New Treatments for Drug Resistant TB

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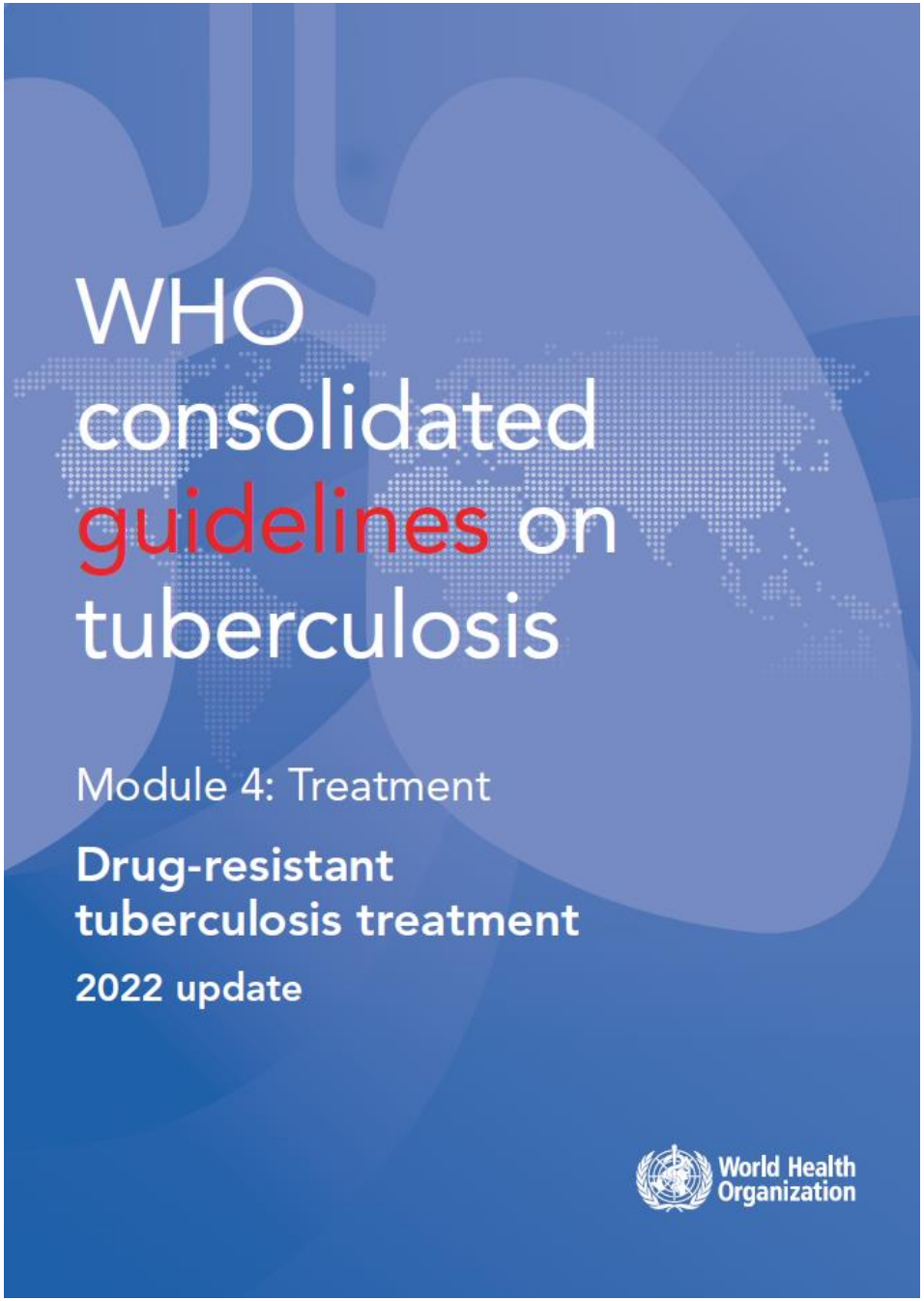

- **Treatment Recommendations:**
- The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB (NEW)
- The 9-month all-oral regimen for MDR/RR-TB (NEW)
- Longer regimens for MDR/RR-TB
- Regimen for rifampicin-susceptible, isoniazid-resistant TB (Hr-TB)

WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022.

