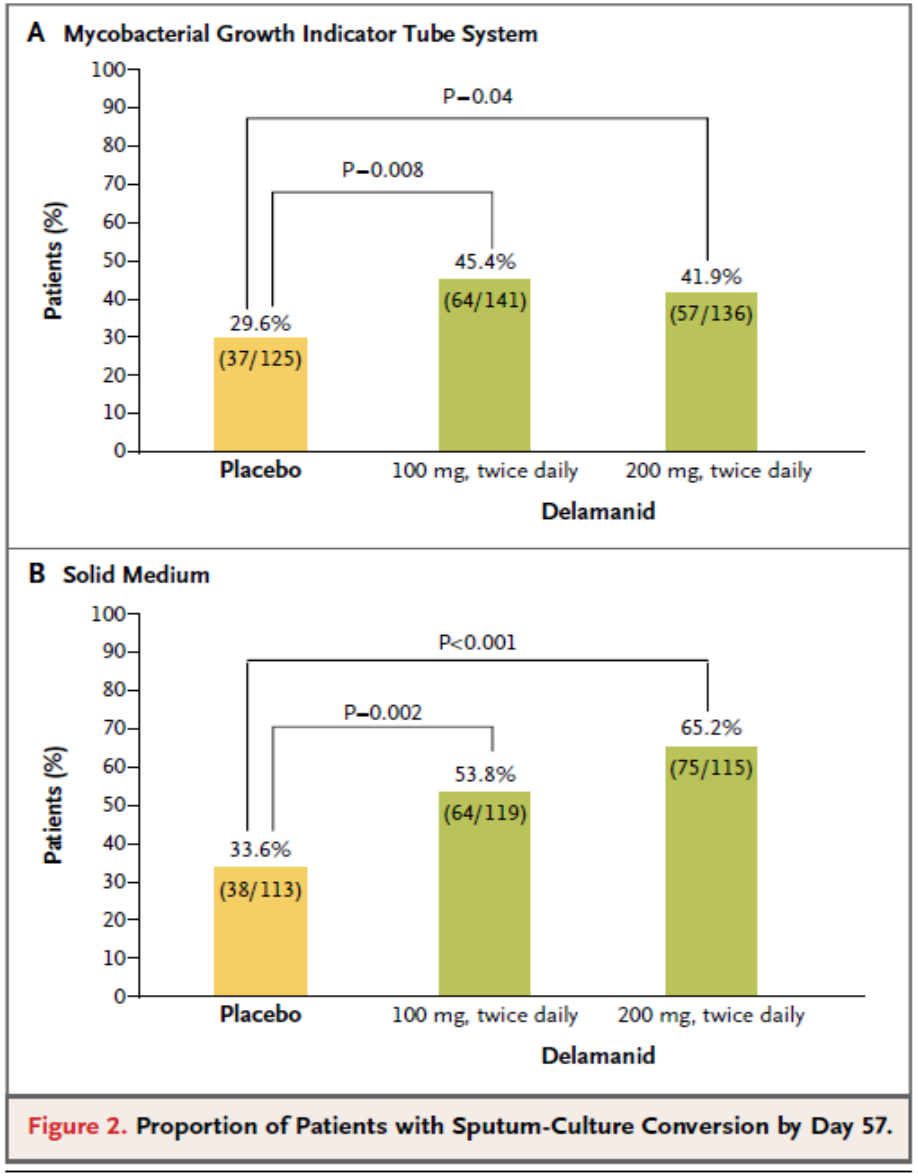


Figure 2. Proportion of Patients with Sputum-Culture Conversion by Day 57.

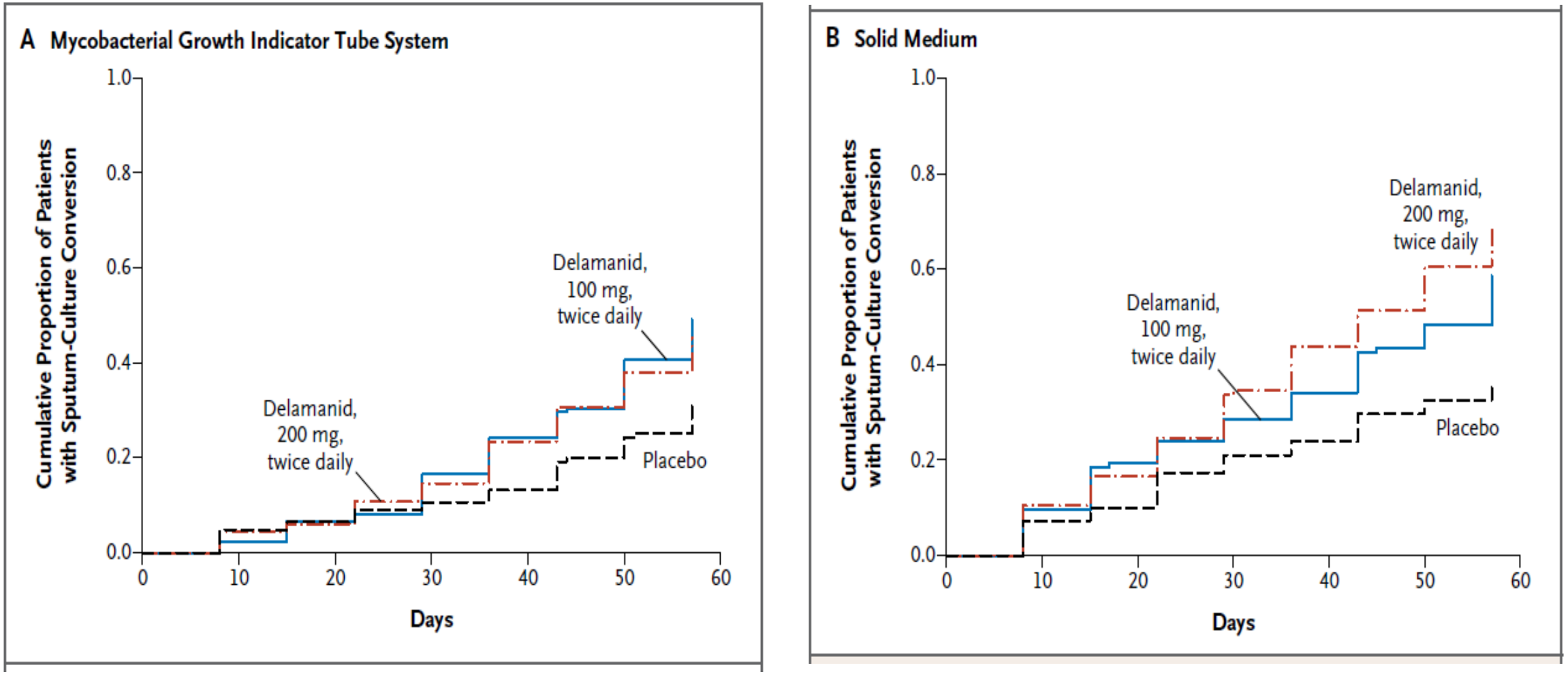


Figure 3. Survival Analysis of Days to Sputum-Culture Conversion, According to Culture Medium Type.

Table 1. Demographic and Baseline Clinical Characteristics of the Modified Intention-to-Treat Population for the Primary Efficacy Analysis.*

Characteristic	Delamanid, 100 mg Twice Daily (N = 141)	Delamanid, 200 mg Twice Daily (N = 136)	Placebo (N = 125)	Total (N = 402)
Age — yr				
Median	36	33	35	35
Range	19–63	18–63	18–63	18–63
Male sex — no. (%)	91 (64.5)	95 (69.9)	89 (71.2)	275 (68.4)
Body-mass index†				
Median	19.8	19.5	19.5	19.6
Range	12–31	12–40	12–31	12–40
Region — no. (%)‡				
Americas	39 (27.7)	38 (27.9)	39 (31.2)	116 (28.9)
Southeast Asia	43 (30.5)	47 (34.6)	45 (36.0)	135 (33.6)
Northeast Asia	29 (20.6)	28 (20.6)	25 (20.0)	82 (20.4)
Eastern Europe or Mediterranean	30 (21.3)	23 (16.9)	16 (12.8)	69 (17.2)
Lung cavities — no. (%)				
Absent	44 (31.2)	43 (31.6)	38 (30.4)	125 (31.1)
Unilateral	60 (42.6)	56 (41.2)	60 (48.0)	176 (43.8)
Bilateral	37 (26.2)	37 (27.2)	27 (21.6)	101 (25.1)
Previous treatment — no. (%)				
<30 days before randomization	11 (7.8)	14 (10.3)	12 (9.6)	37 (9.2)
≥30 days before randomization	130 (92.2)	122 (89.7)	113 (90.4)	365 (90.8)
First-line only	72 (51.1)	73 (53.7)	68 (54.4)	213 (53.0)
Second-line with or without first-line	40 (28.4)	27 (19.9)	23 (18.4)	90 (22.4)
Third-line with or without first-line or second-line	18 (12.8)	22 (16.2)	22 (17.6)	62 (15.4)

No statistcal difference

N Engl J Med. 2012 Jun 7;366(23):2151-60

Table S1 Concomitant Anti-tuberculosis Medications – Intent-to-Treat Population	Trial 204		
Medication Category/Class/ Preferred Term[a,b]	**Delamanid 100 mg BID + OBR N = 161 (%)**	**Delamanid 200 mg BID + OBR N = 160 (%)**	**Placebo + OBR N = 160 (%)**
Category 1 (first-line) medications	133 (82.6)	135 (84.4)	136 (85.0)
Streptomycin	18 (11.2)	24 (15.0)	24 (15.0)
Ethambutol	100 (62.1)	101 (63.1)	95 (59.4)
Isoniazid	17 (10.6)	13 (8.1)	10 (6.3)
Pyrazinamide	118 (73.3)	119 (74.4)	120 (75.0)
Category 2 medications (injectable anti-TB agents)	142 (88.2)	135 (84.4)	143 (89.4)
Amikacin	12 (7.5)	12 (7.5)	15 (9.4)
Kanamycin	97 (60.2)	88 (55.0)	97 (60.6)
Category 3 medications (fluoroquinolones)	155 (96.3)	157 (98.1)	156 (97.5)
Antibacterials for systemic use			
Gatifloxacin	7 (4.3)	10 (6.3)	12 (7.5)
Levofloxacin	94 (58.4)	103 (64.4)	97 (60.6)
Ofloxacin	56 (34.8)	48 (30.0)	50 (31.3)
Category 4 medications	160 (99.4)	158 (98.8)	159 (99.4)
Antimycobacterials			
Aminosalicylic acid	79 (49.1)	84 (52.5)	88 (55.0)
Cycloserine	135 (83.9)	137 (85.6)	136 (85.0)
Ethionamide	49 (30.4)	51 (31.9)	49 (30.6)
Prothionamide	101 (62.7)	97 (60.6)	101 (63.1)
Category 5 medications	26 (16.1)	23 (14.4)	30 (18.8)

