Oral Shorter Regimen for MDR-TB in Korea: Con

전남대학교 병원
권용수

목차

- 2022 WHO에서 제시하는 경구 단기약제치료
- 한국에서 pretomanid
- 경구 단기약제치료 효과 및 안전성에 대한 의문점

2022 WHO

- The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB and pre-XDR-TB (a)
- The 9-month all-oral regimen for MDR/RR-TB (a)

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

Pretomanid (PA-824)

- A novel nitroimidazole
- Inhibiting the synthesis of mycobacterial cell wall components and ketomycolate
- Shows potent anti-mycobacterial activity against both DS and DR *M. tb* clinical isolates.
- The bactericidal and sterilizing activities of this molecule, alone and in combination with first-line anti-TB drugs and/or moxifloxacin, have been exhibited in murine and guinea pig models.
- Approved by FDA: as part of a combination regimen with Bdq and Lzd for pulmonary XDR- or complicated MDR-TB

Pretomanid

- 2019 WHO: BPaL regimen in pre-XDR-TB patients, under operational research conditions.

→ 우리나라는 현재 BPaL 운영 연구 중임

- Indication : pre-XDR-TB
- 2023.3.31 screening: 17, enrolling: 6

The NEW ENGLAND JOURNAL of MEDICINE

Treatment of Highly Drug-Resistant Pulmonary TB

NIX-TB, AN OPEN-LABEL, SINGLE-GROUP STUDY

109 Patients
with confirmed tuberculosis

Three-drug regimen (26 wk)

Bedaquiline

Pretomanid
(recently approved)

Linezolid

XDR tuberculosis
N=71
(65%)

Nonresponsive or treatment-intolerant MDR tuberculosis
N=38
(34%)

Clinical resolution at 6 mo after therapy

90% of all patients had favorable outcomes
95% CI, 83–95

89%
95% CI, 79–95

92%
95% CI, 79–98

Linezolid associated with peripheral neuropathy (81%) and myelosuppression (48%)

F. Conradie et al. 10.1056/NEJMoa1901814

Pretomanid

고시 제2022-312호 요양급여의 적용기준 2022-12-30

구 분	세부인정기준 및 방법
[622] Pretomanid 경구제 (품명: 도브프렐라정 200mg)	허가사항(성인의 **광범위 약제내성 폐결핵**※ 및 **치료 내성 또는 비반응성 다제내성 폐결핵에** 대한 베다퀼린과 리네졸리드와의 병용요법) 범위 내에서 투여시 요양급여 함을 원칙으로 함. o 다만, 동 약제의 요양급여 인정 여부에 대하여 질병관리청에 **사전 신청하여 승인** 받은 경우에 한하여 인정하며, 사전 승인을 위한 절차·방법 및 위원회 구성 등에 대한 세부사항은 질병관리청장이 정함([붙임]참조) ※ 광범위 약제내성 폐결핵 : 이소니아지드, 리팜피신, 플로오르퀴놀론 및 아미카신 등 주사제의 내성이 있는 환자

2) 도브프렐라(프레토마니드) 포함 병용치료

ㅇ **(승인기준)** 성인의 광범위약제내성* 및 치료내성 또는 비반응성** 다제내성폐결핵 환자에 대하여 다음 조건을 만족하고, 베다퀼린, 리네졸리드와의 병용요법을 사용하는 경우 사전심사를 거쳐 신약 사용 가능

* 이소니아지드와 리팜핀 내성이고 한 가지 이상의 퀴놀론계 약제 및 3가지 주사제(카프레오마이신, 카나마이신, 아미카신) 중 한 가지 이상의 약제에 내성을 보이는 결핵

** 부작용 등으로 인해 적절한 2차 약제 처방을 사용할 수 없는 경우 또는 6개월 이상 2차 약제 처방으로 치료하였으나 반응이 없는 경우(객담 배양 음전 실패)

- **(허가사항)** 승인기준을 충족하고 약제 사용 절대 금기증이 아닌 경우

ㅇ **(불허기준)** 약제 사용 절대 금기증에 해당하는 경우

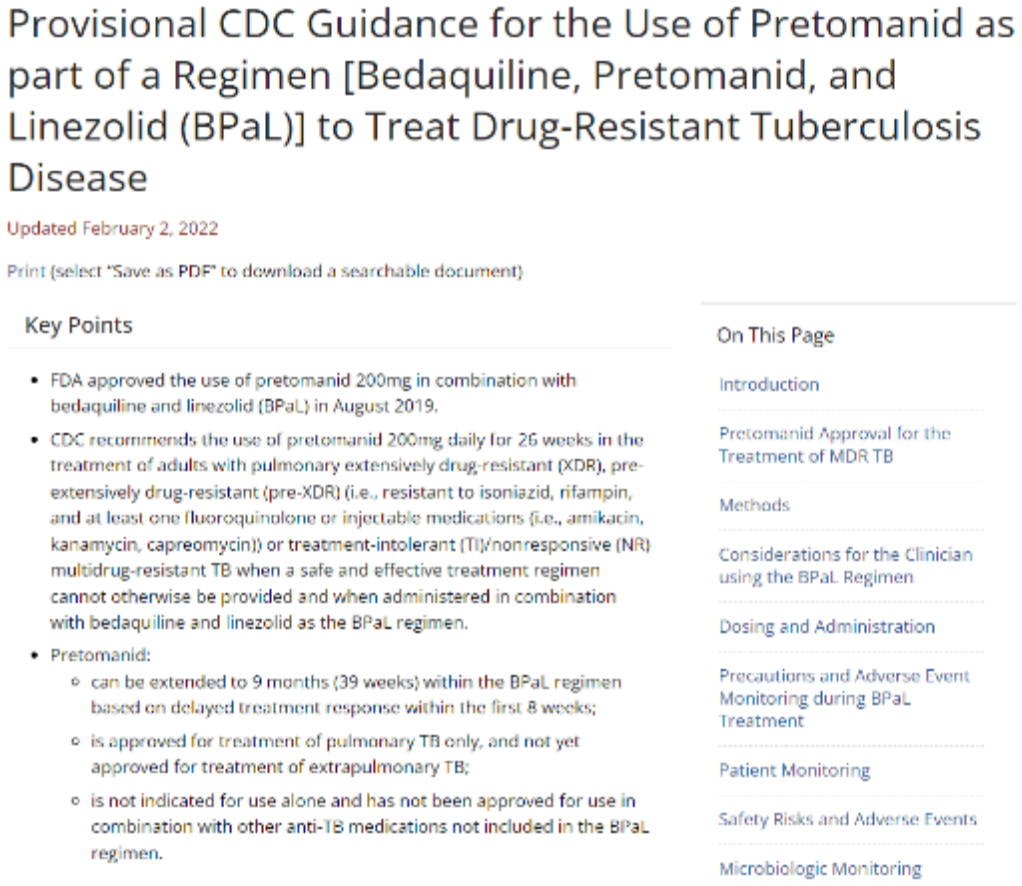
ㅇ **(재심사) 치료계획에 중대한 변경 사항이 있는 경우** 재심사 필요

