Treatment Shortening: Drug Resistant Tuberculosis

Barbara J Seaworth, MD

April 2, 2024

New Directions in TB
April 1 – 2, 2024
Houston, Texas

Barbara J Seaworth, MD has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity

Treatment Shortening part # 1 Drug Resistant Tuberculosis

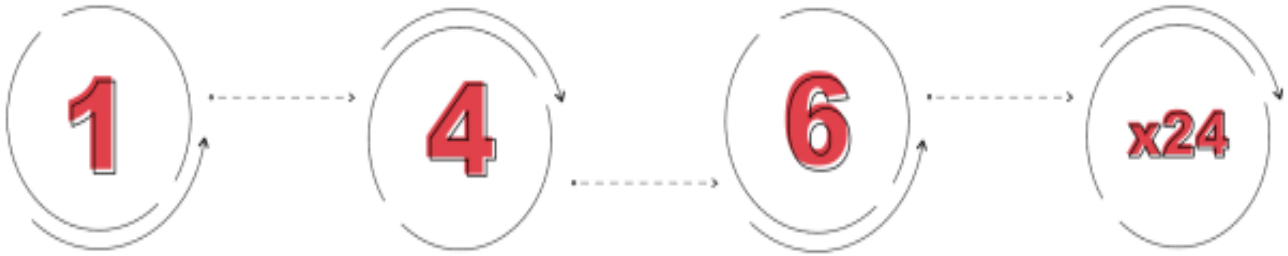
Barbara J Seaworth M.D.
Heartland National TB Center

1/4/6x24

A Campaign to Rally Energy, Political Will & Funding to End TB

The 1/4/6x24 Campaign's name comes from its central demand:

that countries and other duty bearers take action to implement the shortest available regimens – one month or once-weekly for TB prevention, four months for drug-sensitive TB, and six months for drug-resistant TB — by the end of 2024.



one-month or once weekly treatment regimens for TB prevention.

four-month treatment regimens for drug-sensitive TB.

six-month treatment regimens for drug-resistant TB.

by the end of 2024.

A deadline for having in place the "staff, stuff, space, systems, and support" needed for shorter TB regimens to be made accessible to everyone, everywhere as a human right.

& priority research to extend the benefits of short treatment and prevention regimens to any groups who cannot currently use them due to data gaps or research exclusions.

TAG (Treatment Action Group)
TB CAG (Global TB Community Advisory Group)

What is Nearly New (where we are now)?

- Six Month – **all oral** - Short Course regimens for Rifampin Resistant and MDR TB
  - BPaL plus moxifloxacin or **BPaLM** x 26 weeks
    - WHO recommends (2022) for all RR or MDR who are candidates and not resistant to fluoroquinolones
  - **BPaL** x 26 weeks
    - FDA approval for Pretomanid as part of the BPaL regimen 2019

B = Bedaquiline
Pa = Pretomanid*
L = Linezolid 600 mg once daily
M = Moxifloxacin 400 mg once daily
*newest medication – August 2019 FDA approval as BPaL

BPaL Regimen (Nix Trial)

Bedaquiline-Pretomanid-Linezolid


The NEW ENGLAND JOURNAL of MEDICINE

MARCH 5, 2020

Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

Francesca Conradie, M.B., B.Ch., Andreas H. Diacon, M.D., Nosipho Ngubane, M.B., B.Ch., Pauline Howell, M.B., B.Ch., Daniel Everitt, M.D., Angela M. Crook, Ph.D., Carl M. Mendel, M.D., Erica Egizi, M.P.H., Joanna Moreira, B.Sc., Juliano Timm, Ph.D., Timothy D. McHugh, Ph.D., Genevieve H. Wills, M.Sc., Anna Bateson, Ph.D., Robert Hunt, B.Sc., Christo Van Niekerk, M.D., Mengchun Li, M.D., Morounfolu Olugbosi, M.D., and Melvin Spigelman, M.D., for the Nix-TB Trial Team*

Bedaquiline 400 mg (14 days); 200 mg M/W/F
Pretomanid 200 mg daily
Linezolid 1200 mg daily

All Oral
Open Label – Observational
*109 patients
65% XDR
51% HIV +
84% cavitary on CXR
Unresponsive to treatment or intolerant

Favorable Treatment Outcomes
XDR TB 89%
MDR TB 92%
Relapse
XDR TB: 1/MDR TB: 1

Time to Culture Negative: MDR vs XDR TB

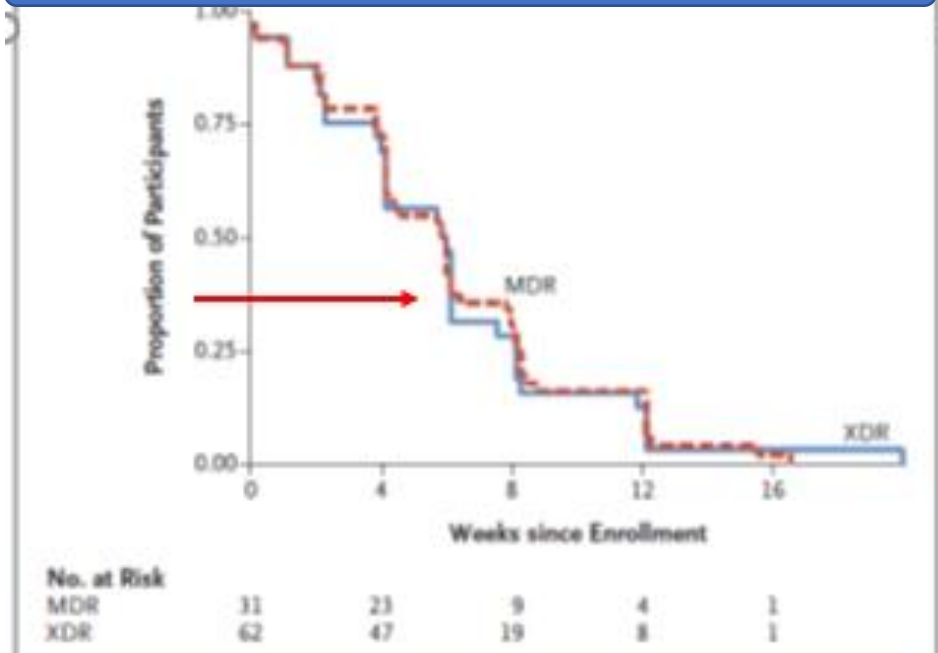


Figure 2. Time to Culture-Negative Status among Patients Who Were Positive at Baseline (Intention-to-Treat Population).