Longer regimens for MDR/RR-TB

WHO Recommendations 2022 (Long Regimen)

Table 3.1. Grouping of medicines recommended for use in longer MDR-TB regimens[a]

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

DST: drug susceptibility testing; ECG: electrocardiogram; GDG: Guideline Development Group; IPD: individual patient data; LPA: line probe assay; MDR-TB: multidrug-resistant TB; TB: tuberculosis.

Treatment duration for most patients (modify according response):

- **Total Duration:** 18–20 months
- **After culture conversion:** 15-17 months.
- **Amikacin / Streptomycin:** 6-7 months.

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Relative risk for (i) treatment failure or relapse and (ii) death (versus treatment success): 2018 IPD meta-analysis

Medicine		Treatment failure or relapse versus treatment success		Death versus treatment success	
		Number treated	Adjusted odds ratio (95% CL)	Number treated	Adjusted odds ratio (95% CL)
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)[b]	290	1.2 (0.5–3.0)[b]
	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)

WHO, 2022

Duration of Treatment (MDR-TB, pre-XDR-TB, XDR-TB

Table 6. Adjusted Estimates of Treatment Success by Duration of Intensive Phase after Culture Conversion, All Forms of Multidrug-Resistant Tuberculosis ($N = 4,122$)

Intervals from Sputum Culture Conversion to End of Intensive-Phase Treatment (*mo*)	No. of Patients		Propensity Score–matched Analysis			
	Treatment Success	Total	No. of Pairs	aOR	95% CI	Risk Difference (95% CI)
0–1.0	239	251	—	1.0	Reference	—
1.01–3.0	668	695	694	1.5	1.0 to 2.3	0.02 (0.00 to 0.03)
3.01–5.0	878	917	906	1.4	1.0 to 2.0	0.02 (0.00 to 0.03)
5.01–7.0	1,158	1,179	1,179	3.3	2.1 to 5.2	0.04 (0.03 to 0.05)
7.01–15.0	1,025	1,080	1,079	1.1	0.8 to 1.5	0.01 (−0.01 to 0.02)

Definition of abbreviations: aOR = adjusted odds ratio; CI = confidence interval.

Table 8. Adjusted Estimates of Treatment Success by Duration of Treatment Interval between Sputum Culture Conversion and End of Treatment, All Forms of Multidrug Resistance ($N = 4,691$)

Interval from Sputum Culture Conversion to End of Treatment (*mo*)	No. of Patients		Propensity Score–matched Analysis			
	Treatment Success	Total	No. of Pairs	aOR	95% CI	Risk Difference (95% CI)
0.1–12.0	360	396	394	0.5	0.4 to 0.7	−0.04 (−0.07 to −0.01)
12.01–15.0	565	593	—	1.0	Reference	—
15.01–18.0	1,206	1,235	1,223	2.1	1.4 to 3.1	0.02 (0.01 to 0.04)
18.01–21.0	1,122	1,158	1,154	1.6	1.1 to 2.3	0.02 (0.00 to 0.03)
21.01–24.0	858	893	889	1.2	0.9 to 1.8	0.01 (−0.01 to 0.02)
24.01–69	386	416	413	0.7	0.4 to 1.0	−0.02 (−0.05 to 0.00)

Definition of abbreviations: aOR = adjusted odds ratio; CI = confidence interval.

Nahid P et al. Am J Respir Crit Care Med Vol 200, Iss 10, pp e93–e142, Nov 15, 2019

The 9-month all-oral regimen for MDR/RR-TB (NEW)

2.1 Recommendation

NEW RECOMMENDATION

No.	Recommendation
2.1	WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. *(Conditional recommendation, very low certainty of evidence)*

WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update

The 9-month all-oral regimen for MDR/RR-TB

Month	1	2	3	4	5	6	7	8	9	10	11
Bedaquline											
Ethionamide*											
Isoniazid (high-dose)											
Levofloxacin / Moxifloxacin											
Ethambutol											
Pyrazinamide											
Clofazimine											

Standard duration of treatment

Additional two months if patient remains smear positive at the end of 4 months

*Ethionamide can be replaced by 2 months of linezolid (600 mg daily).

- **The 9-month all oral regimen recommendation applies to:**
  - People with MDR/RR-TB and without resistance to fluoroquinolones.
  - People without extensive TB disease and without severe extrapulmonary TB.
  - People with less than 1 month exposure to bedaquiline, fluoroquinolones, ethionamide, linezolid and clofazimine (unless resistance has been ruled out).
  - All people regardless of HIV status.

WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update

The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB (NEW)

1.1 Recommendation

NEW RECOMMENDATION

No.	Recommendation
1.1	WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than the 9-month or longer (18-month) regimens in MDR/RR-TB patients. *(Conditional recommendation, very low certainty of evidence)*

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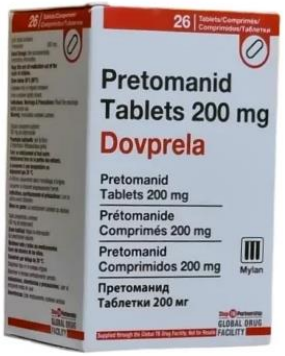
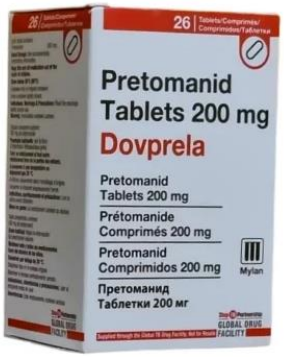
Pretomanid



- Drug Class: Bicyclic nitroimidazole
- Mode of Action: Inhibition of cell wall lipid synthesis.
  - Activated within M. tuberculosis cells by mycobacterial deazaflavin (F420) dependent nitroreductase (Ddn) resulting in release of reactive nitrogen species (e.g. nitric oxide).
- C_{max} increased by 76% when taken with a high calorie meal. T_{max} 4-5 hours

Pretomanid



- Dose: 200mg once daily for 26 weeks, with f
  - No data in renal or hepatic impairment.
  - Safety & efficacy in elderly (>65yrs), children and adolescents has not been established
- Common ADRs (BPaL regimen)*: peripheral neuropathy, GI Upset (e.g. nausea, vomiting, dyspepsia), anaemia, musculoskeletal pain, elevated liver enzymes.
- Very limited data in pregnancy
- Reduced fertility and/or testicular toxicity were observed in male rats and mice, but not in primates or humans.

BPaLM - WHO Recommendations

- DST for fluoroquinolones is strongly encouraged in people with MDR/RR-TB.
  - It should not delay initiation of the BPaLM, but guides decision as to whether to continue or stop moxifloxacin (i.e. BPaLM vs BPaL).

- BPaLM recommendation applies to:
  - People with MDR/RR-TB, or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB).
  - People with confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular and disseminated (miliary) TB.
  - Adults and adolescents aged 14 years and older.
  - All people regardless of HIV status.
  - People with less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid (unless resistance has been ruled out).

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NIX-TB Study

- open-label, single-group study
- 26 weeks treatment:
  - Bedaquiline 400mg once daily for 2wks, then 200mg three times a week for 24 weeks,
  - Pretomanid 200mg daily for 26 weeks
  - Linezolid 1200mg per day for up to 26 weeks (dose adjustment depending on toxic effects)
- N=109 (71 XDR, 38 MDR)

Conradie F. N Engl J Med 2020;382:893-902.

NIX-TB Study Results

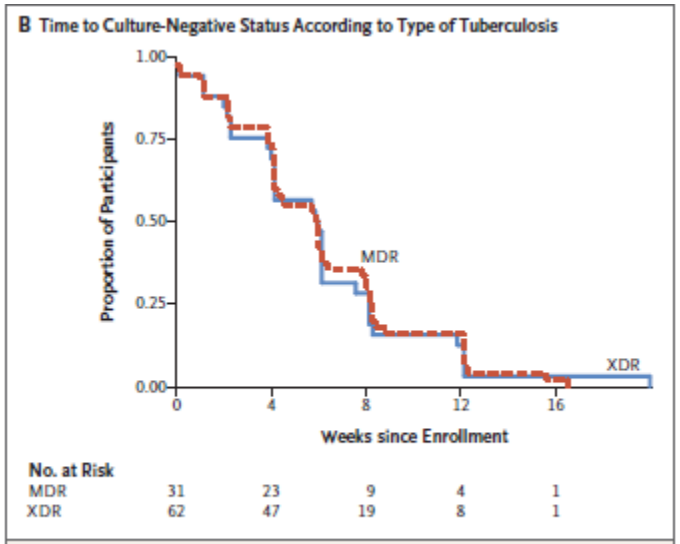


Figure 2. Time to Culture-Negative Status among Patients Who Were Positive at Baseline (Intention-to-Treat Population).