◆ 병용요법 용량

ㅇ 프레토마니드 1정(200mg)을 26주 동안 1일 1회 경구 투여

ㅇ 베다퀼린 400mg을 2주간 1일 1회 경구 투여 후, 투여 간격 최소 48시간으로 24주간 200mg을 주 3회 투여(총 26주)

ㅇ **리네졸리드 1,200mg**을 최대 26주 동안 매일 경구 투여, 이상반응(골수억제, 말초 및 눈의 신경병증)이 발생하는 경우 600mg, 이후 300mg으로 용량을 감량 또는 투여 중단



Provisional CDC Guidance for the Use of Pretomanid as part of a Regimen [Bedaquiline, Pretomanid, and Linezolid (BPaL)] to Treat Drug-Resistant Tuberculosis Disease

Updated February 2, 2022

Print (select "Save as PDF" to download a searchable document)

Key Points

- FDA approved the use of pretomanid 200mg in combination with bedaquiline and linezolid (BPaL) in August 2019.
- CDC recommends the use of pretomanid 200mg daily for 26 weeks in the treatment of adults with pulmonary extensively drug-resistant (XDR), pre-extensively drug-resistant (pre-XDR) (i.e., resistant to isoniazid, rifampin, and at least one fluoroquinolone or injectable medications (i.e., amikacin, kanamycin, capreomycin)) or treatment-intolerant (TI)/nonresponsive (NR) multidrug-resistant TB when a safe and effective treatment regimen cannot otherwise be provided and when administered in combination with bedaquiline and linezolid as the BPaL regimen.
- Pretomanid:
  - can be extended to 9 months (39 weeks) within the BPaL regimen based on delayed treatment response within the first 8 weeks;
  - is approved for treatment of pulmonary TB only, and not yet approved for treatment of extrapulmonary TB;
  - is not indicated for use alone and has not been approved for use in combination with other anti-TB medications not included in the BPaL regimen.

On This Page

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Search

Medicines | Human regulatory | Veterinary regulatory | Committees | News & events | Partners & networks | About us

Dovprela (previously Pretomanid FGK)

Share | RSS

AUTHORISED
This medicine is authorised for use in the European Union.

pretomanid

Table of contents

Overview

Pretomanid FGK is a medicine for treating adults with drug-resistant tuberculosis. It is used to treat tuberculosis that is:

- extensively drug-resistant (resistant to at least 4 antibiotics used for treating tuberculosis, including the standard antibiotics isoniazid and rifampicin);
- multi-drug resistant (resistant to isoniazid and rifampicin) and when antibiotics used for this form of tuberculosis do not work or cause unacceptable side effects.

Pretomanid FGK is used together with bedaquiline and linezolid.

- CDC and EMA
- Recommended for Pre-XDR and XDR

BPaLM/BPaL

- 2019 WHO guidelines 이후 새로운 근거 발견:

  TB-PRACTECAL and ZeNix

→ 2022 WHO guidelines

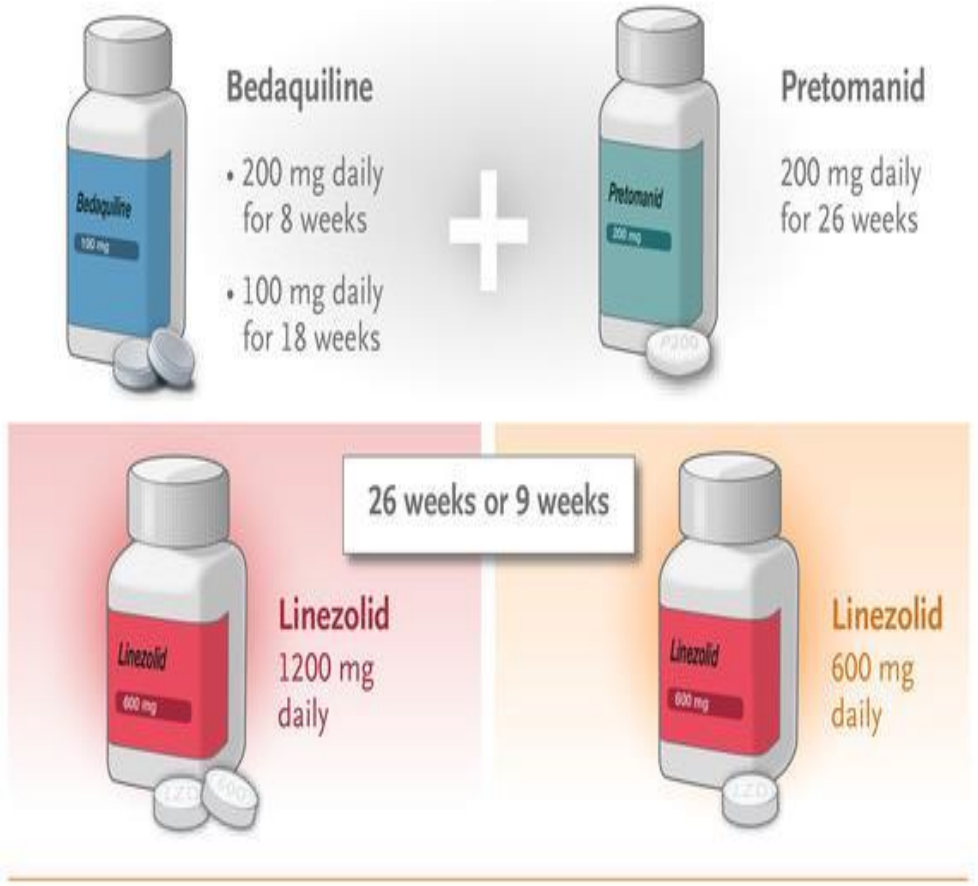
BPaLM in 2022 WHO

Remarks

1. Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/RR-TB, and although it should not delay initiation of the BPaLM, results of the test should guide the decision on whether moxifloxacin can be retained or should be dropped from the regimen – in cases of documented resistance to fluoroquinolones, BPaL without moxifloxacin would be initiated or continued.
2. This recommendation applies to the following:
   a. People with MDR/RR-TB or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB).
   b. People with confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular and disseminated (miliary) TB.[11]
   c. Adults and adolescents aged 14 years and older.
   d. All people regardless of HIV status.
   e. Patients with less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid. When exposure is greater than 1 month, these patients may still receive these regimens if resistance to the specific medicines with such exposure has been ruled out.
3. This recommendation does not apply to pregnant and breastfeeding women owing to limited evidence on the safety of pretomanid.[12]
4. The recommended dose of linezolid is 600 mg once daily, both for the BPaLM and the BPaL regimen.[13]

Zenix

- BPaL: Bedaquiline + Pretomanid + Linezolid
- XDR-TB, pre-XDR-TB, or RR-TB that was not responsive to treatment or for which a second-line regimen had been discontinued because of side effects



N Engl J Med. 2022 Sep 1;387(9):810-823

Zenix

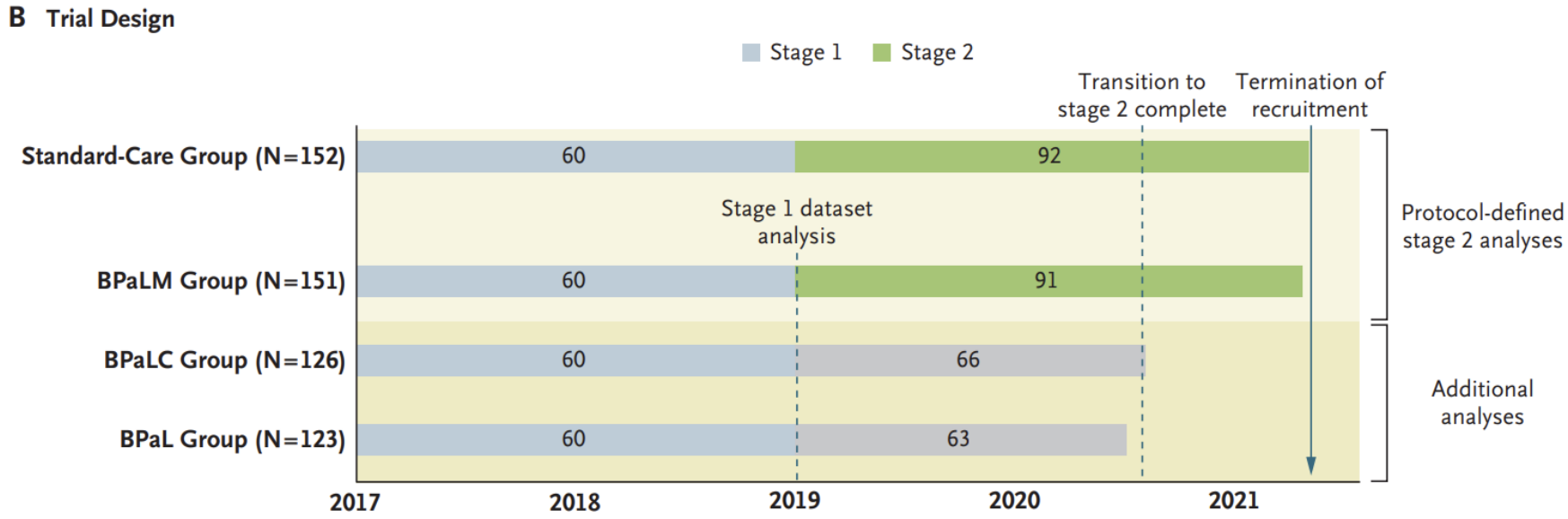
Lzd 용량	1200, 26wk	1200, 9wk	600, 26wk	600, 9wk
Favorable (mITT)	93%	89%	91%	84%

Lzd 용량	1200, 26wk	1200, 9wk	600, 26wk	600, 9wk
N	45	46	45	45
Median age	38	34	38	36
DM	7%	0	2%	11%

N Engl J Med. 2022 Sep 1;387(9):810-823

TB-PRACTECAL

- an open-label, phase 2–3, multicenter, randomized, controlled, noninferiority trial to evaluate the efficacy and safety of three 24-week, all-oral regimens.
- Two stage