BUT …… BPaL Adverse Events

- Adverse Effects:
  - HIV negative: 100%
  - HIV positive: 100%
- Adverse Effects by Linezolid dose
- 1200 mg once daily: 100%
- 600 mg twice daily: 100%

Myelosuppression 48%
Peripheral neuropathy 81%

ZeNIX: Linezolid Optimization Trial
Patients with MDR or XDR TB
Treatment Failure or Intolerant

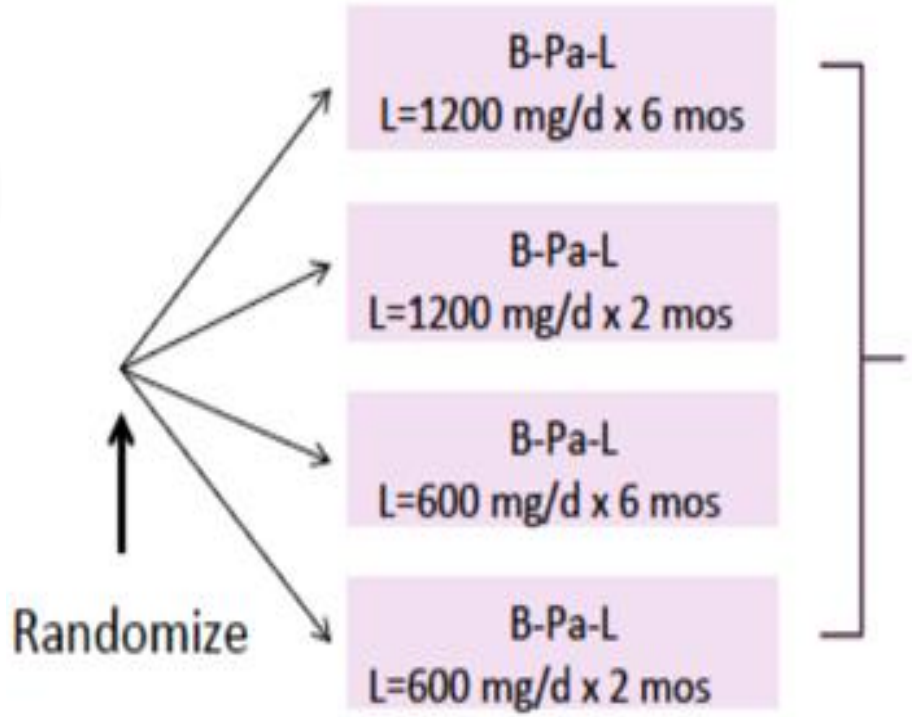
NEJM September 2022

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis

F. Conradie, T.R. Bagdasaryan, S. Borisov, P. Howell, L. Mikiashvili, N. Ngubane, A. Samoilova, S. Skornykova, E. Tudor, E. Variava, P. Yablonskiy, D. Everitt, G.H. Wills, E. Sun, M. Olugbosi, E. Egizi, M. Li, A. Holsta, J. Timm, A. Bateson, A.M. Crook, S.M. Fabiane, R. Hunt, T.D. McHugh, C.D. Tweed, S. Foraida, C.M. Mendel, and M. Spigelman, for the ZeNix Trial Team*



6 months of treatment

30 XDR TB/group and up to 15 pre-XDR or treatment non-response or intolerant MDR TB
45 -46 patients/group

Bedaquiline dose
200 mg daily x 8 weeks
100 mg daily x 18 weeks

ZeNIX: Linezolid Optimization Trial

MDR or XDR TB Treatment Failure or Intolerant

Safety 600 mg x 26 wk.