No statistcal difference

DST information(-)

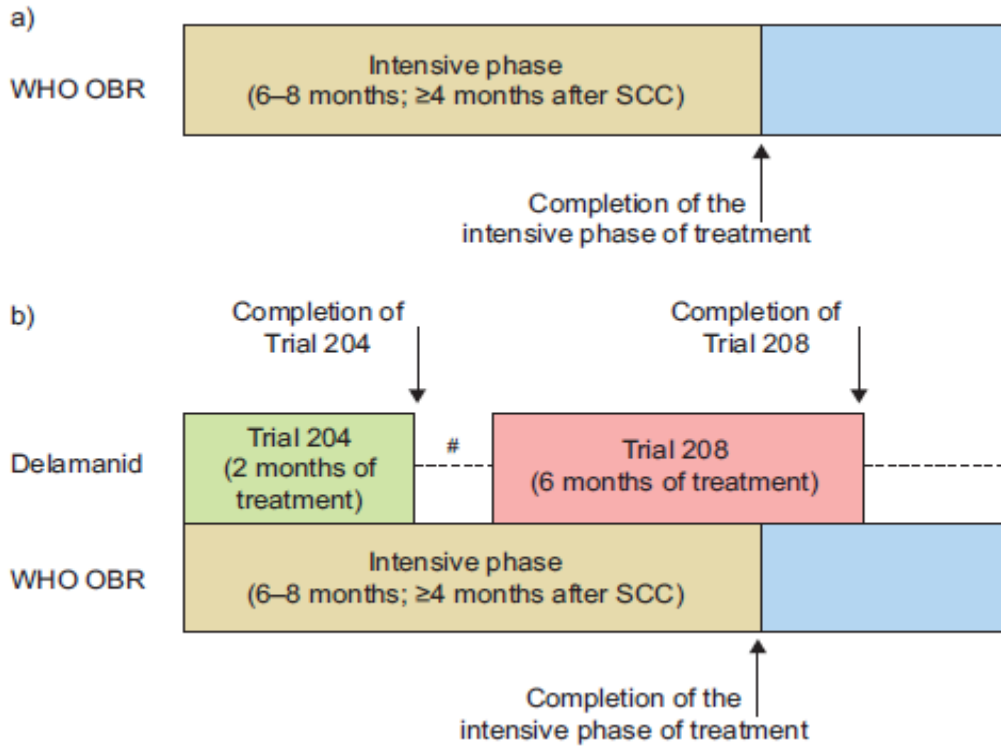
N Engl J Med. 2012 Jun 7;366(23):2151-60

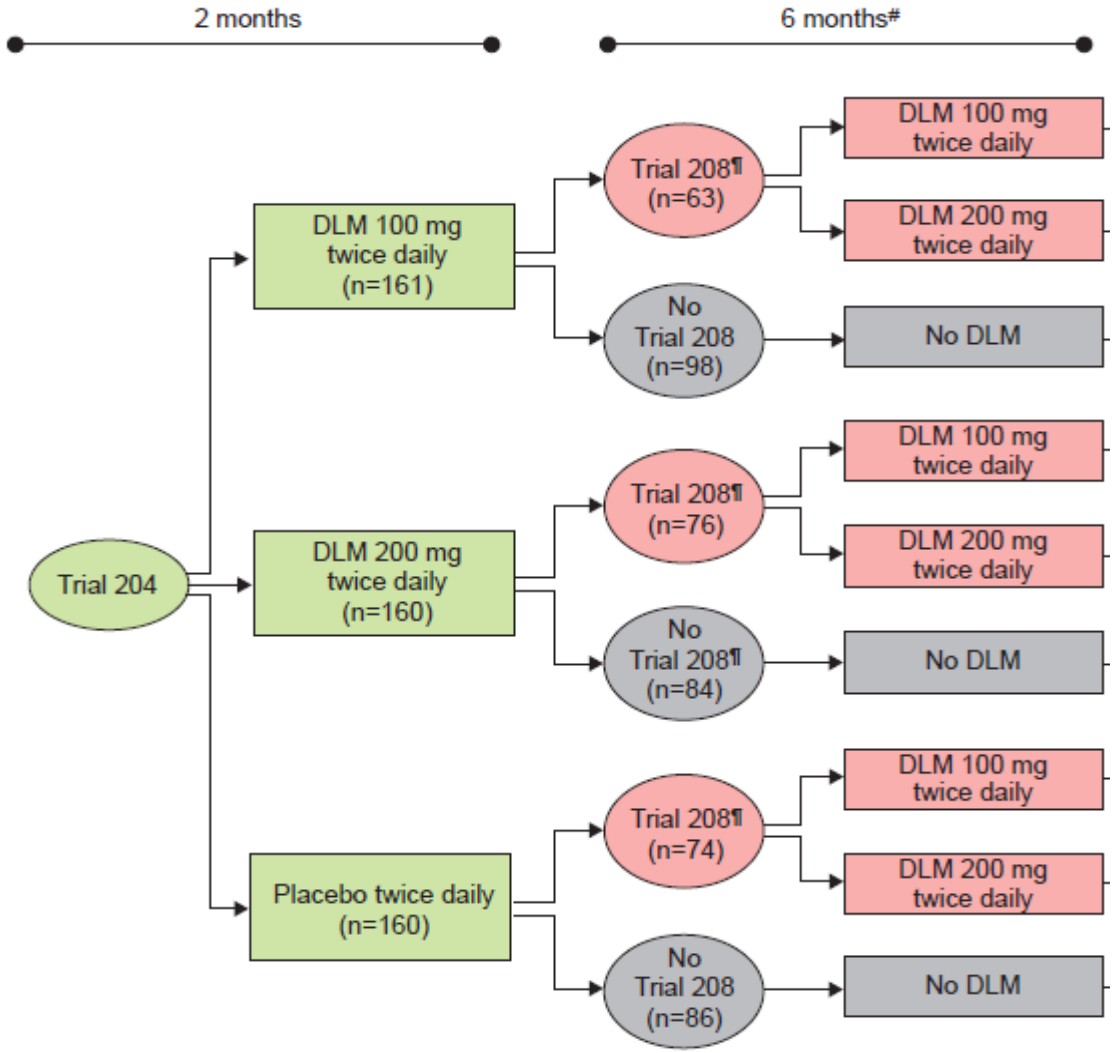
Table S1 Concomitant Anti-tuberculosis Medications – Intent-to-Treat Population	Trial 204		
Medication Category/Class/ Preferred Term[a,b]	**Delamanid 100 mg BID + OBR N = 161 (%)**	**Delamanid 200 mg BID + OBR N = 160 (%)**	**Placebo + OBR N = 160 (%)**
Category 1 (first-line) medications	133 (82.6)	135 (84.4)	136 (85.0)
Streptomycin	18 (11.2)	24 (15.0)	24 (15.0)
Ethambutol	100 (62.1)	101 (63.1)	95 (59.4)
Isoniazid	17 (10.6)	13 (8.1)	10 (6.3)
Pyrazinamide	118 (73.3)	119 (74.4)	120 (75.0)
Category 2 medications (injectable anti-TB agents)	142 (88.2)	135 (84.4)	143 (89.4)
Amikacin	12 (7.5)	12 (7.5)	15 (9.4)
Kanamycin	97 (60.2)	88 (55.0)	97 (60.6)
Category 3 medications (fluoroquinolones)	155 (96.3)	157 (98.1)	156 (97.5)
Antibacterials for systemic use			
Gatifloxacin	7 (4.3)	10 (6.3)	12 (7.5)
Levofloxacin	94 (58.4)	103 (64.4)	97 (60.6)
Ofloxacin	56 (34.8)	48 (30.0)	50 (31.3)
Category 4 medications	160 (99.4)	158 (98.8)	159 (99.4)
Antimycobacterials			
Aminosalicylic acid	79 (49.1)	84 (52.5)	88 (55.0)
Cycloserine	135 (83.9)	137 (85.6)	136 (85.0)
Ethionamide	49 (30.4)	51 (31.9)	49 (30.6)
Prothionamide	101 (62.7)	97 (60.6)	101 (63.1)
Category 5 medications	26 (16.1)	23 (14.4)	30 (18.8)

No statistcal difference

DST information(-)

N Engl J Med. 2012 Jun 7;366(23):2151-60





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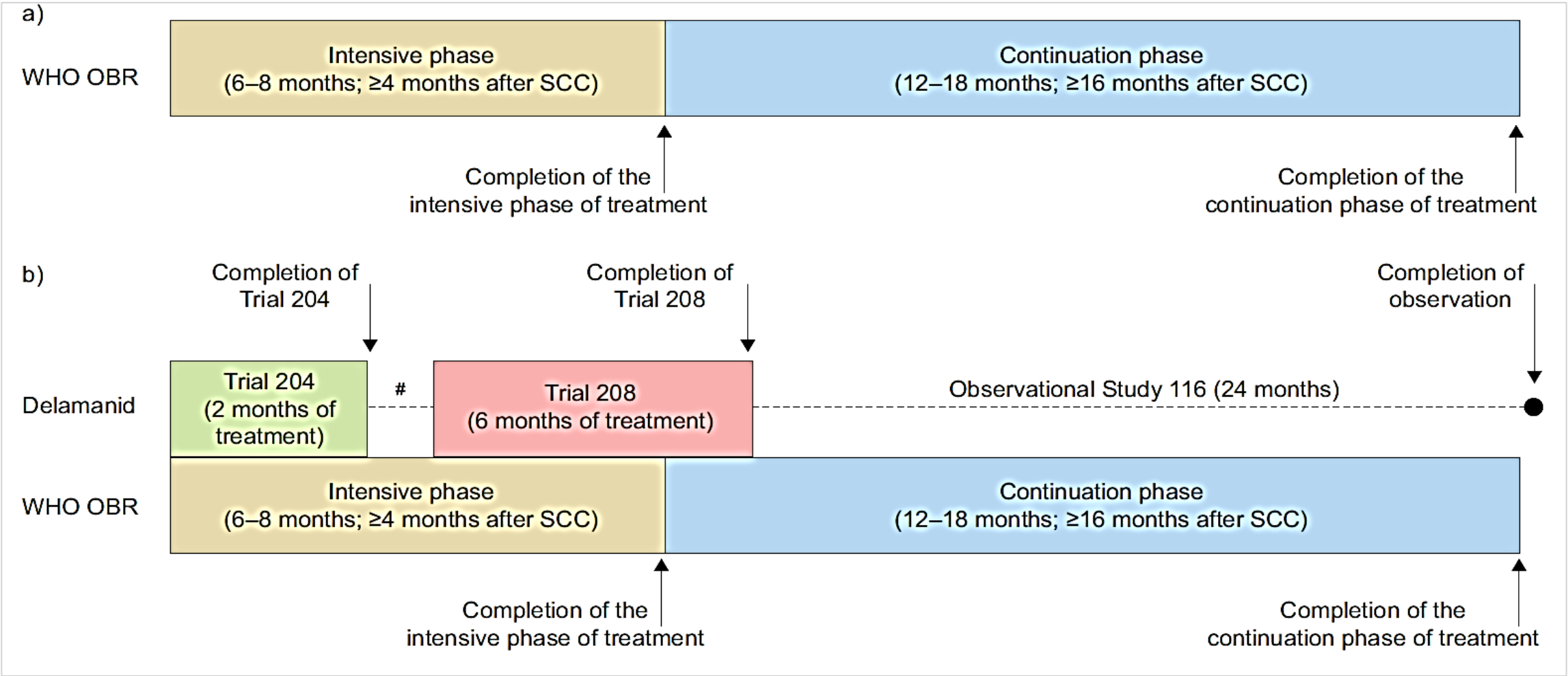