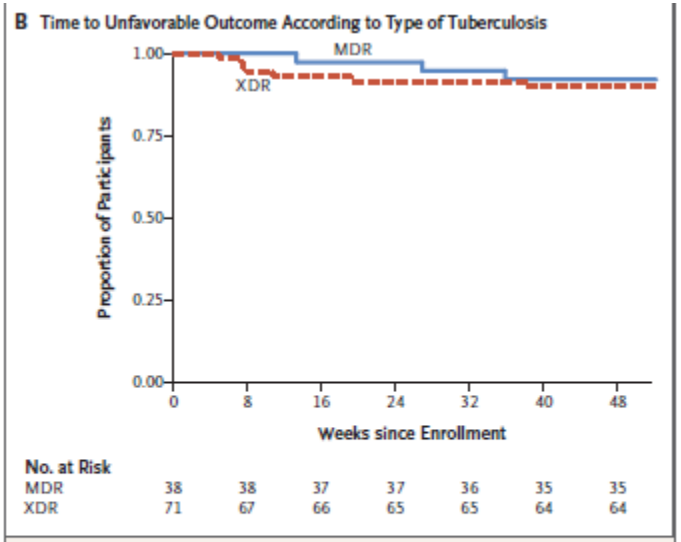


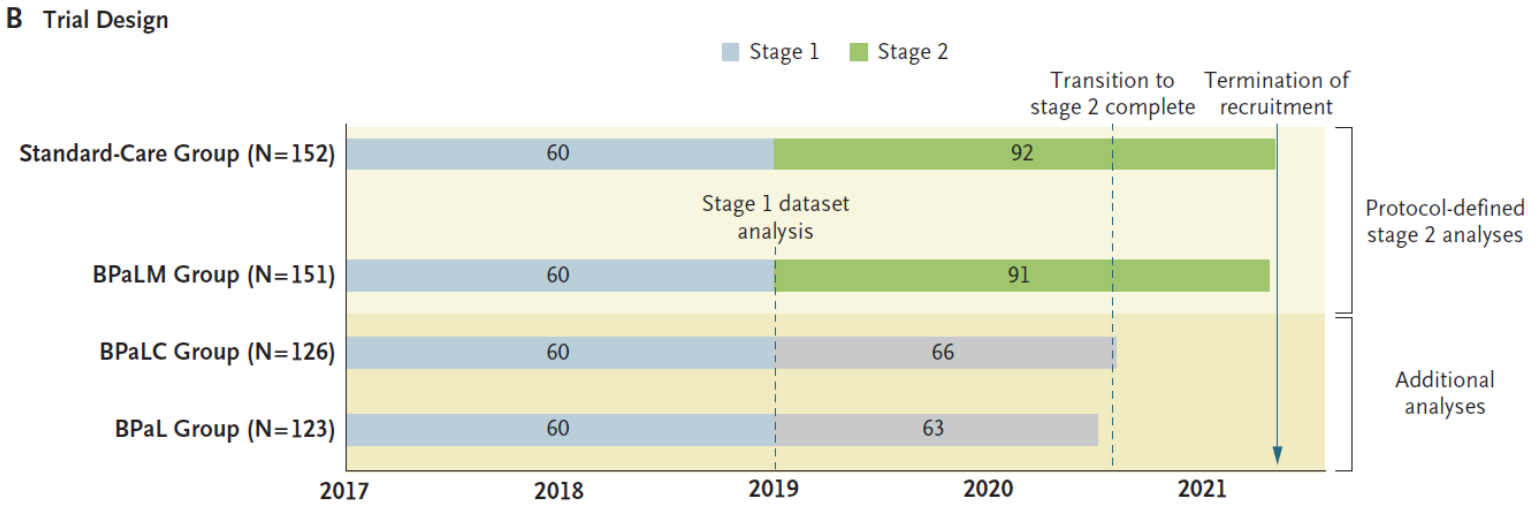
Figure 1. Time to an Unfavorable Outcome (Intention-to-Treat Population).
An unfavorable outcome was defined as treatment failure (bacteriologic or clinical) or disease relapse, with clinical treatment failure defined as a change from the protocol-specified tuberculosis treatment as a result of treatment failure, retreatment for tuberculosis, or tuberculosis-related death through follow-up until 6 months after the end of treatment. MDR denotes multidrug-resistant, and XDR extensively drug-resistant.