24% Peripheral neuropathy

2% Myelosuppression

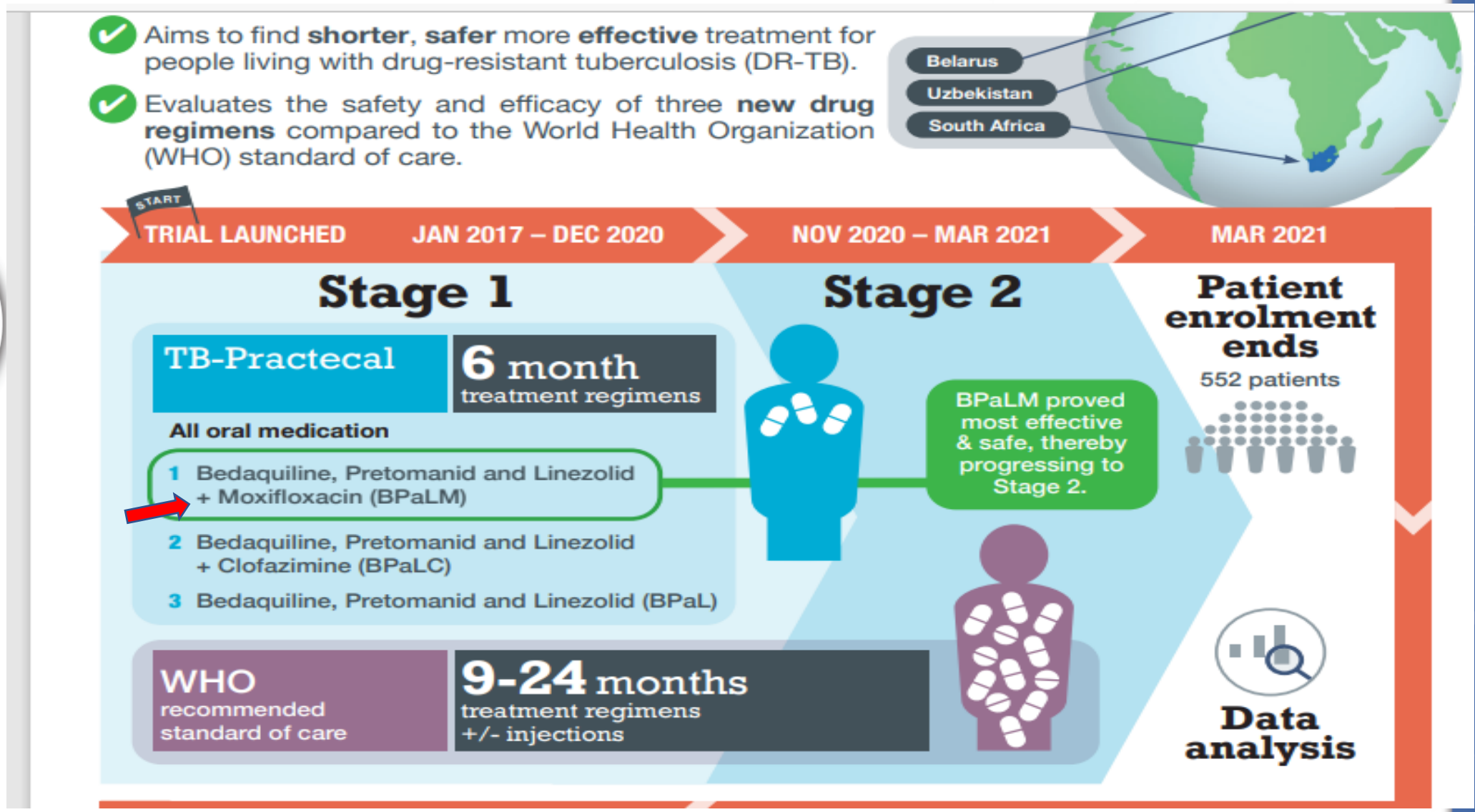
- Only 13% required Linezolid dose modification at 600 mg/day dose

Efficacy

- LZD - 1200mg x 6 mo. - 93%
- LZD - 1200 mg x 9 wks. - 89%
- **LZD - 600 mg x 6 mo. - 91%**
- LZD - 600 mg x 9 wks. – 84%