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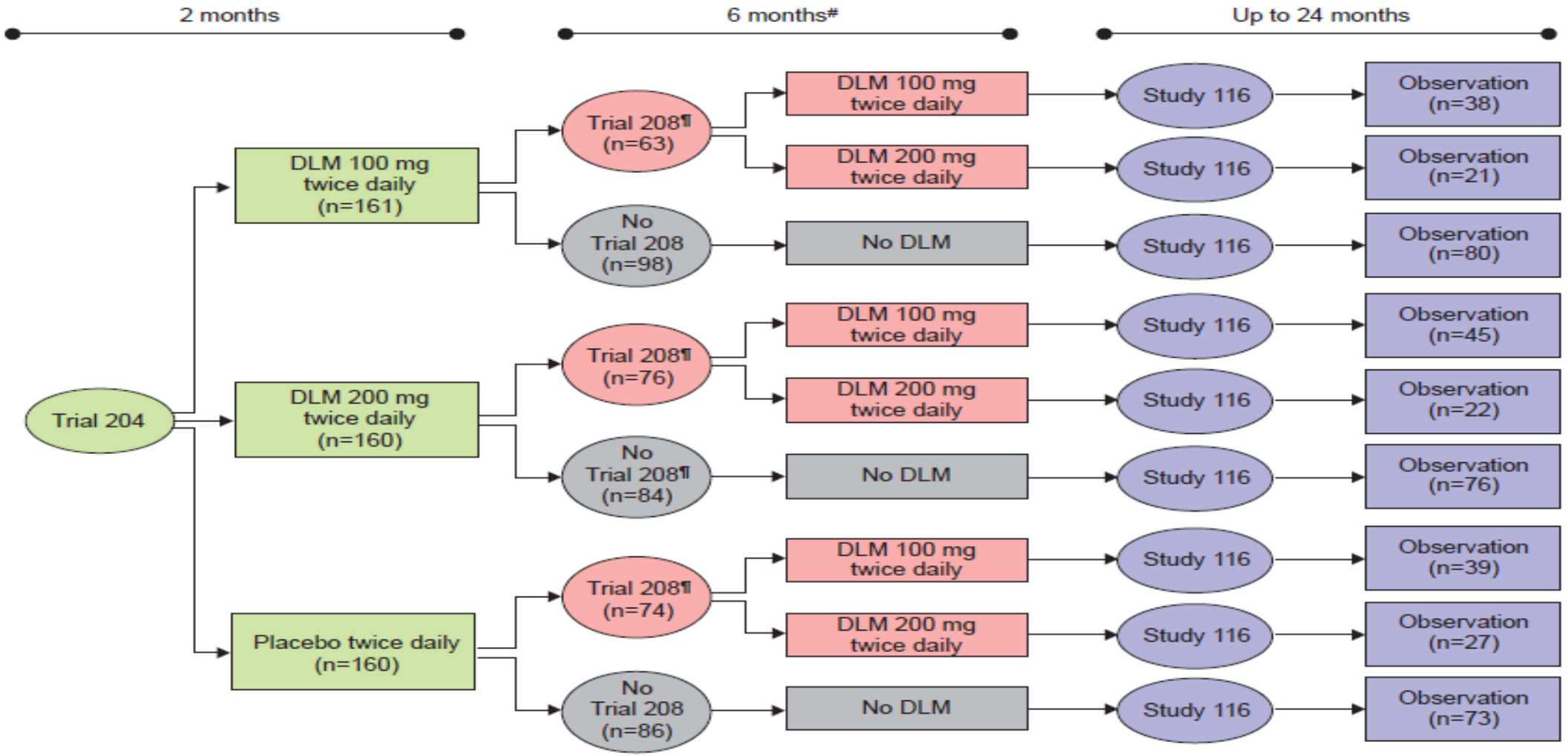

FIGURE 2. Flowchart of intent-to-treat patients in delamanid (DLM) Trial 204, Trial 208 and Study 116. #: patients who did not participate in Trial 208 were eligible for participation in Study 116 following their completion of Trial 204; ¶: time between the completion of Trial 204 and the initiation of Trial 208 was variable and was based on local approval processes.

Eur Respir J. 2013 Jun;41(6):1393-400.

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 N=421

Treatment outcome	Long-term treatment[#]		All patients[+]
		192	
Favourable	143 (74.5; 67.7–80.5)[§]	**126 ; Dlm for 8 months - 74.6% (94/126)**	269 (63.9; 59.1–68.5)
Cured	110 (57.3; 50.0–64.4)	**66 ; Dlm for 6 months - 74.2% (49/66)**	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 ($p \geqslant 0.05$).

Eur Respir J. 2013 Jun;41(6):1393-400.

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 N=421

Treatment outcome	Long-term treatment[#]	Short-term treatment[¶]	[+]
Favourable	143 (74.5; 67.7–80.5)[§]	126 (55.0; 48.3–61.6)[§]	
Cured	110 (57.3; 50.0–64.4)	111 (48.5; 41.8–55.1)	
Completed	33 (17.2; 12.1–23.3)[§]	15 (6.6; 3.7–10.6)[§]	
Unfavourable	49 (25.5; 19.5–32.3)[§]	103 (45.0; 38.4–51.7)[§]	
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)

229

156 ; Dlm for 2 months
– 53.8% (84/156)
73 ; placebo for 2 months
-- 57.5% (42/73)

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 ($p \geqslant 0.05$).

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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 N=421

Treatment outcome	Long-term treatment[#]	Short-term treatment[¶]	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 ($p \geqslant 0.05$).

25.3% of patients who received delamanid for less than 2 months (short term) defaulted during the treatment, compared to 7.8% of patients who received long-term delamanid.

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TABLE 3 Long-term (24 month) treatment outcomes after treatment with delamanid in combination with an optimised background treatment regimen: XDR-TB patients only N=56

Treatment outcome	Long-term treatment[#] N=44	Short-term treatment[¶] N=12	All Patients[+]
Favourable	27 (61.4; 45.5–75.6)	6 (50.0; 21.1–78.9)	33 (58.9; 45.0–71.9)
Cured	11 (25.0; 13.2–40.3)	5 (41.7; 15.2–72.3)	16 (28.6; 17.3–42.2)
Completed	16 (36.4; 22.4–52.2)	1 (8.3; 0.2–38.5)	17 (30.4; 18.8–44.1)
Unfavourable	17 (38.6; 24.4–54.5)	6 (50.0; 21.1–78.9)	23 (41.1; 28.1–55.0)
Died	0 (0.0)[§]	3 (25.0; 5.5–57.2)[§]	3 (5.4; 1.1–14.9)
Failed	14 (31.8; 18.6–47.6)	3 (25.0; 5.5–57.2)	17 (30.4; 18.8–44.1)
Defaulted	3 (6.8; 1.4–18.7)	0.0 (0.0)	3 (5.4; 1.1–14.9)

Data are presented as n (%; 95% CI). XDR-TB: extensively drug-resistant tuberculosis. [#]: 44 patients received delamanid (100 mg and/or 200 mg twice a day) for at least 6 months; [¶]: 12 patients received delamanid (100 mg or 200 mg twice a day) or placebo for 2 months; [+]: n=56; [§]: 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 ($p \geqslant 0.05$).

Improved treatment outcomes were not observed in patients with XDR-TB who received long-term delamanid compared with those administered with short-term delamanid.

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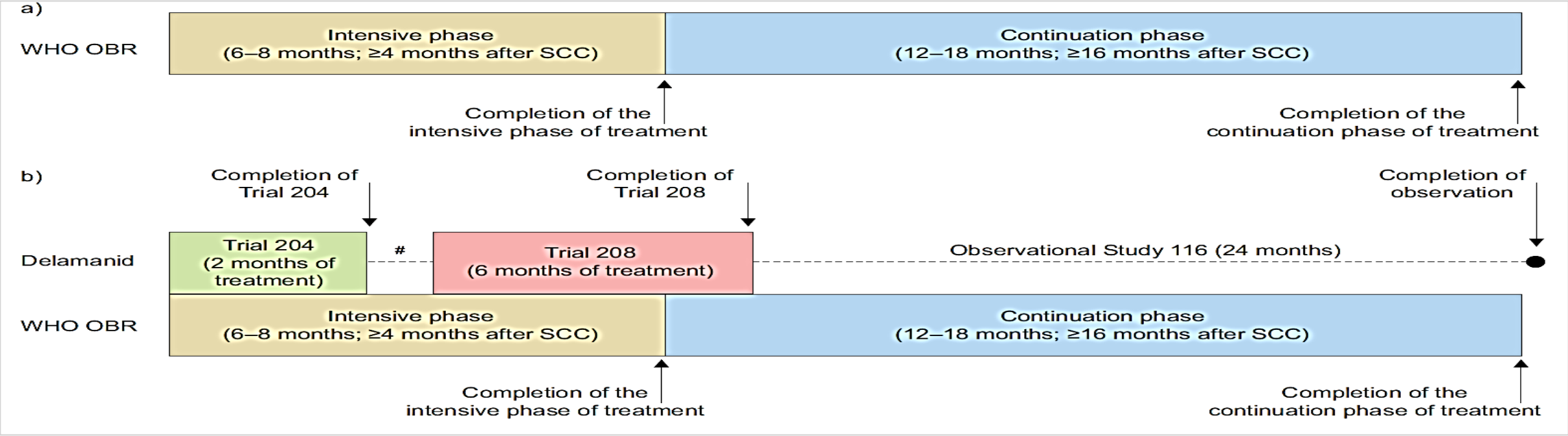

limitations

. XDR-TB patients should be interpreted cautiously in light of the relatively small sample size.