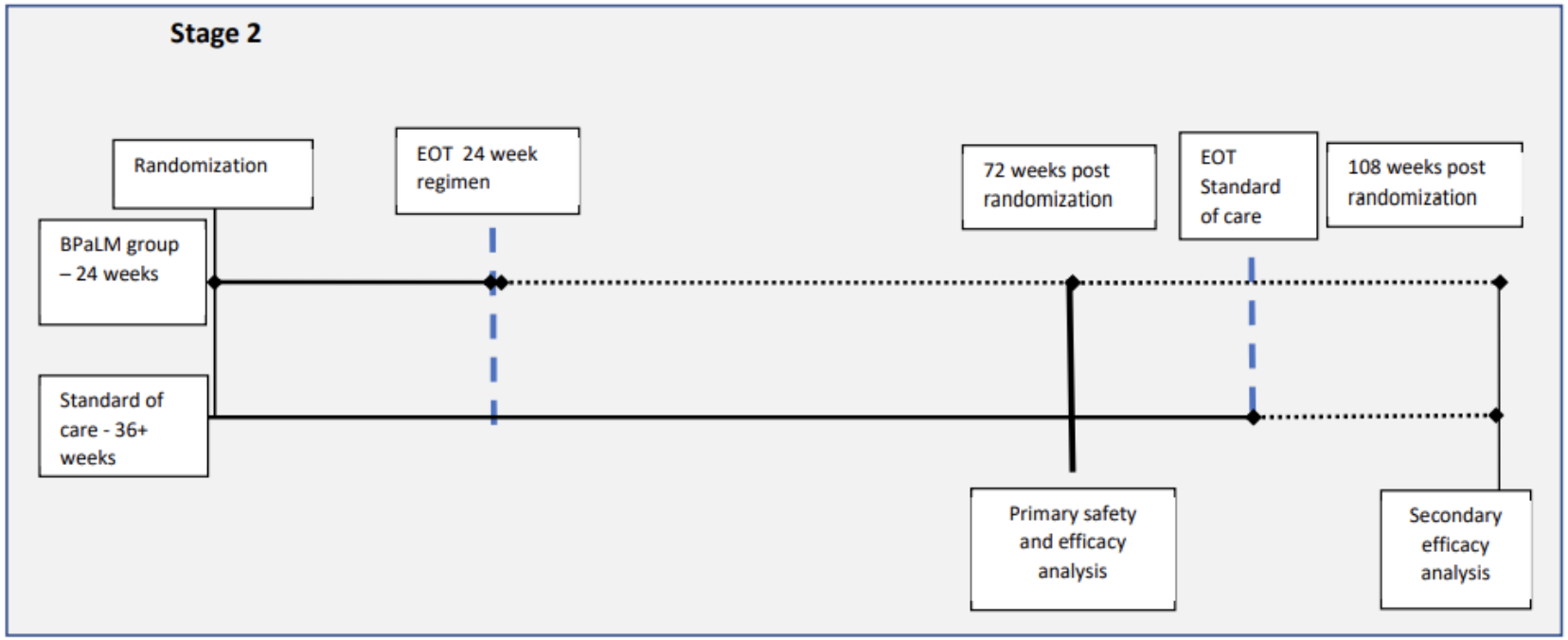
Lzd: 600mg for 16 weeks then 300mg for 8 weeks

N Engl J Med. 2022 Dec 22;387(25):2331-2343.

TB-PRACTECAL

- The BPaLM regimen was selected for analysis in stage 2 of the trial.

Figure S1b. Trial design – stage 2



N Engl J Med. 2022 Dec 22;387(25):2331-2343.

Role of Mfx

- BPaLM vs BPaL in TB-PRACTECAL

N Engl J Med. 2022 Dec 22;387(25):2331-2343.

	BPaLM	BPaL
8 weeks culture conversion	77.1%	45.7%
8 weeks discontinuation	7.7%	9.8%
Favorable outcome	89%	77%

BPaL → MDR-TB 치료에 충분히 효과적 치료법인가?

Poor outcome in control of TB-PRACTECAL

6.1.3 Control regimens

Locally approved standard of care which is as much as possible consistent with the WHO recommendations for the treatment of M/XDR-TB. This is an algorithm and hence the constituent drugs would change depending on the proven or expected DST of the infecting bacilli. The current algorithm includes the use of at least five drugs including a later generation quinolone (Mfx or Lfx), a second line injectable (Cm or Km or Am), Z and two of Pto/Eto, Cs/Trd, Lzd or Cfz. Other drugs such as ethambutol, High dose isoniazid, B, delamanid, PAS, Imipenem/cilastatin and meropenem may also be used. A standardised shortened course regimen or modified shortened course for MDR-TB patients with no second line drug resistance may be used if approved locally.

Most patients in the standard-care group received at least two WHO group A drugs3 as part of their regimen (Table S7); these drugs were fluoroquinolones (in 95%), linezolid (in 77%), and bedaquiline (in 76%)

ADRs	49%
동의철회	17%

	10%
ollow-up	10%
Median age	52
DM	18%

N Engl J Med. 2022 Dec 22;387(25):2331-2343.

Hongjo Choi. et al. J Korean Med Sci. 2023 Feb 6;38(5):e33

신약심사위원회 권고에 따른 치료성적

All patients with MDR-TB who were submitted for approval for the use of new TB drugs, including bedaquiline and delamanid.
Duration : 2016.9 – 2019.12
Treatment: 2016 WHO guidelines and 2017 Korean guideline based regimen

	Total	With new TB drugs	Without new TB drugs	P-value
Number	614	615	13	
Culture conversion	98%	98%	100%	1.000
Time to culture conversion, days	34 (13–70)	34 (13–70)	32 (10–90)	0.890
Final outcomes	771	741	30	
Cured	56%	57%	33%	0.013
Completed	24%	23%	53%	0.001
Failure	4%	4%	0%	0.627
Died	11%	11%	10%	1.000
Loss to follow-up	5%	5%	3%	1.000
Treatment success	80%	80%	87%	0.486

Int J Tuberc Lung Dis. 2023 Jan 1;27(1):55-60.