TB-Practecal Clinical Trial

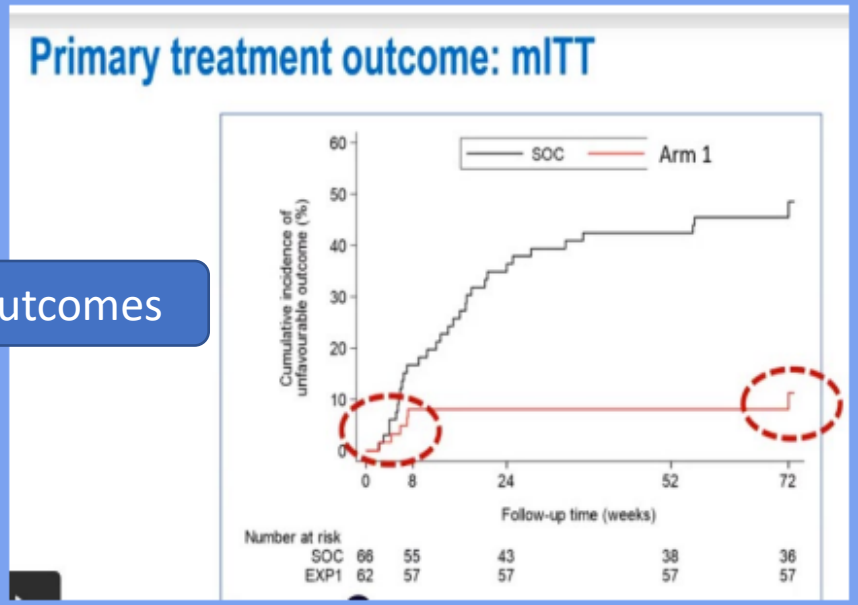
randomized, controlled



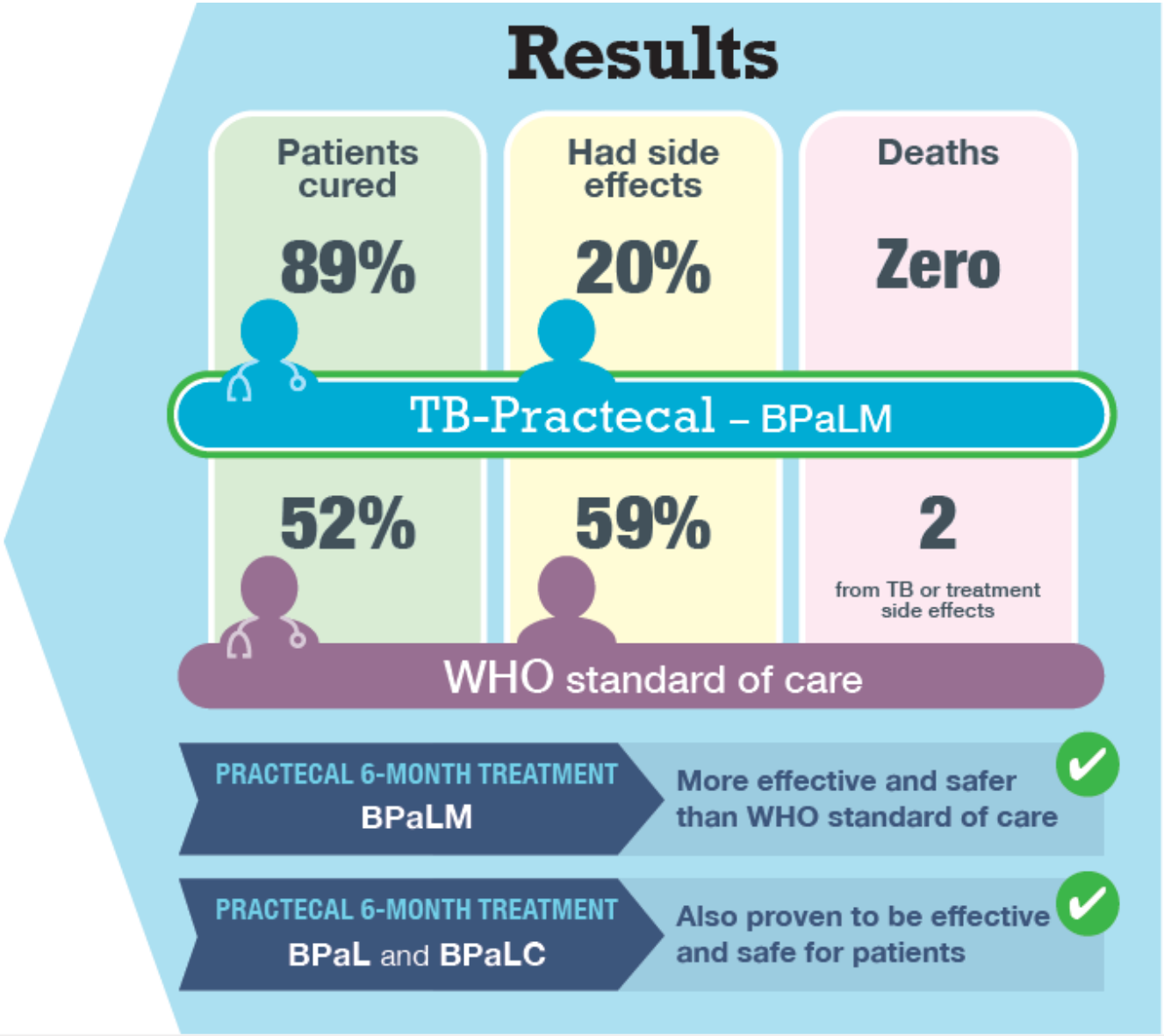
TB-PRACTECAL - Efficacy

- Arm 1: BPaLM: 89% favorable
- Arm 2: BPaLC: 81% favorable
- Arm 3: BPaL(modified): 77% favorable
- Arm 4: SOC: 52% favorable

Cumulative incidence of unfavorable outcomes



TB PRACTECAL



TB-Practecal

BPaLM vs BPaLC vs BPaL vs Standard of Care

PIPELINE REPORT 2022

Study Name (Type of TB; Sample Size)	Study Arms Experimental Regimens [Control Regimen]	Key Findings		
TB-PRACTECAL NCT02589782 (RR-/MDR-TB Pre-XDR-TB; 552)	(a) 6BPaLzM (b) 6BPaLzC (c) 6BPaLz (d) [9–20mo local SOC]	**Primary Efficacy Outcome:** **All three bedaquiline- and pretomanid-based regimens demonstrated non-inferiority and an improved safety profile compared with the standard-of-care group (mITT).** The NI margin was 12%.		
		Unfavorable outcomes:		**Risk difference, experimental - control (95% confidence interval)**
		(a)	7 (11%)	-37 (-53 to -22)
		(b)	12 (19%)	-30 (-45 to -14)
		(c)	14 (23%)	-25 (-41 to -9)
		(d)	32 (48%)	NA
		Primary Safety Outcome: **The incidence of AEs was lower in the groups receiving bedaquiline- and pretomanid-based regimens.**		
			Any serious or grade 3+ AEs	Deaths
		(a)	14 (19%)	0 (0%)
		(b)	23 (32%)	1 (2%)
		(c)	15 (22%)	0 (0%)
		(d)	43 (59%)	2 (3%)

Nyang'wa BT, Berry C, Kazounis E, et al. A 24-week, all-oral regimen for rifampin-resistant tuberculosis. 2022 December 22. N Engl J Med;387:2331–2343. doi: 10.1056/NEJMoa2117166.

Short course treatment options for drug resistant TB

6 – 9 months

All oral

Core drugs:

Bedaquiline

Pretomanid

Linezolid

Moxifloxacin

- **BPaL** 6 months; may extend to 9
- **BPaLM** 6 months; may extend to 9
- **BDQ, LZD (2), Moxi core** 9 months
  - WHO includes in regimen:
    - BDQ, LZD (2), Moxi, high dose INH, EMB, PZA, Clofazimine x 4-6 months
    - moxifloxacin, clofazimine, EMB, PZA x 4 months
  - U.S. would likely include in regimen:
    - BDQ, LZD, Moxi throughout 9 – 12 months plus
    - Clofazimine or PZA
    - Cycloserine

(B)BDQ = bedaquiline, Pa = pretomanid, (L) LZD = linezolid, (M) Moxi = moxifloxacin