. variable processes and procedures in the variety of study sites including timing of sputum culture assessment.

. information bias: retrospective capture of data for some patients completing Trial 204 earlier in its conduct

. considerable gap in delamanid treatment between parent Trial 204 and extension Trial 208

. variability in the delamanid dose administered across the two trials.

Eur Respir J. 2013 Jun;41(6):1393-400.

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 Mar;7(3):249-259.

	Delamanid plus OBR	Placebo plus OBR	Risk ratio (95% CI)	p value
Primary endpoint				
Days to MGIT sputum culture conversion by 6 months (MITT-MGIT)	51 (29–98)	57 (43–85)	1·17 (0·91–1 ·51)	0·22
Secondary and exploratory endpoints				
2-month sputum culture conversion (MITT-MGIT)	132/226 (58·4%)	54/101 (53·5%)	1·096 (0·889–1·352)	0·38
6-month sputum culture conversion (MITT-MGIT)	198/226 (87·6%)	87/101 (86·1%)	1·017 (0·927–1·115)	0·71
Sustained sputum culture conversion at month 18 (MITT-MGIT)	180/226 (79·6%)	83/101 (82·2%)	0·969 (0·866–1 ·084)	0·59
Sustained sputum culture conversion at month 30 (MITT-MGIT)	173/226 (76·5%)	78/101 (77·2%)	0·991 (0·872–1·172)	0·90
Treatment success at month 30 (MITT-MGIT)*	173/226 (76·5%)	78/101 (77·2%)	0·991 (0·872–1·127)	0·90
30-month all-cause mortality (ITT)	18/341 (5·3%)	8/170 (4·7%)	1·122 (0·498–2·527)	0·78
30-month tuberculosis-related mortality (ITT)	9/341 (2·6%)	3/170 (1·8%)	1·496 (0·410–5·453)	0·54
Investigator-assessed favourable end-of-treatment (OBR) outcome (MITT-MGIT)	182/224 (81·3%)	85/101 (84·2%)	0·965 (0·869–1·073)	0·53
Development of resistance to delamanid (ITT)	3/341 (0·9%)	0/170	..	..

Data are median number of days (IQR) or n/N (%), unless otherwise indicated. OBR=optimised background regimen. MITT=modified intention-to-treat population. MGIT=BACTEC MGIT 960 system. ITT=intention-to-treat population. *A full list of treatment outcomes is given in the appendix.

Table 2: **Primary, secondary, and exploratory endpoints**

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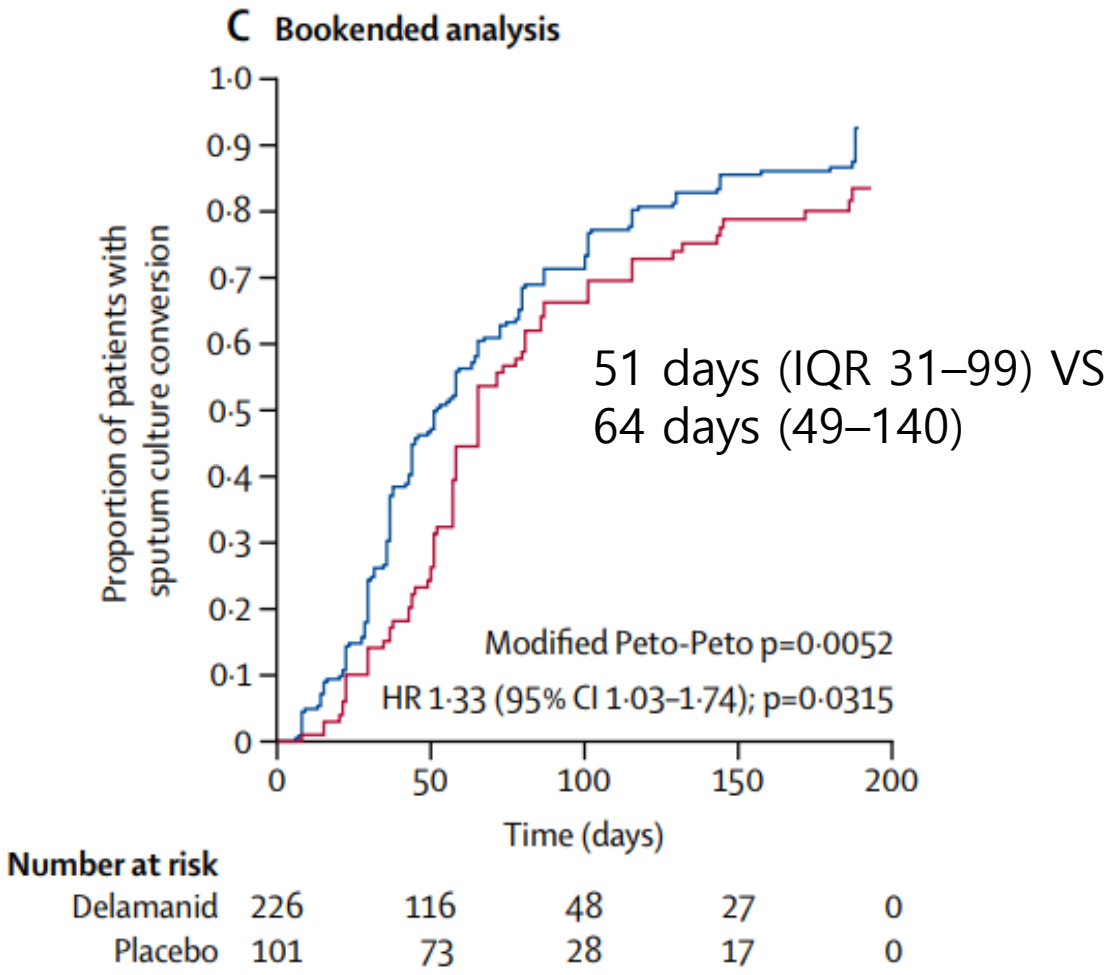
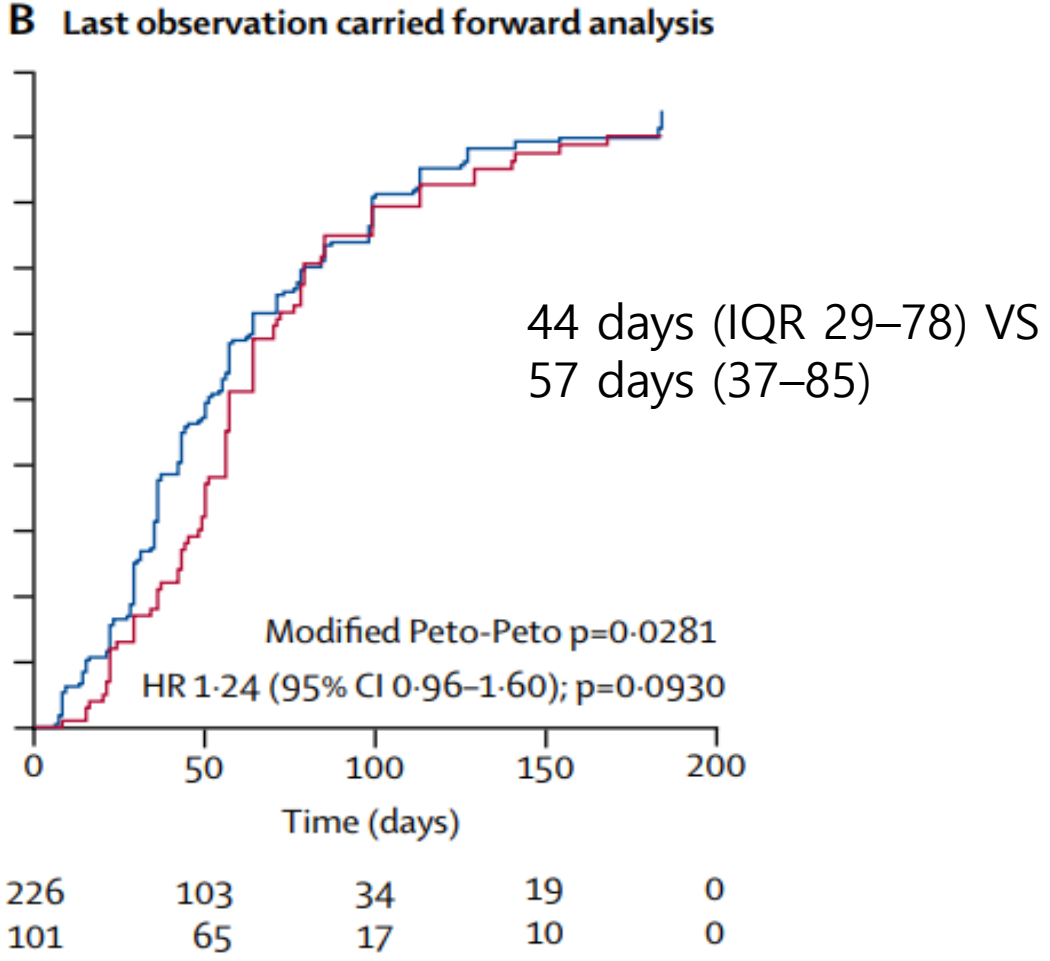
Figure Kaplan-Meier estimates of distribution of time to sputum culture conversion over 6 months, modified intention-to-treat population





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	Delamanid plus OBR (n=226)	Placebo plus OBR (n=101)	Total (n=327)
Age, years			
Median	32	31	31
Range	18–64	18–68	18–68
Sex			
Male	162 (71·7%)	76 (75·2%)	238 (72·8%)
Female	64 (28·3%)	25 (24·8%)	89 (27·2%)
Body-mass index, kg/m²			
Median	20·0	20·6	20·2
IQR	18·1–22·4	17·7–22·3	18·0–22·3
Region			
Southeast Asia	64 (28·3%)	30 (29·7%)	94 (28·7%)
Eastern Europe and Mediterranean	57 (25·2%)	23 (22·8%)	80 (24·5%)
South America	80 (35·4%)	35 (34·7%)	115 (35·2%)
Sub-Saharan Africa	25 (11·1%)	13 (12·9%)	38 (11·6%)
Resistance			
Multidrug-resistant tuberculosis	177 (78·3%)	79 (78·2%)	256 (78·3%)
Pre-extensively drug-resistant tuberculosis	39 (17·3%)	20 (19·8%)	59 (18·0%)
Injectable resistance	23 (10·2%)	16 (15·8%)	39 (11·9%)
Quinolone resistance	16 (7·1%)	4 (4·0%)	20 (6·1%)
Extensively drug-resistant tuberculosis	10 (4·4%)	2 (2·0%)	12 (3·7%)
Bilateral cavitation	51 (22·6%)	21 (20·8%)	72 (22·0%)
Number of drugs in background regimen, mean (SD)	6·5 (1·5)	6·3 (1·6)	6·4 (1·5)
HIV-positive patients	12 (5·3%)	6 (5·9%)	18 (5·5%)
CD4-positive cells, cells/mm³			
≤200	1 (8·3%)	1 (16·7%)	2 (11·1%)
>200–350	6 (50·0%)	2 (33·3%)	8 (44·4%)
>350	5 (41·7%)	3 (50·0%)	8 (44·4%)

Data are n (%), unless otherwise stated. OBR=optimised background regimen.