Dosing of linezolid

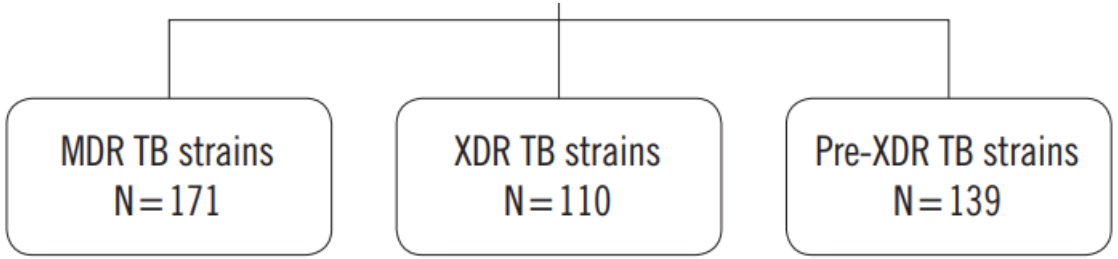
The ZeNix trial used several different dosing and duration schemes of linezolid, with the aim of determining the optimal administration schedule for this medicine. Linezolid is known to cause several potentially serious adverse effects; among those of most concern are peripheral neuropathy, optic neuritis and myelosuppression *(40)*. The GDG review of the ZeNix trial data identified the optimal dosing for linezolid to be 600 mg once a day for 26 weeks, and this arm of the ZeNix trial was used for the main comparisons. Study participants in this arm of the trial received 600 mg of linezolid once daily for 26 weeks, with a reduction to 300 mg daily allowed in the event of linezolid specific toxicities. In the TB-PRACTECAL trial, dosing of linezolid was slightly different – participants were given 600 mg daily for 16 weeks and then 300 mg daily for the remaining 8 weeks (the duration of BPaLM in this trial was 24 weeks).

The GDG panel considered that it would be preferable to use linezolid 600 mg/daily throughout the regimen, but the dose can be reduced to 300 mg/daily if necessary to mitigate toxicity.

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

300mg/day는 충분할까?

- The MICs of linezolid were ≤ 0.5 mg/L in the H37Rv control strain.
- 결핵연구원 420개 clinical strain



Ann Lab Med 2018;38:563-568

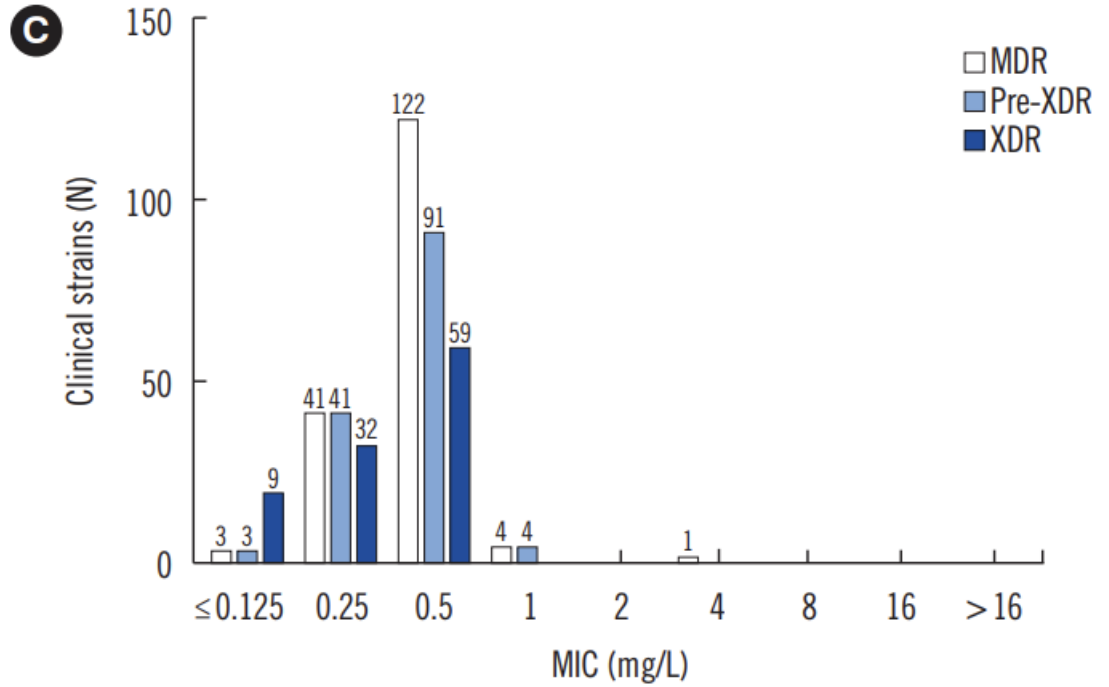


Fig. 2. Overall MIC distribution for 420 clinical strains: (A) Delamanid, (B) bedaquiline, and (C) linezolid MICs. The number above each bar indicates the number of strains.
Abbreviations: MIC, minimum inhibitory concentration; MDR, multidrug-resistant tuberculosis; XDR, extensively drug-resistant tuberculosis; Pre-XDR, pre-extensively drug-resistant tuberculosis.

TABLE 1 Demographic data for patients included in the model

Characteristic[a]	Value for data set			
	Brazil (n = 19)	Georgia (n = 69)	U.S. centers (n = 16)	Combined (n = 104)
Median age (yr) (IQR)	46.6 (32.3–62.2)	35.0 (27.4–48.1)	39.0 (24.0–47.0)	37.1 (27.3–49.0)
No. (%) of male patients	11 (68.8)	52 (75.4)	15 (78.9)	78 (75.0)
Median wt (kg) (IQR)	61.2 (52.4–75.7)	64.0 (57.0–71.0)	55.9 (50.2–58.1)	60.0 (54.2–69.8)
Median BMI (kg/m^2) (IQR)	23.2 (19.0–26.5)	21.0 (18.7–22.9)	19.5 (18.2–21.7)	20.8 (18.7–23.2)
Median CrCL (ml/min) (IQR)	101.1 (66.7–122.0)	101.6 (79.0–125.6)	94.3 (75.2–107.3)	100.7 (75.7–120.3)
Linezolid dose (mg)	600	600 (except one who received 300)	300–600	300–600

[a]IQR, interquartile range; BMI, body mass index; CrCL, creatinine clearance.