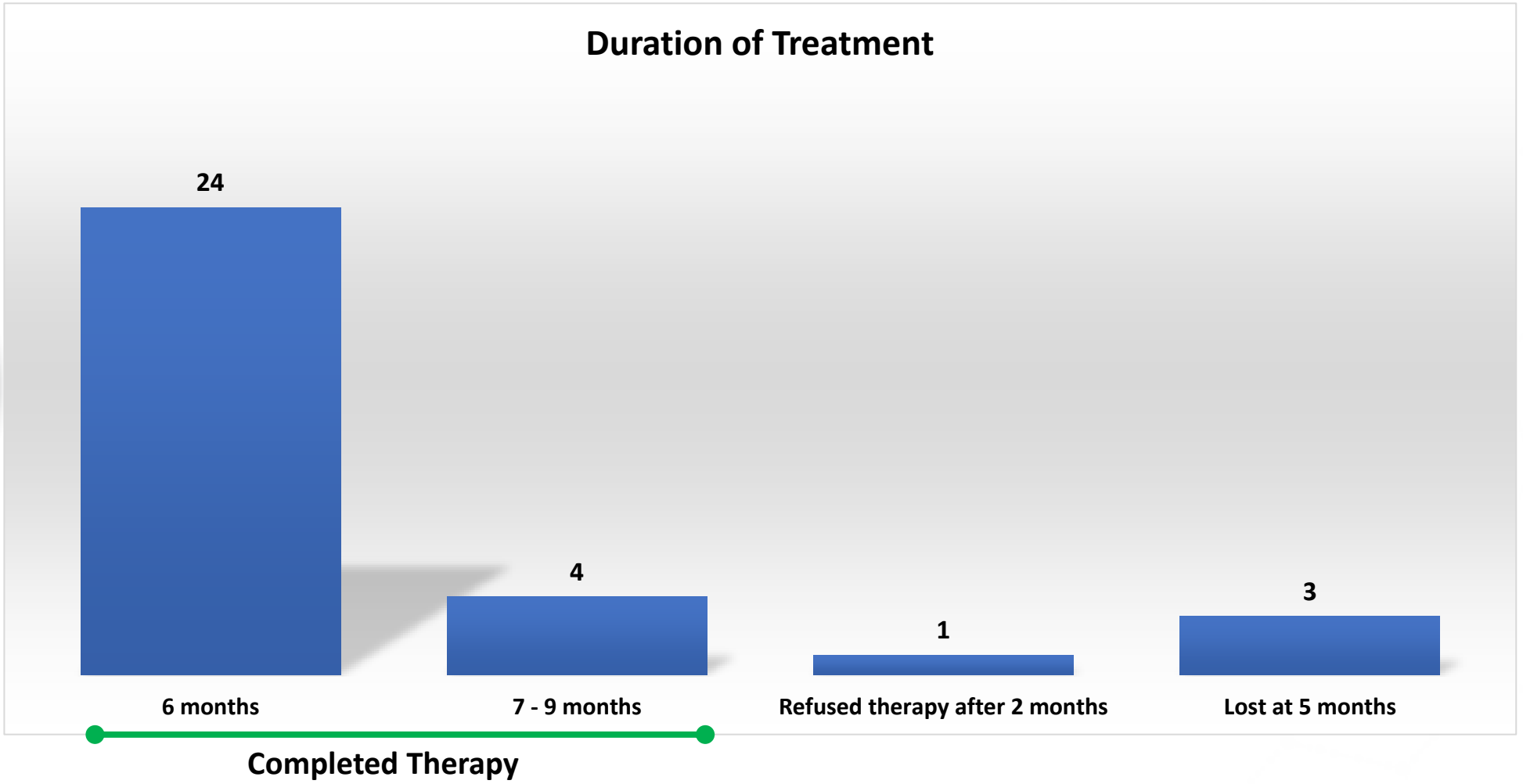
Characteristics of Drug Resistant TB treated in Texas with BPaL and BPaLM 2021 – 6/2023

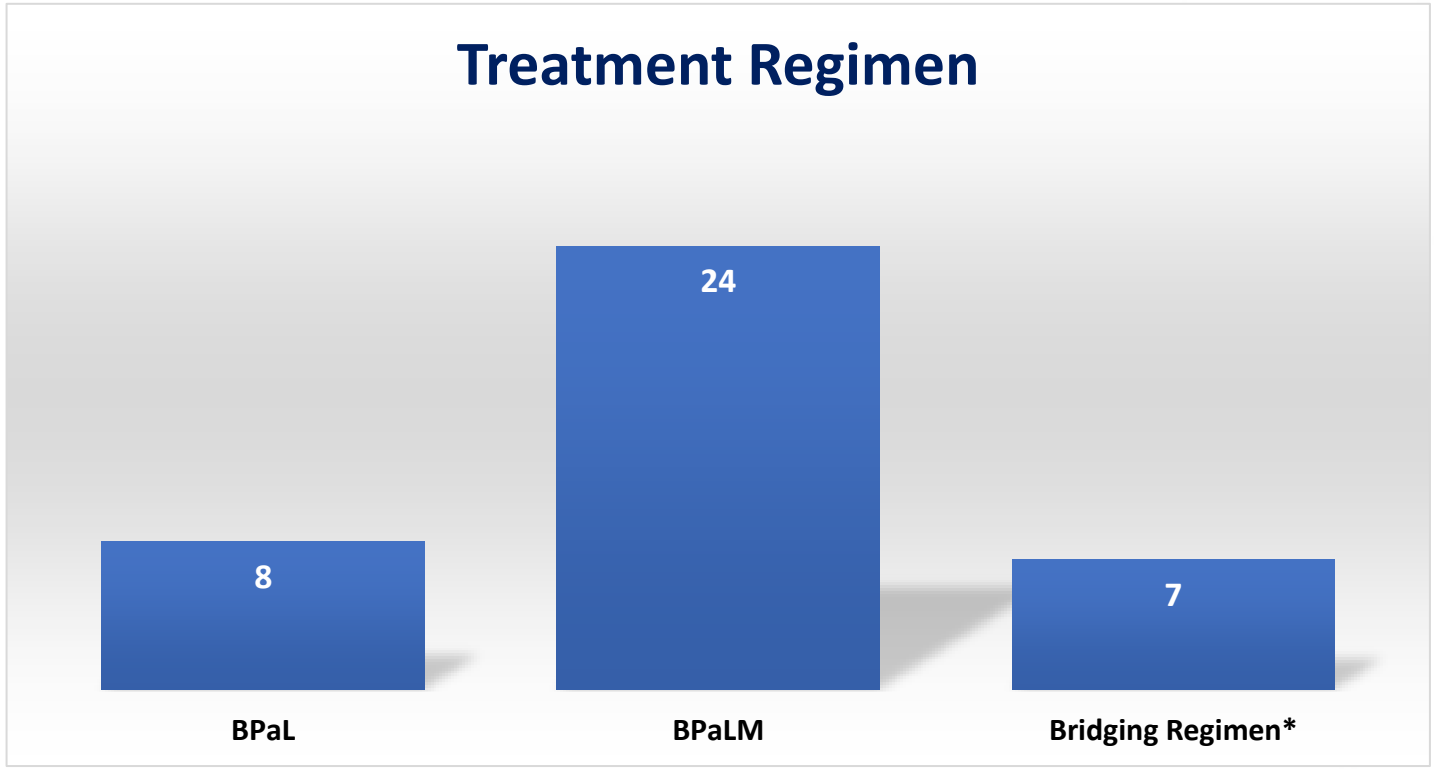
Diagnosis	
Pulmonary TB (PTB)	23
PTB + Extra Pulmonary TB*	9