Table 1: **Baseline characteristics, modified intention-to-treat population**

Median time to SCC over 6 months by primary analysis method in post-hoc analyses

Subgroup	Median time to SCC (Days)		P value
	DLM+OBR	PLC+OBR	
Bilateral cavitation이 있는 환자 제외	45	57	0.036
Quinolone-resistance가 있는 환자 제외	49	57	0.029
Bilateral cavitation과 Quinolone-resistance 동반 환자 제외	50	57	0.024

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	Delamanid plus OBR	Placebo plus OBR
Pyrazinamide	1/86 (1·2%)	2/39 (5·1%)
Streptomycin	0/99	1/36 (2·8%)
Ethambutol	5/135 (3·7%)	6/64 (9·4%)
Injectable agents*	10/192 (5·2%)	5/83 (6·0%)
Ofloxacin	3/101 (3·0%)	2/54 (3·7%)
Moxifloxacin or levofloxacin, or both	2/184 (1·1%)	3/85 (3·5%)

Data are n/N (%). Denominators differ by drug and treatment group based on the number of patients susceptible at baseline. OBR=optimised background regimen.
*Kanamycin, amikacin, and capreomycin.

Table 3: **Acquired resistance to anti-tuberculosis agents**

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Over-performance of placebo:

The routine use of late generation quinolones

- 89% of patients in this trial received a late-generation quinolone within 30 days of randomisation compared with less than 1% in a previous phase 2 trial of delamanid
- treatment with injectable streptomycin decreased from 20% to less than 1%.

Highly active repurposed drugs, linezolid and clofazimine

rapid diagnostic tests (eg, Xpert MTB/RIF)

Underperformance of delamanid

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

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However, a consistent, more favourable outcome (in terms of directionality and magnitude of effect) was seen with delamanid in the primary, sensitivity, and subgroup analyses.

- bookending method for sensitivity analyses

The post-hoc observation of lower proportions of acquired resistance with patients administered delamanid.

limitations.

First, the high placebo response might have underpowered

Second, definitions for treatment outcomes change

Third, tailored and unrestricted individual optimised background regimens

This study supports the view that evaluating a single anti-MDR tuberculosis drug using an add-on approach to the existing standard of care might no longer be useful.

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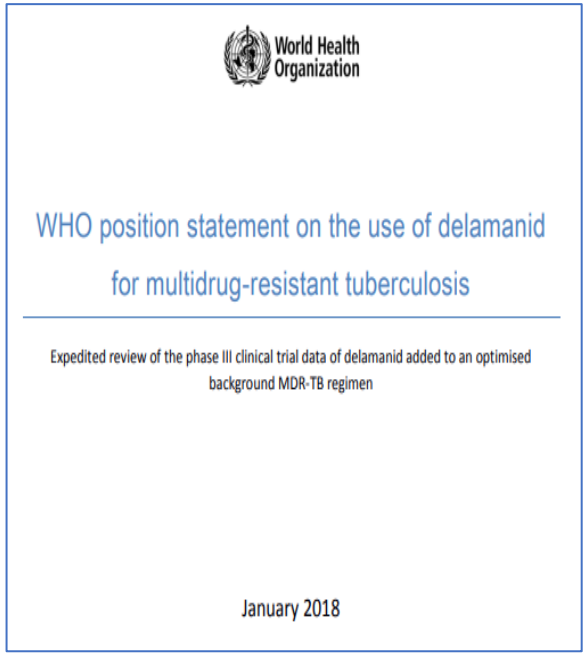

The favourable outcomes and high patient retention on Trial 213 were achieved through greatly enhanced efforts to ensure that participants were engaged in their care and not lost to follow-up – an essential message for routine clinical and programmatic care of MDR-TB patients.

INT J TUBERC LUNG DIS 24(10):1095–1102

http://dx.doi.org/10.5588/ijtld.20.0082

Bedaquiline and delamanid result in low rates of unfavourable outcomes among TB patients in Eswatini

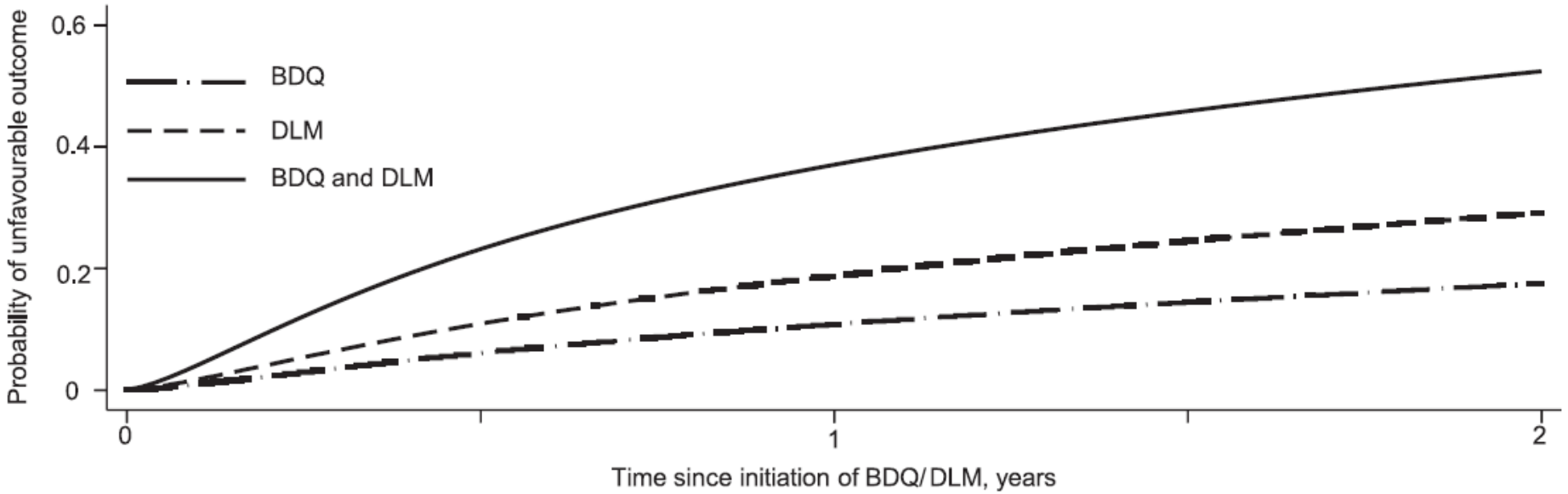

Figure Standardised failure curves by baseline drug after fitting the covariate adjusted flexible parametric model.

	(*n* = 352)		Univariate analysis‡			Multivariate analysis‡		
New drug	*n*	%	cHR	95%CI	*P* value	aHR	95%CI	*P* value
BDQ	292	83.0	Reference			Reference		
DLM	40	11.4	2.61	1.33–5.12	0.005	1.88	0.86–4.11	0.116
BDQ and DLM	20	5.7	4.00	1.93–8.30	<0.0005	4.49	1.61–12.57	0.004

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

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Clin Infect Dis 2020 Dec 3;71(9):2336-2344.

prospective, observational study among patients with MDR-TB in Georgia, comparison study

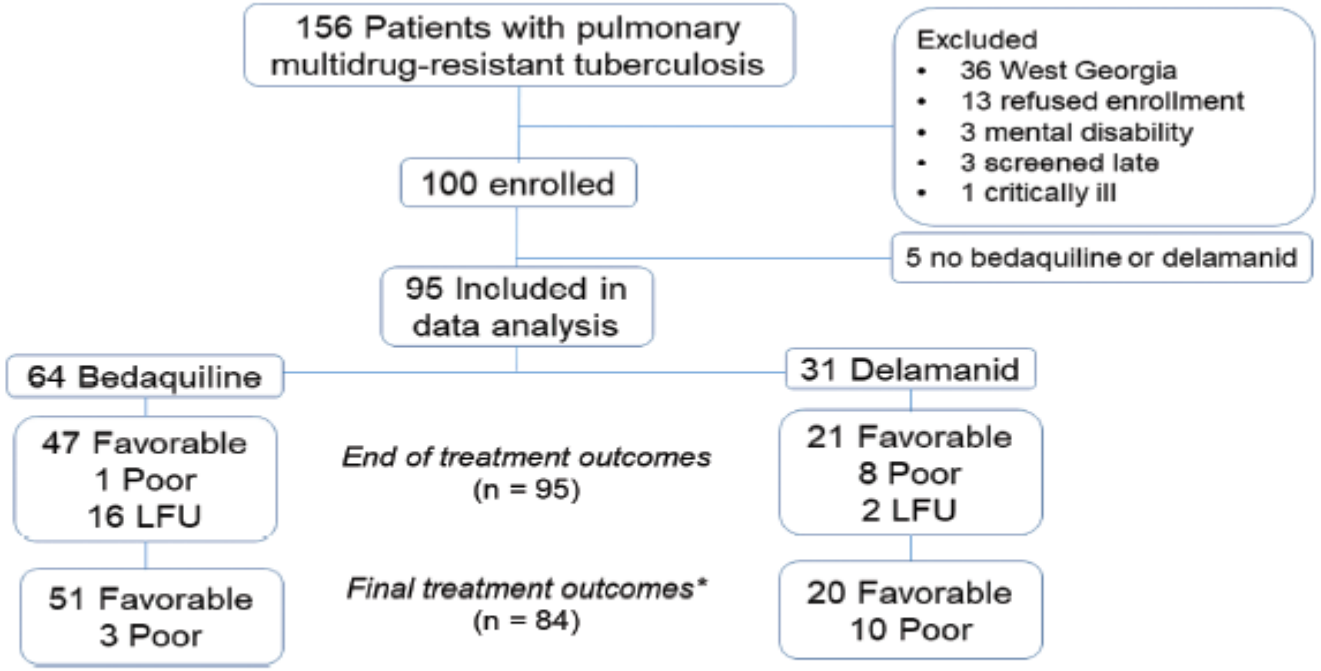


Figure 1. Study flow diagram including patient clinical treatment outcomes. *Patients with LFU during treatment and no post treatment follow-up were excluded while those with post treatment follow-up were included and final outcomes were determined by follow up culture results. Abbreviation: LFU, loss to follow-up.