TABLE 3 PK/PD breakpoints and probability of achieving C_{min}s of >2 and >7 mg/liter for the simulated dosage regimens[a]

Dosage regimen (mg)	PK/PD breakpoint[b] (mg/liter)
Once daily	
300	0.13
450	0.25
600	0.25
900	0.50
1,200	0.50

- PK/PD breakpoint is defined as the highest MIC at which the probability of target attainment is >90%

AAC 2020; 64: e01174-20

DISCUSSION

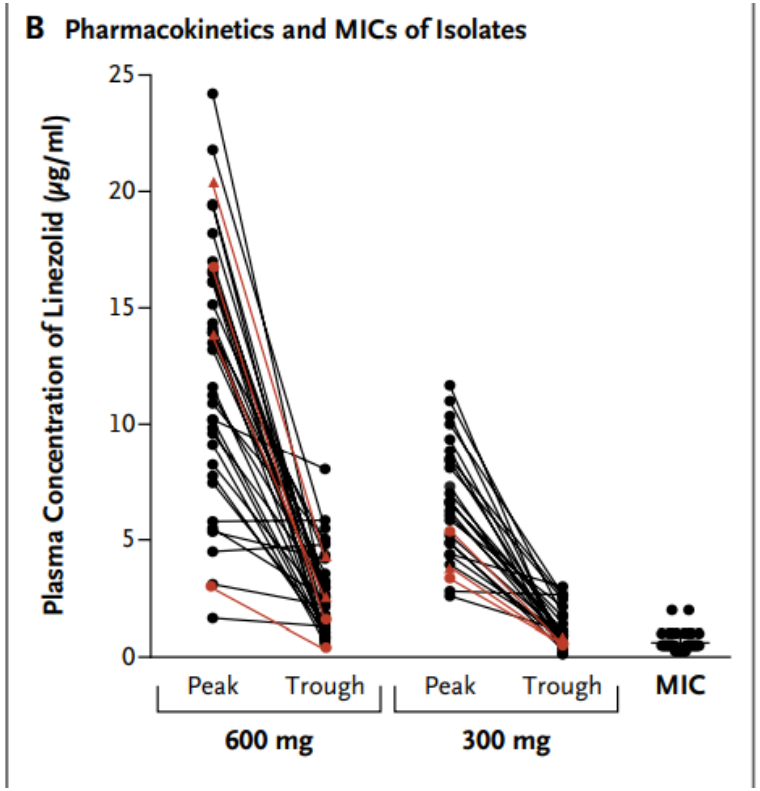
Our results provide valuable insight into dosing schemes for linezolid that may maximize benefit and limit toxicity. Our simulations found that a dosing regimen of 300 mg daily will likely not be effective given its PK/PD breakpoint of 0.125 mg/liter, which is at the lower end of the wild-type MIC distribution for linezolid and lower than the proposed epidemiological cutoff (ECOFF) of 0.5 mg/liter. On the contrary, dosing

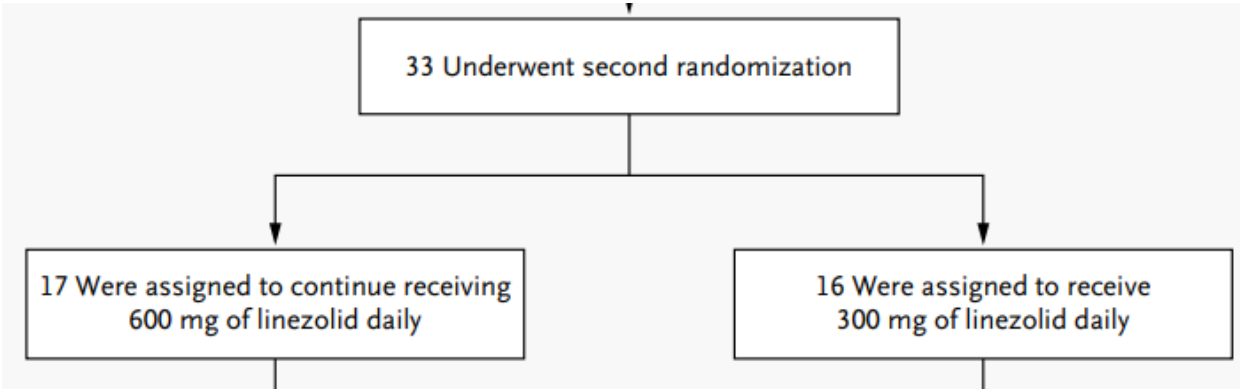
AAC 2020; 64: e01174-20

PHARMACOKINETICS

The maximal and minimal plasma concentrations that we observed for linezolid (Fig. 4B) are generally in agreement with published pharmacokinetic data in patients with other infectious diseases.[22,32,33] Considering that the plasma protein binding of linezolid is approximately 30%, plasma levels of free linezolid were above the measured minimum inhibitory concentration for each isolate during the entire dosing interval in almost all patients taking 600 mg per day. Among those taking 300 mg per day, the trough level was lower than the mean minimum inhibitory concentration in nine patients, including the two in whom linezolid resistance developed during treatment with that dose. The two doses provided

9/16=56%





NEJM 2012;367:1508

Lzd 용량: 2022 WHO guidelines

Table 1.3. PICO questions and decisions of the GDG panel

#	PICO	Population	Intervention	Comparator [data source]	Sub-PICO	Recommendation
3	Should BPaL regimens with lower linezolid exposure (dose or duration) be used instead of the original BPaL regimen in patients who are eligible for BPaL regimen?	MDR/RR-TB or pre-XDR-TB	BPaL (1 200 mg – 9 weeks)	BPaL 1200–26 [ZeNix][a]	3.2	Conditional against the intervention
			BPaL (600 mg – 26 weeks)		3.3	Conditional for the intervention
			BPaL (600 mg – 9 weeks)		3.4	Conditional against the intervention
			BPaL (600 mg then 300 mg)		3.5	No recommendation because the panel felt that comparison of data from different trials was less reliable and indirect

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

However, when the patient has a recurrence (<3%), they were shown to have acquired increased bedaquiline MIC that could be considered resistance. Therefore, I would recommend to keep the patient on 600mg throughout the 6 months when using BPaL without moxifloxacine.