First Case 8/3/2021

 # starting treatment
2021 (5)
2022 (16)
2023 (11)-
who finished treatment in 2023

Age at Diagnosis	
0 – 17	1
18 – 39	14
40 – 59	6
60 – 70	5
70 or greater	6


Duration of Treatment
24
4
1
3
6 months
7 - 9 months
Refused therapy after 2 months
Lost at 5 months
Completed Therapy



- **Bridging regimen** – Adequate treatment regimen for RR or MDR/pre-XDR or XDR TB prior to start of BPaL or BPaLM
- **BPaLM** (Bedaquiline, Pretomanid, Linezolid and Moxifloxacin)
- **BPaL** (Bedaquiline, Pretomanid, Linezolid)

Management of Patient When MDR/RR TB is Suspected/Identified

- **Stop RIPE treatment**
  - Contact a consultant to help with an empiric (bridging) regimen pending more information

- **Submit specimen to CDC** for Molecular Detection of Drug Resistance (MDDR – sequencing) to confirm rifampin resistance testing once Xpert identifies rifampin resistance

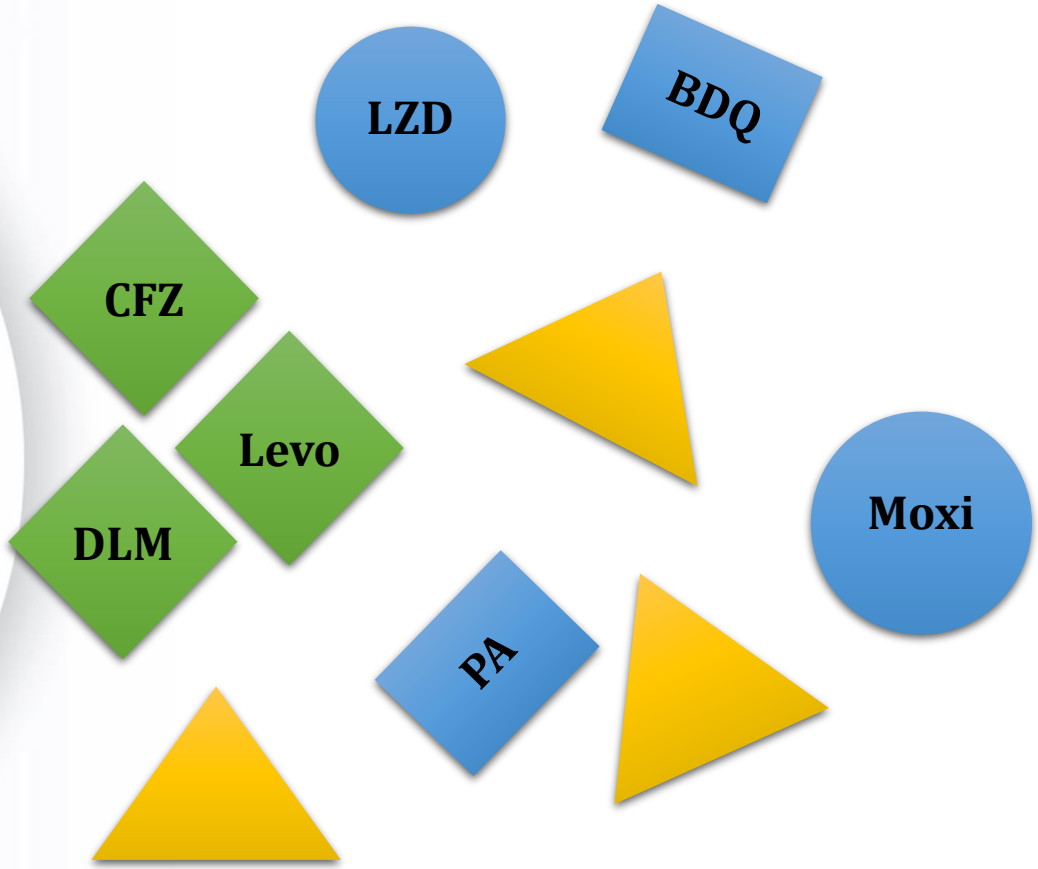
- Obtain initial assessments needed to decide on the initial regimen
  - LAB: CBC, CMP, calcium, magnesium, potassium, TSH
  - Assess for visual acuity, Ishihara, peripheral neuropathy
  - EKG
  - Other medical comorbidities/medications
- **Strongly consider bridging regimen (results of MDDR > 7-10 days)**

What else are we waiting for?

- **Expanded use of BPaLM or BPaL**
  - Children < 14 currently being studied
  - Pregnancy – currently being studied
  - CNS TB – no studies underway but some limited evidence that bedaquiline and pretomanid enter CNS
  - Other types of extra-pulmonary/ extensive TB disease
  - TB in special populations
    - Elderly
    - Transplants
    - Chemotherapy/Dialysis/Immunosuppressive medications
- **New drugs and regimens**
  - Reports of BDQ resistance and BPaL/BPaLM relapse

WHAT IS NEW?

TB Medication Soup Bowl



New MDR
FDA Approved

Repurposed Drug –
Essential Components

MDR - others

Investigational Drugs

22 new or investigational compounds
11 from new class or new mechanism
11 potentially advantage alterations to existing drugs

BDQ – bedaquiline CFZ – Clofazimine DLM – delaminid Levo – levofloxacin LZD – linezolid Moxi – moxifloxacin PA – pretomanid

endTB

evaluates safety of treatment regimens containing both BDQ and Delamanid

Clinical Infectious Diseases

MAJOR ARTICLE

Safety of Treatment Regimens Containing Bedaquiline and Delamanid in the endTB Cohort