Table 1. Characteristics of Patients with Multidrug-resistant Tuberculosis Receiving a Bedaquiline- or Delamanid-Based Treatment Regimen

Characteristic	Delamanid, n = 31, n (%)	Bedaquiline, n = 64, n (%)	P[a]
Diabetes mellitus	4 (13)	8 (13)	.96
Hepatitis C antibody positive	7 (23)	13 (20)	.80
HIV infection	0	2 (3)[c]	.32
Known mental health disorder	0	0	
Tuberculosis presentation			
Case definition			.25
New	10 (32)	32 (50)	
Prior treatment with first-line drugs	6 (19)	8 (13)	
Prior treatment with second-line drugs	15 (48)	24 (38)	
Disease location			.98
Pulmonary only	30 (97)	62 (97)	
Pulmonary and extrapulmonary[d]	1 (3)	2 (3)	
Chest radiology			
Multilobar	20 (65)	52 (81)	.07
Bilateral	18 (58)	37 (58)	.98
Cavity	21 (68)	37 (58)	.35
Bilateral cavities	5 (16)	13 (20)	.63
AFB sputum smear positive[e]	24 (77)	48 (75)	.80
Drug resistance			
Extensive drug resistance	9 (29)	12 (19)	.26
Median baseline laboratory values (IQR)			
White blood cell count	9.4 (7.1–12.8)	8.8 (7.4–11.0)	.33
Hemoglobin	12.0 (10.9–14.1)	12.8 (11.4–14.0)	.30
Platelets	371 (283–466)	371 (293–430)	.97
Creatinine	.77 (.70–.87)	.69 (.60–.84)	.03
Alanine transaminase	17 (11–24)	17 (12–25)	.88
Albumin, n = 37	3.6 (3.4–4.0)	3.6 (3.0–4.0)	.72

Clin Infect Dis 2020 Dec 3;71(9):2336-2344.

Table 2. Treatment Characteristics and Clinical Outcomes of Patients With Multidrug-resistant Tuberculosis Receiving a Bedaquiline- or Delamanid-Based Treatment Regimen

Characteristic, median (IQR)	Delamanid, n = 31	Bedaquiline, n = 64	*P*
Days from SLD initiation to starting bedaquiline or delamanid	4 (0–31)	15 (0–71)	.14
Initiated bedaquiline or delamanid <15 days from treatment start	19 (61)	34 (53)	.45
Bedaquiline or delamanid duration, days	182 (173–206)	171 (166–190)	
Initial hospitalization duration, days	111 (72–209)	103 (64–174)	.27
Subsequent hospitalizations	1 (1–2)	1 (1, 2)	.49
Follow-up sputum cultures	11 (9–13)	12 (9–14)	.83
Adjunctive surgical resection, n (%)	1 (3)	5 (8)	.39
Treatment duration, days	533 (283–608)	549 (394–609)	
Initial companion drugs, n (%)			
Linezolid	25 (81)	50 (78)	.78
Clofazamine	26 (81)	43 (67)	.09
Imipenem	11 (36)	9 (14)	.01
Pyrazinamide	4 (13)	7 (11)	.78
Ethambutol	1 (3)	5 (8)	.39
Levofloxacin or moxifloxacin	11 (36)	25 (39)	.74
Capreomycin or kanamycin	19 (61)	43 (67)	.57
Para-aminosalicylic acid	5 (16)	15 (23)	.41
Cycloserine	20 (65)	58 (91)	.002
Prothionamide	6 (19)	26 (41)	.04
Median drugs received, n (IQR)	5 (4–6)	5 (5, 6)	.17
Median effective drugs received, n (IQR)	4.0 (3.5–5)	4.0 (4)	.98
Effective Class A or B drugs received	2 (2–3)	2 (2, 3)	.43

Clin Infect Dis 2020 Dec 3;71(9):2336-2344.

Table 2. Treatment Characteristics and Clinical Outcomes of Patients With Multidrug-resistant Tuberculosis Receiving a Bedaquiline- or Delamanid-Based Treatment Regimen

Median drugs received, n (IQR)	5 (4–6)	5 (5, 6)	.17
Median effective drugs received, n (IQR)	4.0 (3.5–5)	4.0 (4)	.98
Effective Class A or B drugs received	2 (2–3)	2 (2, 3)	.43
Clinical outcomes, n (%)			
Median follow-up time since treatment initation, days (IQR)	905 (812–992)	855 (716–1016)	.72
Median follow-up time post–treatment outcome, days (IQR)	396 (258–579)	367 (230–545)	.57
Sputum culture conversion, n = 91	23 (74)	59 (98)	
Culture conversion within 60 days, n = 91	15 (48)	38 (63)	[a]
Culture conversion within 180 days, n = 91	23 (74)	57 (95)	[a]
Acquired drug resistance	11 (36)	6 (10)	<.01
Initial treatment outcome			
Cured	17 (54)	42 (66)	
Completed	4 (13)	5 (8)	
Loss to follow-up	2 (7)	16 (25)	
Failure	6 (19)	1 (2)	
Death	2 (7)	0	
Loss to follow-up with recategorized outcomes, n = 18			
Poor	1 (3)	1 (2)	
Favorable	0	5 (8)	
Relapse	1 (3)	1 (2)	
Overall treatment outcomes, n = 84	…	…	[a]
Poor	10 (33)	3 (6)	
Favorable	20 (67)	51 (94)	

Clin Infect Dis 2020 Dec 3;71(9):2336-2344.

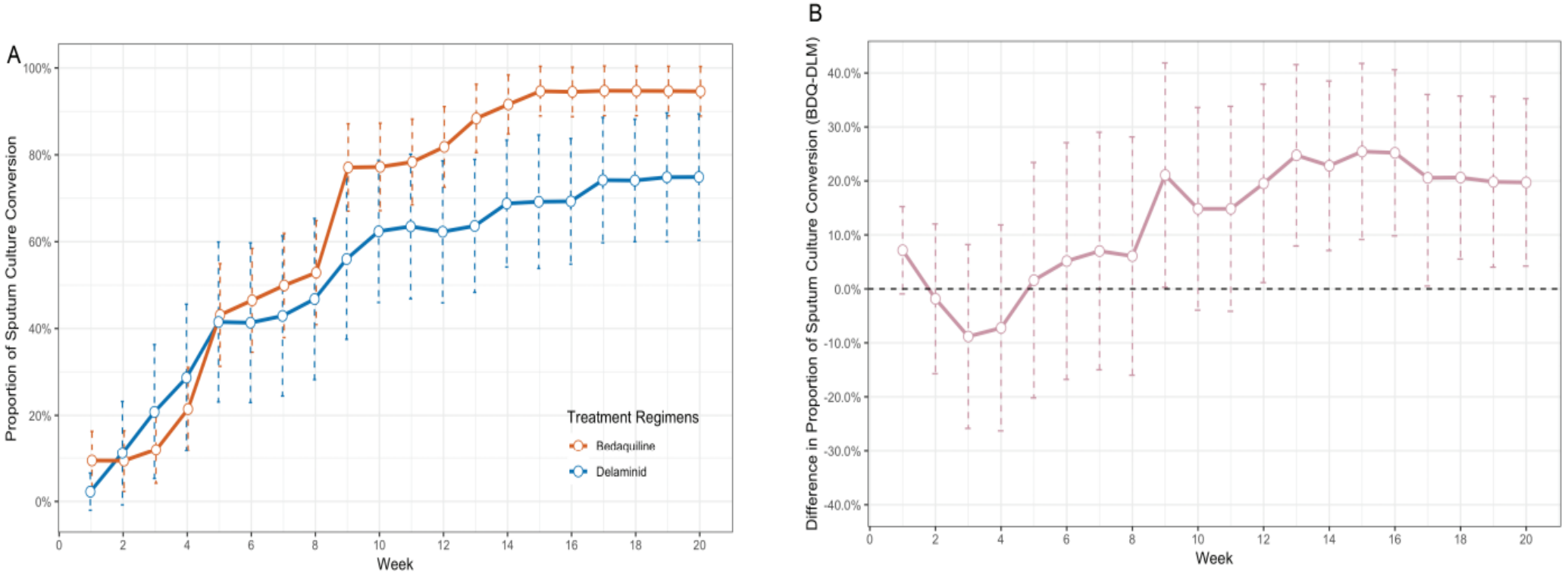


Figure Sputum culture conversion among patients with multidrug-resistant tuberculosis receiving a bedaquiline- or delamanid-based treatment regimen.

Table 4. Adjusted Sputum Culture Conversion Rates and Treatment Outcomes Among Patients With Multidrug-resistant Tuberculosis Receiving a Bedaquiline- or Delamanid-Based Treatment Regimen

Outcome	Delamanid (95% CI)	Bedaquiline (95% CI)	*P* Value	E Value
SCC at 2 months, n = 91	.47 (.27–.68)	.67 (.56–.78)	.10	1.23
SCC at 6 months, n = 91	.74 (.60–.88)	.95 (.89–1.00)	<.01	1.56
Favorable outcomes, n = 84	.72 (.61–.82)	.96 (.91–1.00)	<.01	1.98

Clin Infect Dis 2020 Dec 3;71(9):2336-2344.