All the best in helping patients who really deserve much shorter, safe and effective treatment.

Regards

Bern

Dr Bern-Thomas Nyang'wa
Medical Director
Médecins Sans Frontières

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

Remarks

1. The 9-month all-oral regimen consists of bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide and clofazimine (for 4 months, with the possibility of extending to 6 months if the patient remains sputum smear positive at the end of 4 months), followed by treatment with levofloxacin/ moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months). Ethionamide can be replaced by 2 months of linezolid (600 mg daily).
2. A 9-month regimen with linezolid instead of ethionamide may be used in pregnant women, unlike the regimen with ethionamide.
3. This recommendation applies to:
   a. people with MDR/RR-TB and without resistance to fluoroquinolones;
   b. patients without extensive TB disease[22] and without severe extrapulmonary TB;[23]
   c. patients with less than 1 month exposure to bedaquiline, fluoroquinolones, ethionamide, linezolid and clofazimine; when exposure is greater than 1 month, these patients may still receive this regimen if resistance to the specific medicines with such exposure has been ruled out;
   d. all people regardless of HIV status;
   e. children (and patients in other age groups) who do not have bacteriological confirmation of TB or resistance patterns but who do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB).

2022 Curry guidelines

The 2022 WHO standardized, 9-month regimen consists of:

- **Intensive Phase:** $BDQ_{(6\ months)}$ + [(MXF or LFX) + CFZ + PZA + EMB + $INH^{HD}]_{(4\ months)}$ + LZD (600 mg)$_{(2\ months)}$ or ETA $_{(4\ months)}$; *may extend 4 month drugs to 6 months if smear positive at the end of 4 months.*
- **Continuation Phase:** [(MXF or LFX) + CFZ + PZA + EMB]$_{(5\ months)}$

The WHO standardized 9-month regimen has **limited application in higher-resource countries** due to the eligibility criteria that excludes use if documented resistance is found to any drug used in the regimen (exception for high-dose INH).

Treatment outcomes 24 months after initiating short, all-oral bedaquiline-containing or injectable-containing rifampicin-resistant tuberculosis treatment regimens in South Africa: a retrospective cohort study

Norbert Ndjeka, Jonathon R Campbell, Graeme Meintjes, Gary Maartens, H Simon Schaaf, Jennifer Hughes, Xavier Padanilam, Anja Reuter, Rodolfo Romero, Farzana Ismail, Martin Enwerem, Hannetjie Ferreira, Francesca Conradie, Kogieleum Naidoo*, Dick Menzies**

Lancet Infect Dis 2022; 22: 1042–51

Published Online

Summary

Background There is a need for short and safe all-oral treatment of rifampicin-resistant tuberculosis. We compared outcomes up to 24 months after treatment initiation for patients with rifampicin-resistant tuberculosis in South Africa treated with a short, all-oral bedaquiline-containing regimen (bedaquiline group), or a short, injectable-containing

Final treatment outcomes 24 months post-initiation‡

Treatment success	478 (69%)	396 (57%)	..
Treatment failure and recurrence	4 (1%)	17 (2%)	..
Died	162 (24%)	199 (28%)	..
Lost to follow-up	44 (6%)	87 (12%)	..

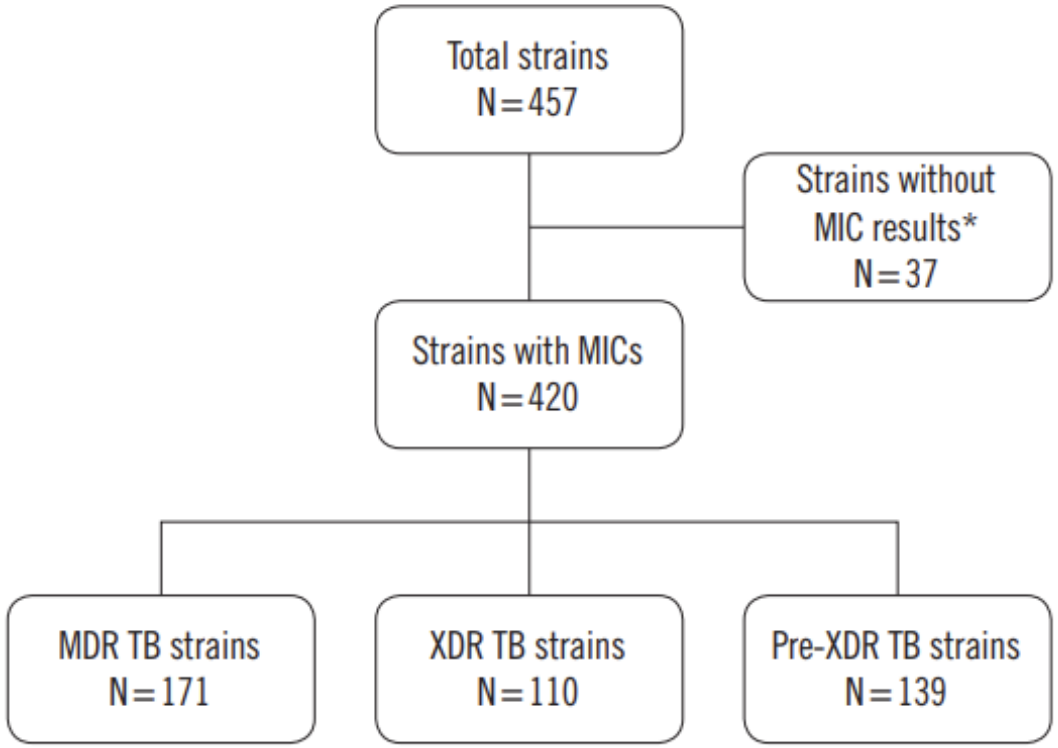
Phenotypic drug resistance rates in Korea

All patients with MDR-TB who were submitted for approval for the use of new TB drugs, including bedaquiline and delamanid.