Catherine Hewison,[1,a,©] Uzma Khan,[2,a] Mathieu Bastard,[3] Nathalie Lachenal,[4] Sylvine Coutisson,[4] Elna Osso,[5] Saman Ahmed,[6] Palwasha Khan,[2] Molly F. Franke,[5] Michael L. Rich,[5,7] Francis Varaine,[1] Nara Melikyan,[3] Kwonjune J. Seung,[5,7] Malik Adenov,[8] Sana Adnan,[9] Narine Danielyan,[10] Shirajul Islam,[11] Aleeza Janmohamed,[6] Hayk Karakozian,[12] Maureen Kamene Kimenye,[13] Ohanna Kirakosyan,[14] Begimkul Kholikulov,[15] Aga Krisnanda,[16] Andargachew Kumsa,[17] Garmaly Leblanc,[18] Leonid Lecca,[19] Mpiti Nkuebe,[20] Shahid Mamsa,[9] Shrivani Padayachee,[21] Phone Thit,[22] Carole D. Mitnick,[5,7,b] and Helena Huerga[3,b]; on behalf of the endTB Study Observational Study Team

[1]Medical Department, Médecins Sans Frontières, Paris, France; [2]Interactive Research and Development Global, Singapore, Singapore; [3]Field Epidemiology Department, Epicentre, Paris, France; [4]Pharmacovigilance Unit, Médecins Sans Frontières, Geneva, Switzerland; [5]Partners In Health, Boston, Massachusetts, USA, and Department of Global Health and Social Medicine, Harvard Medical School, Boston, Massachusetts, USA; [6]Interactive Research and Development, Karachi, Pakistan; [7]Brigham and Women's Hospital, Boston, Massachusetts, USA; [8]National Scientific Center of Phthisiopulmonology, MOH RK (NSCP MOH RK), Almaty, Kazakhstan; [9]Indus Health Network, Karachi, Pakistan; [10]Medical Department, Médecins Sans Frontières, Tbilisi, Georgia; [11]Interactive Research and Development, Dhaka, Bangladesh; [12]Medical Department, Médecins Sans Frontières, Bishkek, Krygystan; [13]National Tuberculosis Program, Nairobi, Kenya; [14]Medical Department, Médecins Sans Frontières, Yerevan, Armenia; [15]Medical Department, Médecins Sans Frontières, Minsk, Belarus; [16]Aga Krisnanda, Interactive Research and Development, Jakarta, Indonesia; [17]Partners In Health, Addis Ababa, Ethiopia; [18]Zanmi Lasante, Cange, Haiti; [19]Socios En Salud Sucursal Peru, Lima, Peru; [20]Partners In Health, Maseru, Lesotho; [21]Interactive Research and Development, Durban, South Africa; and [22]Medical Department, Médecins Sans Frontières, Yangon, Myanmar

Background. Safety of treatment for multidrug-resistant tuberculosis (MDR/RR-TB) can be an obstacle to treatment completion. Evaluate safety of longer MDR/RR-TB regimens containing bedaquiline and/or delamanid.

Methods. Multicentre (16 countries), prospective, observational study reporting incidence and frequency of clinically relevant adverse events of special interest (AESIs) among patients who received MDR/RR-TB treatment containing bedaquiline and/or delamanid. The AESIs were defined a priori as important events caused by bedaquiline, delamanid, linezolid, injectables, and other commonly used drugs. Occurrence of these events was also reported by exposure to the likely causative agent.

Results. Among 2296 patients, the most common clinically relevant AESIs were peripheral neuropathy (26.4%), electrolyte depletion (26.0%), and hearing loss (13.2%) with an incidence per 1000 person months of treatment, 1000 person-months of treatment 21.5 (95% confidence interval [CI]: 19.8–23.2), 20.7 (95% CI: 19.1–22.4), and 9.7 (95% CI: 8.6–10.8), respectively. QT interval was prolonged in 2.7% or 1.8 (95% CI: 1.4–2.3)/1000 person-months of treatment. Patients receiving injectables (N = 925) and linezolid (N = 1826) were most likely to experience events during exposure. Hearing loss, acute renal failure, or electrolyte depletion occurred in 36.8% or 72.8 (95% CI: 66.0–80.0) times/1000 person-months of injectable drug exposure. Peripheral neuropathy, optic neuritis, and/or myelosuppression occurred in 27.8% or 22.8 (95% CI: 20.9–24.8) times/1000 patient-months of linezolid exposure.

Conclusions. AEs often related to linezolid and injectable drugs were more common than those frequently attributed to bedaquiline and delamanid. MDR-TB treatment monitoring and drug durations should reflect expected safety profiles of drug combinations.

Clinical Trials Registration. NCT03259269.

Keywords. MDR-TB; adverse events; new drugs; QT prolongation; linezolid.

The treatment for multidrug-resistant/rifampin-resistant tu- events (AEs) experienced by patients receiving these mul-

endTB 9 months

BDQ or Delamanid – no pretomanid

Study Name	Experimental Arms [Control]	For Treatment of	Number of Participants	Phase	Status [Est. Completion Date]
Drug-Resistant TB					
endTB NCT02754765	9BLzMZ 9BLzLxCZ 9BLzLxDZ 9DLzLxCZ 9DMCZ [9–20mo SOC]	MDR-TB	754	III	Fully enrolled [Sept 2023]

end TB

Non-inferior to SOC

Trial regimens	Bedaquiline	Delamanid	Clofazimine	Linezolid	Fluoroquinolone	Pyrazinamide
9BLMZ	B			L	M	Z
9BCLLfxZ	B		C	L	Lfx	Z
9BDLLfxZ	B	D		L	Lfx	Z
9DCLLfxZ		D	C	L	Lfx	Z
9DCMZ		D	C		M	Z
Control	Standard of care for the treatment of rifampicin-resistant and fluoroquinolone-susceptible tuberculosis. Composed according to latest World Health Organization guidelines, as they evolved during the trial. This group included mostly participants treated with the 18-month conventional regimen.					