Table 3. Adverse Events That Occurred or Worsened during Treatment.

Event*	HIV Status		Linezolid Regimen		Overall (N=109)
	Negative (N=53)	Positive (N=56)	600 mg Twice Daily (N=44)	1200 mg Daily (N=65)	
	number (percent)				
Adverse event	53 (100)	56 (100)	44 (100)	65 (100)	109 (100)
Adverse event leading to death	3 (6)	3 (5)	4 (9)	2 (3)	6 (6)
Serious adverse event	10 (19)	9 (16)	13 (30)	6 (9)	19 (17)
Grade 3 or 4 adverse event	27 (51)	35 (62)	27 (61)	35 (54)	62 (57)

- Serious ADRs in 19 (17%)
- Peripheral neuropathy in 88 (81%) - similar for Lzd 600mg BD vs. 1200mg OD.
- Optic neuritis in 2
- Myelosuppression in 52 (48%)
- ALT/AST rises in 17 (2 >3xULN)

TB-PRACTECAL Study: Design



Stage 1. Primary outcome: culture conversion in MGIT liquid medium at 8 weeks after randomization
Stage 2. Primary outcome: unfavourable status (composite of death, treatment failure, treatment discontinuation, loss to follow-up, or recurrence of TB) at 72 weeks after randomisation

Inclusion criteria include:	Exclusion criteria include:
• Age 15+ • M. tuberculosis in sputum • Rif Resistance (excluded if known resistance to Bdq, pretomanid, Lzd or Dld)	• Prior use of bedaquiline and/or pretomanid and/or linezolid and/or delamanid for one or more months;

Table 2 Investigational regimen drugs and dosing

Bedaquiline	400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 22 weeks
Pretomanid	200mg once daily for 24 weeks
Moxifloxacin	400 mg once daily for 24 weeks
Linezolid	600mg daily for 16 weeks then 300mg daily for the remaining 8 weeks (or earlier when moderately tolerated)
Clofazimine	50 mg (less than 33 kg), 100 mg (more than 33 kg) for 24 weeks

Berry et al. Trials (2022) 23:484; Nyang'wa et al. New Engl J Med 2022; 387:2331-43. DOI: 10.1056/NEJMoa2117166

TB-PRACTECAL Study: Results

Stage 1

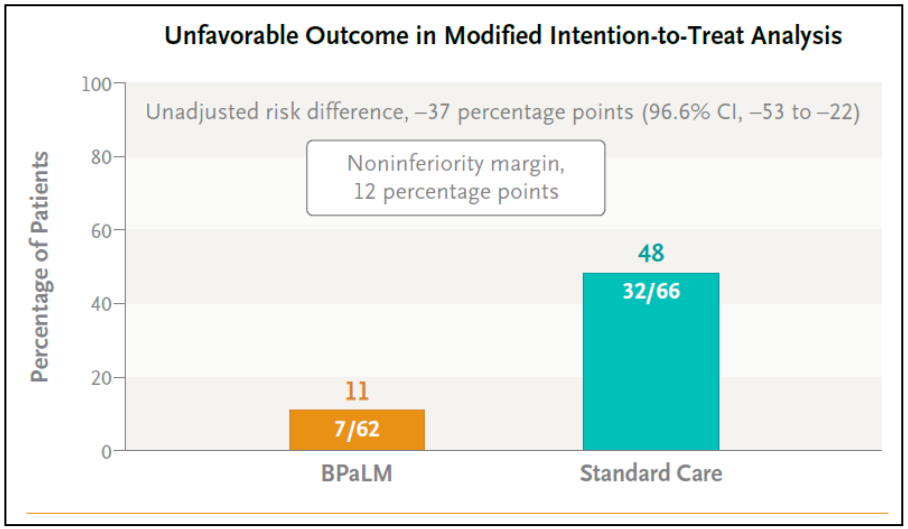
Primary efficacy and safety outcomes at week 8 (modified-intention-to-treat population)

Table S8. Stage 1 primary efficacy and safety outcomes at week 8 (modified-intention-to-treat population, stage 1 analysis)