Duration : 2016.9 – 2019.12

Drug	Total
Number	768
Ethambutol	**66%**
Pyrazinamide	**64%**
Kanamycin	21%
Amikacin	17%
Cycloserine	5%
Prothionamide	19%
Para-aminosalicylic acid	18%
Levofloxacin	**38%**
Moxifloxacin	**36%**
Linezolid*	3/466 (0.6)
Bedaquiline*	1/172 (0.6)
Delamanid*	7/172 (4.1)

신약과 Lzd 내성 발생



Ann Lab Med **2018**;38:563-568

- **Bdq: 48 (11%)** were resistant, based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint of 0.25 mg/L.
- **Dlm: 41 (10%)** were resistant based on the critical concentration of 0.2 mg/L, as suggested by Otsuka Pharmaceutical

Bdq, Dlm, Lzd 내성 확인 가능?

AFB sensitivity 나406 D6013003

◆ AFB culture 결과

◆ 약제 감수성 검사 결과

※ 대조배지상 발육정도 3+

약제명	기준농도 (㎍/mL)	균발육정도	판정결과	약제명	기준농도 (㎍/mL)	균발육정도	판정결과
INH	0.2	3+	R	TH	40.0	-	S
RMP	40.0	3+	R	CS	30.0	-	S
SM	10.0	-	S	OFLX	4.0	-	S
EMB	2.0	-	S	PAS	1.0	-	S
KM	30.0	-	S	CPM	40.0	-	S
RBT	20.0	3+	R	MXF	1.0	-	S
AMK	30.0	-	S	LFX	2.0	-	S

Pyrazinamidase Test (S) ※S : 감수성, R : 내성

*균발육표시법

- : No growth, 1+ : ≤100 colony, 2+ : 101-200 colony, 3+ : 201-500 colony, 4+ : 3+이상 융합 발육

◆ 결핵균 감별검사 : *Mycobacterium tuberculosis*

검사자: 전희선 M.T.(31647) 보고자: 이규택 M.D.(670) 오예진 M.D.(1062) [1 / 1

Pa 간독성

Table 4 Safety data*

	DS-TB					RR-TB
	Total† ($n = 271$) *n* (%)	HRZE ($n = 68$) *n* (%)	$4Pa_{100}MZ$‡ ($n = 65$) *n* (%)	$4Pa_{200}MZ$‡ ($n = 71$) *n* (%)	$6Pa_{200}MZ$‡ ($n = 67$) *n* (%)	$6Pa_{200}MZ$‡ ($n = 13$) *n* (%)
Peak ALT result						
>3xULN	40 (14.8)	5 (7.4)	9 (13.8)	12 (16.9)	14 (20.9)	1 (7.7)
>5xULN	27 (9.9)	4 (5.9)	4 (6.2)	9 (12.6)	10 (14.9)	1 (7.7)
>10xULN	16 (5.9)	2 (2.9)	4 (6.2)	5 (7.0)	5 (7.5)	1 (7.7)
Mean change from baseline in QTcF (95% CI)#	—	9.2 (5.4–12.9)	13.3 (10.0–16.6)	17.6 (13.8–21.5)	18.3 (15.1–21.5)	13.7 (2.5–23.8)
Deaths	12 (4.4)	2 (2.9)	4 (6.2)	3 (4.2)	3 (4.5)	1 (7.7)

Table 5 Deaths in the trial

Treatment group*†	Trial day (post-randomisation)	Trial status	Cause of death	Relationship of adverse event(s) to trial drug‡
DS-TB $4Pa_{100}MZ$	Day 482	Follow-up	Fell down from bulldozer at work	Not related
	Day 305	Follow-up	Haematemesis	Not related
	Day 39	On treatment	Fulminant liver failure	Possibly related
	Day 436	Follow-up	Massive haemoptysis	Not related
DS-TB $4Pa_{200}MZ$	Day 343	Follow-up	Sepsis	Not related
	Day 28	On treatment	Hepatotoxicity	Possibly related
	Day 34	On treatment	Liver failure with hepatic encephalopathy	Possibly related

INT J TUBERC LUNG DIS 2021;25:305–314

요약

1. Pretomanid의 현재 요양급여 기준으로는 일부 환자에서만 사용 가능하다.
2. 경구 단기 약제 조합 연구의 대상자 수가 너무 적다.
3. 퀴놀론 내성 결핵에서 BPaL 효과는 더 많은 연구가 필요하다.
4. Lzd 용량 및 기간에 대한 추가 연구가 필요하다.
5. 신약과 Lzd 내성 발생에 대한 철저한 감시가 필요하다.
6. Pa의 안전성에 대한 관찰 및 추가 연구가 필요하다.

결론 및 제시

- 결론: 현재 우리나라에서는 경구 단기치료를 당장 적용하기는 어렵다.
- Pa의 요양급여기준 개정이 시급하다.
- 퀴놀론 노출이 없었던 초치료 RR/MDR-TB
  - Xpert MTB/RIF 또는 mDST에서 RR 확인 → BPaLM
  - FQ 내성 확인 → 개별 장기 치료
- 다제내성 결핵의 재치료 또는 과거 퀴놀론 노출 MDR-TB

  → 개별 장기 치료
- Bdq, Pa 사용이 어려운 Z 감수성 환자

  → 9개월 Dlm, Lzd, Lfx, Z
- 다제내성 결핵은 전문의료기관에서