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]

Clin Infect Dis 2020 Dec 3;71(9):2336-2344.

prospective, observational study among patients with MDR-TB in Georgia, comparison study

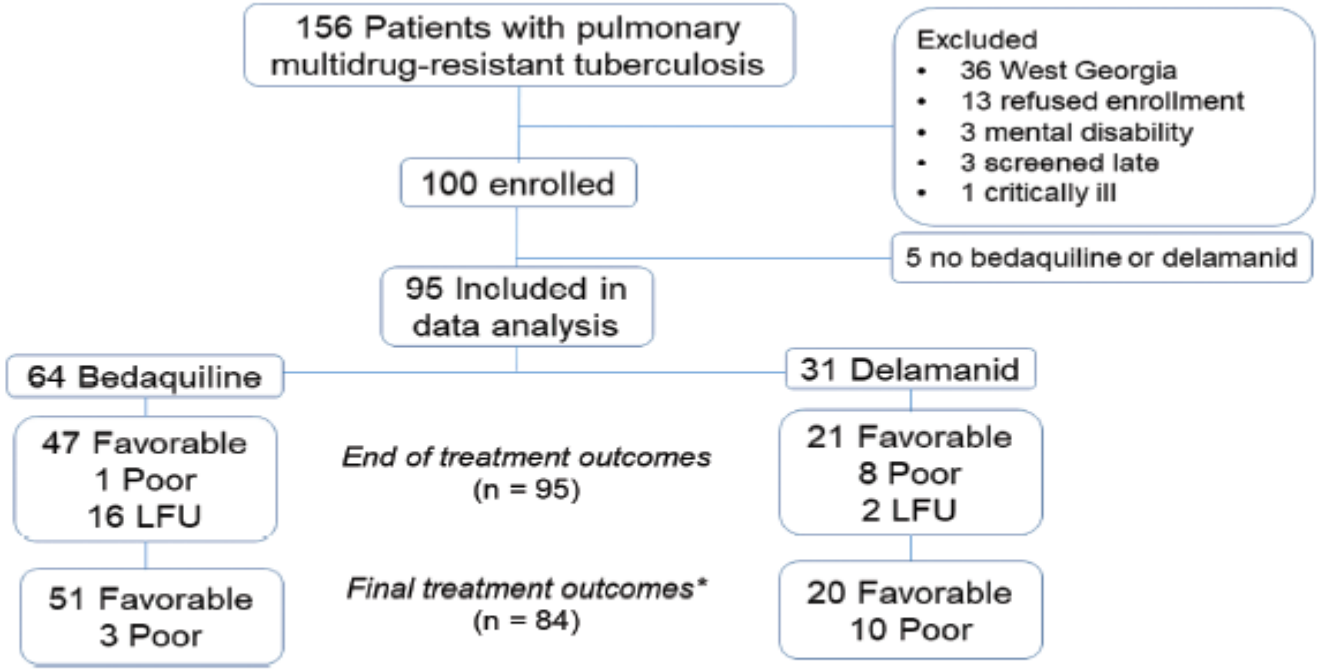


Figure 1. Study flow diagram including patient clinical treatment outcomes. *Patients with LFU during treatment and no post treatment follow-up were excluded while those with post treatment follow-up were included and final outcomes were determined by follow up culture results. Abbreviation: LFU, loss to follow-up.

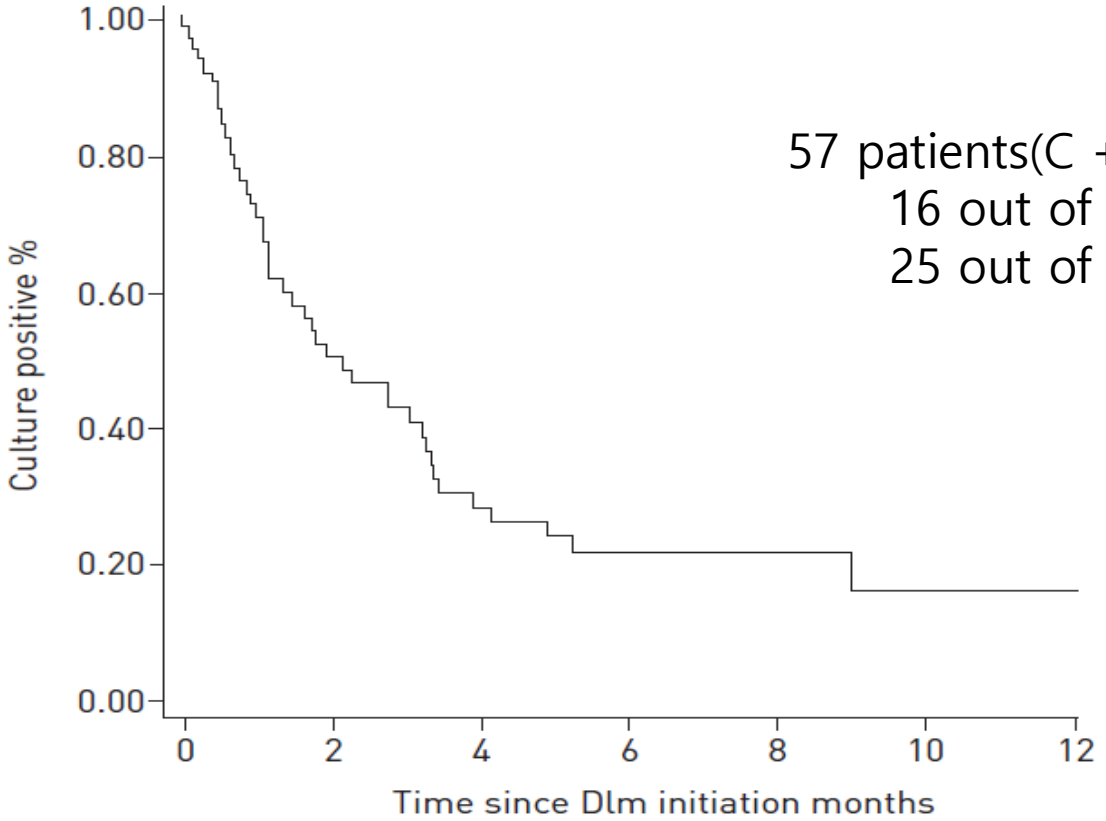
Correspondence regarding “Delamanid for rifampicin-resistant tuberculosis: a retrospective study from South Africa”

The cohort of 103 patients, 77% HIV-positive
November 2015 to August 2017
- median (IQR) duration on Dlm: 6.3 (4.3–12.0) months;
- Dlm for more than 6 months: 54 (52%)
- Bdq: 32 (31%); Fluoroquinolone (Fq) resistance: 26 (81%)

Treatment success 57 (55%), loss to follow-up 22 (21%), death 14 (14%), failure six (6%)

Eur Respir J 2020 Jul 23;56(1):2000837.

Delamanid for rifampicin-resistant tuberculosis: a retrospective study from South Africa



57 patients(C +) at Dlm initiation;
16 out of 31 (52%) SCC within 2 months
25 out of 31 (81%) within 6 months

Eur Respir J 2018 ;51:1800017

TABLE 1 Unadjusted and adjusted analysis of factors associated with time to unsuccessful outcomes among 103 patients from Khayelitsha, South Africa who initiated regimens containing delamanid (Dlm) from November 2015 to August 2017 for the treatment of rifampicin-resistant tuberculosis (RR-TB)

	Unsuccessful outcome[#]	Successful outcome[¶]	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Sex						
Male	31 (73.8)	29 (50.9)	2.4 (1.2–4.9)	0.015	3.0 (1.4–6.3)	**0.003**
Female	11 (26.2)	28 (49.1)	1.0 (reference)		1.0 (reference)	
Age years						
0–24	2 (4.8)	11 (19.3)	0.23 (0.06–0.97)	0.045		
25–49	37 (88.1)	38 (66.7)	1.0 (reference)			
⩾50	3 (7.1)	8 (14.0)	0.57 (0.17–1.9)	0.35		
Body mass index kg·m^{-2}						
<18	10 (25.0)	16 (25.4)	1.2 (0.58–2.4)	0.65		
⩾18	26 (65.0)	43 (68.3)	1.0 (reference)			
Missing	4 (10.0)	4 (6.4)	1.5 (0.52–4.3)	0.46		
HIV and CD4 cell count per mm^3						
HIV negative	4 (9.5)	17 (29.8)	1.0 (reference)		1.0 (reference)	
HIV positive, CD4 <200	23 (54.8)	22 (38.6)	3.5 (1.2–10.2)	0.022	3.8 (1.2–11.6)	**0.020**
HIV positive, CD4 ⩾200	12 (28.6)	15 (26.3)	3.1 (0.99–9.7)	0.052	2.6 (0.80–8.6)	0.11
HIV positive, CD4 missing	3 (7.1)	3 (5.3)	2.2 (0.48–9.7)	0.32	1.9 (0.38–9.0)	0.44
Resistance classification						
RR-TB	29 (69.1)	35 (61.4)	1.0 (reference)		1.0 (reference)	
Fluoroquinolone resistance	13 (31.0)	22 (38.6)	0.46 (0.22–0.97)	0.042	0.44 (0.16–1.2)	0.099
Previous TB treatment						
None	15 (35.7)	26 (45.6)	1.0 (reference)			
First- or second-line TB treatment previously	27 (64.3)	31 (54.4)	1.2 (0.65–2.3)	0.54		
Received a regimen containing the combination of Bdq and Dlm						
Yes	12 (28.6)	19 (33.3)	1.0 (reference)		1.0 (reference)	
No	30 (71.4)	38 (66.7)	1.5 (0.77–3.1)	0.23	0.69 (0.28–1.7)	0.42

Data are presented as n (%) or unadjusted/adjusted hazard ratios with 95% confidence intervals. Bold text indicates significance at p<0.05. Bdq: bedaquiline. [#]: total n=42; [¶]: total n=57.

Eur Respir J 2020 Jul 23;56(1):2000837.

Treatment success 57 (55%), loss to follow-up 22 (21%), death 14 (14%), failure six (6%)

HIV infection still plays a leading role in driving unsuccessful outcomes despite access to new drugs.

high proportion of early deaths at 6 months (71

higher frequency of loss to follow-up among HIV-positive patients

the effective role of the combination in improving outcomes among the most difficult to treat patients

Eur Respir J 2020 Jul 23;56(1):2000837.