	Standard of care	BPaLM	BPaLC	BPaL
Number with culture conversion in liquid media at 8 weeks post randomization, n/N (%)	N/A	37/48 (77.1%)	33/49 (67.3%)	21/46 (45.7%)
[85 % CI]		[66.4, 85.6]	[56.2, 77.2]	[34.4, 57.3]
Patients with treatment discontinuation for any reason and death at 8 weeks post randomization, n/N (%)	N/A	4/52 (7.7 %)	3/52 (5.8 %)	5/51 (9.8%)
[90% CI]		[2.7, 16.7]	[1.6, 14.2]	[3.9, 19.5]

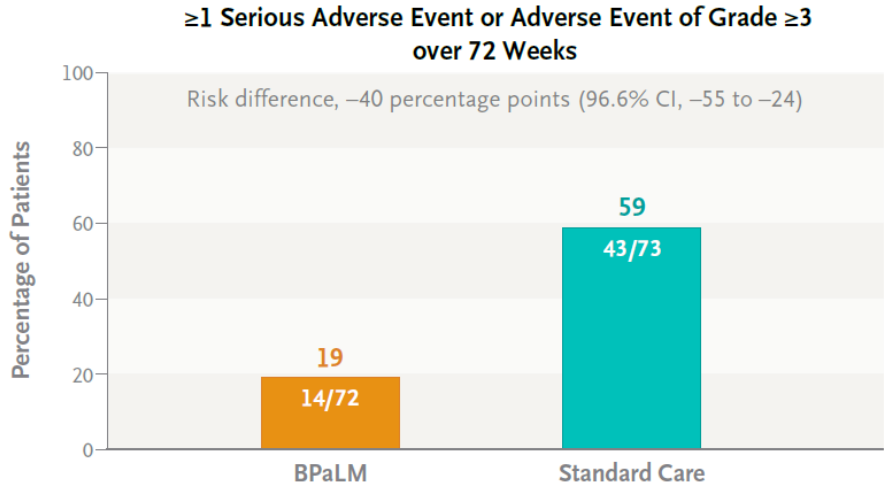
Stage 2

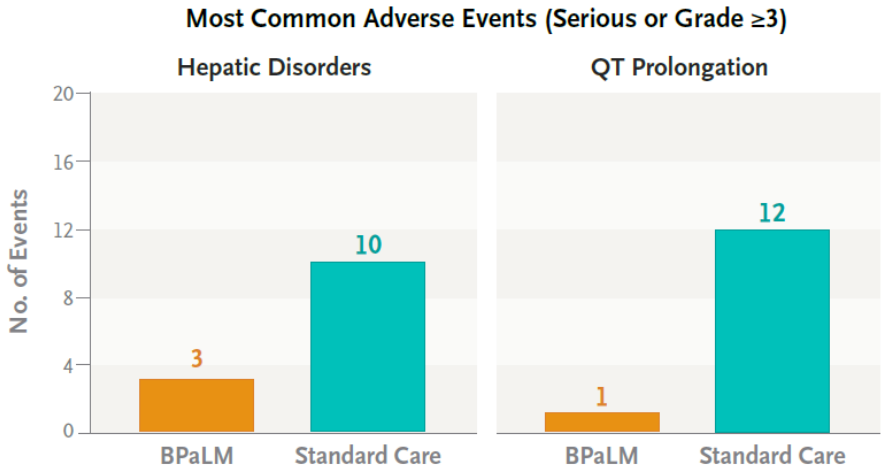
Primary efficacy: Unfavourable Outcome (modified-intention-to-treat population)



Nyang'wa et al. New Engl J Med 2022; 387:2331-43. DOI: 10.1056/NEJMoa2117166

TB-PRACTECAL Study: Safety





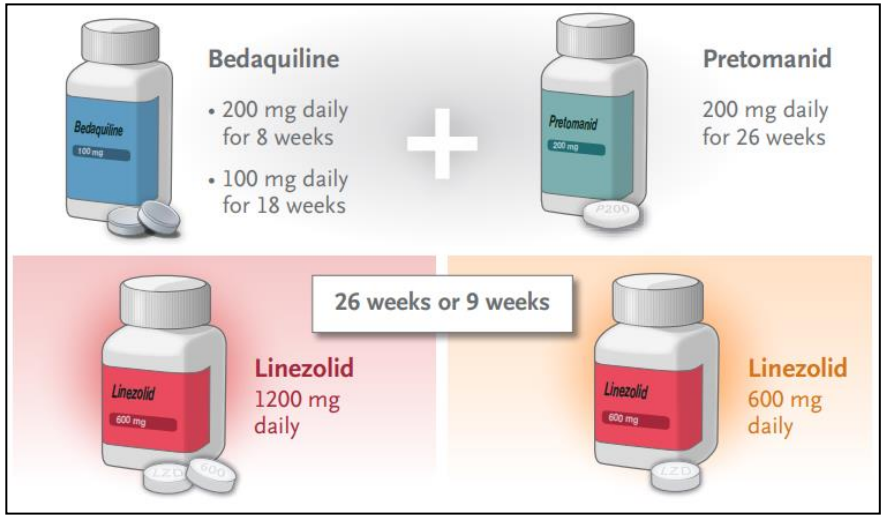
Most common adverse events - <u>Number of Patients</u> in the *As Treated population*, (BPaLM vs. standard care):

- Hepatic disorders: 4% (3/72) vs. 11% (8/73)
- QT prolongation: 1% (1/72) vs. 14% (10/73)
- Peripheral neuropathy: 9% (14/151) vs. 19% (28/150)
- No episodes of optic neuropathy were observed

Nyang'wa et al. New Engl J Med 2022; 387:2331-43. DOI: 10.1056/NEJMoa2117166

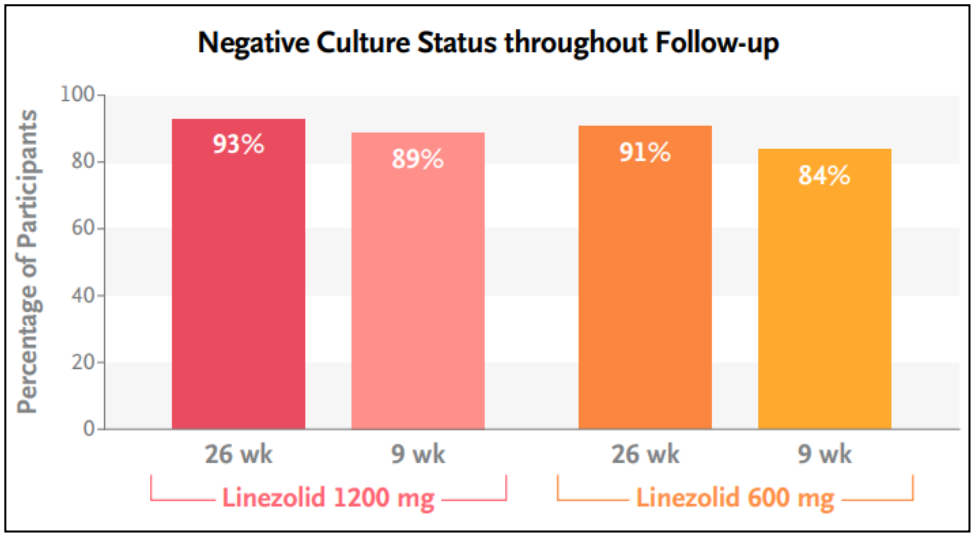
ZeNIX Study

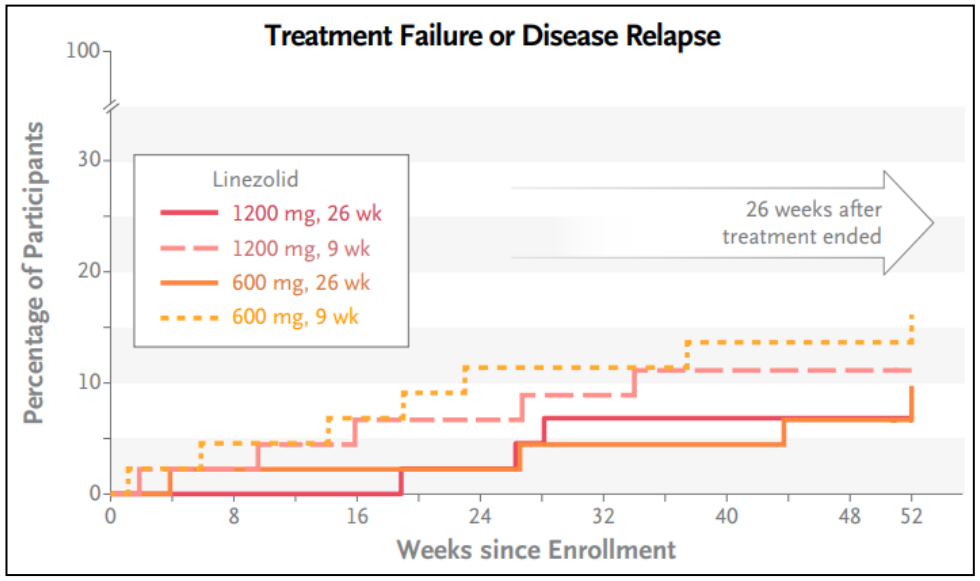
- Partially blind, randomized trial (1:1:1:1) in pulmonary XDR, pre-XDR, or RR-TB, non-responsive to treatment or after stopping 2nd-line regimen due to ADRs.
- N=181
- 26 weeks treatment