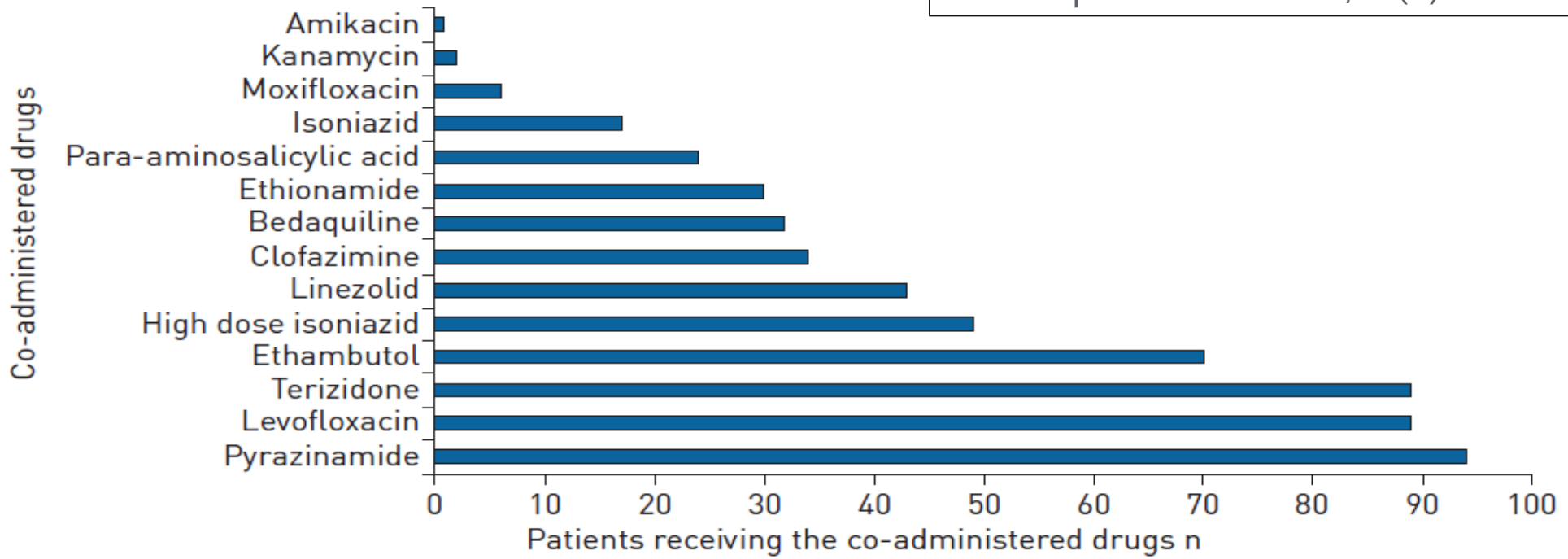


FIGURE 1 Number of rifampicin-resistant tuberculosis drugs co-administered at delamanid initiation between November 1, 2015 and August 31, 2017 in Khayelitsha, South Africa.

Effectiveness and safety of delamanid- or bedaquiline-containing regimens among children and adolescents with multidrug resistant or extensively drug resistant tuberculosis: A nationwide study from Belarus, 2015-19

Monaldi Archives for Chest Disease 2021; volume 91:1646

Culture Conversion in Patients Treated with Bedaquiline and/or Delamanid:
A Prospective Multicountry Study

Am J Respir Crit Care Med . 2021 Jan 1;203(1):111-119.

Outcome of treatment of MDR-TB or drug-resistant patients treated with bedaquiline and delamanid:Results from a large global cohorts

PULMOE-1605; No. of Pages 10, 2021 Feb.

A regimen containing bedaquiline and delamanid compared to bedaquiline in patients with drug-resistant tuberculosis

Eur Respir J 2020; 55: 1901181

Compassionate Use of Delamanid in Adults and Children for Drug-resistant TB: 5-year Update

***Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.02483-2020)**

Injectable-free regimens containing bedaquiline, delamanid, or both for adolescents with rifampicin-resistant tuberculosis in Khayelitsha, South Africa

EClinicalMedicine 20 (2020) 100290

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

Respir Med. 2020 Jun;167:105956. doi: 10.1016/j.rmed.2020.105956.

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

Eur Respir J 2019; 54: 1900811

Final treatment outcomes of delamanid containing regimens in patients with MDR-/XDR-TB in South Korea Eur Respir J 2019; 54: 1900811

Characteristics	Total
Subjects n	49
Male	29 (59.2)
Age years	47.0 (32.0–58.0)
Body mass index kg·m^{-2}	20.7 (18.6–23.2)
Previous TB treatment	
New	22 (44.9)
First-line drug only	7 (14.3)
Second-line drug	20 (40.8)
Sputum AFB smear positive[§]	16 (32.7)
Sputum MTB culture positive[§]	29 (59.2)
Radiological finding	
Bilateral lung involvement	29 (59.2)
Cavity	27 (55.1)
Number of resistant drugs	8.0 (5.5–9.0)
Companion drug[f]	
Fluoroquinolone	28 (57.1)
Injectable	35 (71.4)
Linezolid	31 (63.3)
Clofazimine	17 (34.7)
Meropenem/clavulanic acid	6 (12.2)
Number of companion drugs[f]	5.0 (4.0–6.0)
Number of drugs after delamanid discontinuation	5.0 (4.0–5.0)
Total treatment duration days	607.0 (538.5–719.5)
Surgical resection	2 (4.1)
Treatment outcome	
Treatment success	40 (81.6)
Cured	39 (79.6)
Treatment completed	1 (2.0)
Unfavourable treatment outcome	9 (18.4)
Treatment failed	3 (6.1)
Died	3 (6.1)
Lost to follow-up	1 (2.0)
Not evaluated	2 (4.1)

Table 3 Clinical characteristics and treatment outcomes of MDR-TB patients diagnosed during different time periods

	MDR-TB patients (1996–2000) (n = 86)	MDR-TB patients (2001–2005) (n = 125)	MDR-TB patients (2006–2010) (n = 123)	P value
Parameter	Cohort 1	Cohort 2	Cohort 3	
Age, years, median [IQR]	41.0 [26.0–55.3]	35.0 [25.0–50.0]	37.0 [27.0–56.0]	0.099
Male sex	52 (60.5)	72 (57.6)	69 (56.1)	0.819
Comorbidities	31 (36.0)	44 (35.2)	36 (29.3)	0.498
Albumin, g/dl, median [IQR]	3.8 [3.5–4.1]	4.0 [3.7–4.3]	4.2 [3.9–4.5]	<0.001
XDR-TB	19 (22.1)	24 (19.2)	26 (21.1)	0.866
Number of drugs used, median [IQR]	6.0 [5.0–8.0]	6.0 [5.0–7.0]	5.0 [5.0–6.0]	0.002
Treatment duration, months, median [IQR]	41.5 [25.0–72.3]	31.5 [25.0–50.0]	24.4 [18.4–27.3]	<0.001
Surgical resection	37 (43.0)	26 (20.8)	18 (14.6)	<0.001
Fluoroquinolone use	71 (82.6)	108 (86.4)	113 (91.9)	0.124
Later-generation fluoroquinolone use	67 (77.9)	103 (82.4)	113 (91.9)	0.015
Injectable drug use	66 (76.7)	99 (79.2)	90 (73.2)	0.533
Pyrazinamide use	52 (60.5)	56 (44.8)	61 (49.6)	0.079
Para-aminosalicylic acid use	69 (80.2)	92 (73.6)	89 (72.4)	0.400
Cycloserine use	79 (91.9)	113 (90.4)	109 (88.6)	0.735
Prothionamide use	75 (87.2)	100 (80.0)	94 (76.4)	0.150
Linezolid use	0	3 (2.4)	12 (9.8)	0.001
Adverse drug reactions	31 (36.5)	44 (35.2)	31 (25.2)	0.275
Treatment success				
Total	46 (53.5)	86 (68.8)	103 (83.7)	<0.001
Cure	43 (50.0)	64 (51.2)	92 (74.8)	
Completed	3 (3.5)	22 (17.6)	11 (8.9)	
Unfavourable outcomes				
Total	40 (46.5)	39 (31.2)	20 (16.3)	<0.001
Failure	24 (27.9)	16 (12.8)	7 (5.8)	
Relapse	3 (3.5)	3 (2.4)	2 (1.6)	
Death	9 (10.5)	10 (8.0)	5 (4.1)	
Default	4 (4.6)	10 (8.0)	6 (4.8)	
Relapse rate (cases per 1000 person-years)	10.9	6.9	8.2	0.174

MDR-TB = multidrug-resistant TB; IQR = interquartile range; XDR-TB = extensively drug-resistant tuberculosis.

Int J Tuberc Lung Dis 2015 May;19(5):525-30.

Summery

- 1. Efficacy of delamanid is still questioned and further analyses of larger cohorts from programmatic settings with more follow-up time are needed.

- 2. The optimised use of delamanid combined with effective drugs could achieve a high treatment success rate in RR/MDR-TB patients.

Study treatment regimens

Each experimental regimen will contain at least one new drug, in combination with up to four companion drugs. The control regimen will be composed according to local interpretation of WHO guidance and may include a new drug if indicated.

Trial Regimens	Bedaquiline	Delamanid	Clofazimine	Linezolid	Fluoroquinolone	Pyrazinamide
endTB 1 BeLiMoZ	Be			Li	Mo	Z
endTB 2 BeCLiLeZ	Be		C	Li	Le	Z
endTB 3 BeDeLiLeZ	Be	De		Li	Le	Z
endTB 4 DeCLiLeZ		De	C	Li	Le	Z
endTB 5 DeCMoZ		De	C		Mo	Z
endTB 6 Control	Standard of care control, composed according to WHO Guidelines, including the possible use of De or Be					

STUDY PROTOCOL Open Access

Delamanid, linezolid, levofloxacin, and pyrazinamide for the treatment of patients with fluoroquinolone-sensitive multidrug-resistant tuberculosis (Treatment Shortening of MDR-TB Using Existing and New Drugs, MDR-END): study protocol for a phase II/III, multicenter, randomized, open-label clinical trial

Myungsun Lee[1], Jeongha Mok[2], Deog Kyeom Kim[3], Tae Sun Shim[4], Won-Jung Koh[5], Doosoo Jeon[6], Taehoon Lee[7], Seung Heon Lee[8], Ju Sang Kim[9], Jae Seuk Park[10], Ji Yeon Lee[11], Song Yee Kim[12], Jae Ho Lee[13], Kyung-Wook Jo[4], Byung Woo Jhun[5], Young Ae Kang[12], Joong Hyun Ahn[9], Chang-Ki Kim[14], Soyoun Shin[15], Taeksun Song[16], Sung Jae Shin[17], Young Ran Kim[1], Heejung Ahn[18], Seokyung Hahn[18], Ho Jeong Won[18], Ji Yeon Jang[18], Sang Nae Cho[1] and Jae-Joon Yim[19*]

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