Conradie F. N Engl J Med 2022;387:810-23.

ZeNix Study - Results





ZeNix - Safety

Variable	Bedaquiline–Pretomanid–Linezolid Regimen				Total (N=181)
	Linezolid, 1200 mg, 26 wk (N=45)	Linezolid, 1200 mg, 9 wk (N=46)	Linezolid, 600 mg, 26 wk (N=45)	Linezolid, 600 mg, 9 wk (N=45)	
	number of participants (percent)				
≥1 Grade 3 or higher adverse event	14 (31)	11 (24)	9 (20)	11 (24)	45 (25)
≥1 Serious adverse event	3 (7)	4 (9)	1 (2)	3 (7)	11 (6)
Death from any cause	0	1 (2)	0	0	1 (1)
Tuberculosis-related death	0	0	0	0	0
≥1 Episode of optic neuropathy†‡	4 (9)	0	0	0	4 (2)
≥1 Episode of peripheral neuropathy‡§	17 (38)	11 (24)	11 (24)	6 (13)	45 (25)
Severity of event in participants with ≥1 episode of peripheral neuropathy§¶					
Grade 1	10 (22)	7 (15)	10 (22)	6 (13)	33 (18)
Grade 2	7 (16)	4 (9)	1 (2)	0	12 (7)
≥1 Episode of myelosuppression‖	10 (22)	7 (15)	1 (2)	3 (7)	21 (12)
Hemoglobin level					
<8 g/dl and below baseline level	0	1 (2)	0	0	1 (1)
<25% below baseline level	9 (20)	4 (9)	0	0	13 (7)
Absolute neutrophil count <750/mm³ and below baseline level	1 (2)	3 (6)	1 (2)	3 (7)	8 (4)
Platelet count <50,000/mm³ and below baseline level	0	0	0	0	0
Liver-related serious adverse event	0	1 (2)	1 (2)	1 (2)	3 (2)
QTcF interval >60 msec above baseline value	0	2 (4)	0	1 (2)	3 (2)
Maximum QTcF interval ≥500 msec	0	1 (2)	0	1 (2)	2 (1)
Any interruption, dose reduction, or discontinuation of	23 (51)	14 (30)	6 (13)	6 (13)	49 (27)

Implications for Practice

- NHS England are currently reviewing commissioning in line with the WHO 2022 update.
- NHSE funding currently not available, and IFR approval is unlikely.
- Pretomanid is available for use in the UK:
  - Supply is EMA Approved / Italian marketed sotck (26 tablets per pack)
  - Imported via Tanner CH or specialist importer
  - Package price is €2851 + shipping costs + fees ± VAT (total ~ €24,000 for 6 months)

Other Considerations with BPaLM

Dosing:

- Bedaquiline: either dosing regimen used in trials
  - daily throughout treatment: 200 mg once daily for 8 weeks followed by 100 mg once daily; *or*
  - daily for loading dose and three times per week thereafter: 400 mg once daily for 2 weeks followed by 200 mg three times per week.
- Pretomanid 200mg once daily throughout the regimen
- Linezolid 600 mg/daily throughout the regimen
  - Dose can be reduced to 300 mg/daily if necessary to mitigate toxicity
- Moxifloxacin 400mg once daily throughout the regimen

Drug-Drug Interactions:

- Efavirenz
- QTc prolonging drugs
- strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, St. John's wort, rifamycins)
- strong CYP3A4 inhibitors (e.g. azoles, > 2 weeks of macrolide antibiotics other than azithromycin)
- monoamine oxidase inhibitors
- drugs known to induce myelosuppression (e.g. azathioprine and cytotoxic agents).

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