Superior

Figure **1**. *Composition of endTB trial regimens*

B denotes bedaquiline, L linezolid, M moxifloxacin, Z pyrazinamide, C clofazimine, Lfx levofloxacin, D delamanid

This give may give an option other than older individualized regimen when isolate is resistant to or patient is intolerant to Bedaquiline - 9CLLfxZ

endTB

PIPELINE REPORT 2023

Table 1. Key Findings from Recently Completed Treatment-Shortening Trials

Study Name [Type of TB; Sample Size]	Study Arms Experimental Regimens [Control Regimen]	Key Findings
endTB NCT02754765 (MDR-TB, N=754)	(a) 9BLzMZ (b) 9BLzLxCZ (c) 9BDLzLxCZ (d) 9DLzLxCZ (e) 9DMCZ (f) [9–20mo local SOC]	**Primary Efficacy Outcome:** **Three of the five nine-month endTB regimens (a, b, c) demonstrated noninferiority to the SOC (mITT and PP analyses). Regimen b also demonstrated superiority.** The NI margin was 12%.

Met margin of non-inferiority

superior

Favorable outcomes (mITT):			Risk difference, experimental - control (95% confidence interval)
(a)	105/118 (89.0%)	89	8.3 (-0.8 to 17.4)
(b)	104/115 (90.4%)	90.4	9.8 (0.9 to 18.7)
(c)	104/122 (85.2%)	85.2	4.6 (-4.9 to 14.1)
(d)	93/118 (78.8%)	78.8	-1.9 (-12.1 to 8.4)
(e)	89/104 (85.6%)		4.9 (-4.9 to 14.7)
(f)	96/119 (80.7%)		NA

Primary Safety Outcome:

The nine-month regimens had similar safety to the SOC regimen.

Similar safety

	Any grade 3 or 4 AEs	Any serious AEs	Deaths
(a)	69 (54.8%)	18 (14.3%)	3 (2.4%)
(b)	68 (55.7%)	16 (13.1%)	1 (0.8%)
(c)	78 (61.4%)	20 (15.8%)	3 (2.4%)
(d)	75 (60.5%)	18 (14.5%)	4 (3.2%)
(e)	72 (60.0%)	20 (16.7%)	2 (1.7%)
(f)	79 (62.7%)	21 (16.7%)	2 (1.6%)

Mitnick C, Khan U, Guglielmetti L, et al. SP01 Innovation to guide practice in MDR/RR-TB treatment: efficacy and safety results of the endTB trial. Presented at: Union World Conference on Lung Health. 2023 November 15. https://theunion.floq.live/event/worldconf2023/symposia?objectClass=timeslot&objectId=64ef5819e0400915b209e22f&type=detail.

81.5% of control regimen conformed to WHO guidance

BEAT Tuberculosis (South Africa)

6BDLz (Lx, C or both) no pretomanid

Allows treatment during pregnancy and for children < 14

Study Name (Type of TB; Sample Size)	Study Arms Experimental Regimens [Control Regimen]	Key Findings
BEAT Tuberculosis NCT04062201 (RR-/MDR-TB, Pre-XDR; 374 enrolled, 199 included in interim analysis)	**87% favorable outcome** (a) 6BDLz (Lx, C, or both) (b) [9–12mo SOC]	**Primary Efficacy Outcome:** **The six-month bedaquiline- and delamanid-based regimen had similar efficacy to the standard-of-care regimen (ITT).** The NI margin was 10%.

Unfavorable outcomes:		Risk difference, experimental-control (95% confidence interval)
(a)	13 (13%)	-1.4 (-10.9 to 8.1)
(b)	14 (14%)	NA

Primary Safety Outcome:
The six-month bedaquiline- and delamanid-based regimen had similar safety to the standard-of-care regimen.

	Any grade 3 or 4 AEs	Any serious AEs	Deaths
(a)	49 (25.7%)	33 (17.3%)	7 (3.7%)
(b)	51 (27.9%)	31 (16.9%)	6 (3.3%)

Similar safety and efficacy
But compared to newer SOC

Conradie F, Phillips P, Badet T, et al. High rate of successful outcomes treating RR-TB with a delamanid-bedaquiline regimen in BEAT Tuberculosis: an interim analysis. Presented at the Union World Conference on Lung health during LBTB The Union/CDC late-breaker session on TB. 2022 November

BEAT-TB India 6 BDLzC (no Pretomanid)

BEAT-TB India
CTRI/2019/01/017310

(Pre-XDR-TB; 165; PLHIV not included)

(a) 6BDLzC

(b) [none]

Favorable outcome 91%

Primary Efficacy Outcome:
The six-month bedaquiline- and delamanid-containing regimen was efficacious, producing a favorable outcome among 91% of participants at treatment completion and 86% of participants six months later (mITT).

Unfavorable outcomes:		Risk difference, experimental-control (95% confidence interval)
(a)	14 (9%)	NA
(b)	NA	NA

Primary Safety Outcome:
The six-month bedaquiline- and delamanid-containing regimen was generally safe with most AEs easily identified and managed (e.g., anemia, neuropathy, skin hyperpigmentation).

	Any grade 3 or 4 AEs	Any serious AEs	Deaths
(a)	47 events	33 events	4 deaths
(b)	NA	NA	NA

Padmapriyadarsini C, Vohra V, Bhatnagar A, et al. Bedaquiline, delamanid, linezolid and clofazimine for treatment of pre-extensively drug-resistant tuberculosis. Clin Infect Dis. 2022 Jun 29:ciac528. doi: 10.1093/cid/ciac528.

MDR-END 9 DLzLxZ No BDQ or Pretomanid (Korea)

MDR-END
NCT02619994
(MDR-TB; 214; PLHIV not included)

(a) 9DLzLxZ
(b) [20mo IA-containing regimen]

Non – inferior to SOC but longer regimen with IA Favorable outcome 70.6%

Primary Efficacy Outcome:
The nine-month delamanid-based regimen demonstrated non-inferiority to a 20-month injectable-containing regimen–the standard of care in 2014 (mITT). The NI margin was -10%.

Unfavorable outcomes:		**Risk difference, experimental-control (95% confidence interval)**
(a)	25 (29.4%)	4.4 (-9.5 to ∞)
(b)	18 (25%)	NA

Primary Safety Outcome:
No statistically significant differences in safety were detected between arms.

	Any grade 3 or 4 AEs	Any serious AEs	Deaths
(a)	29 (36.7%)	20 (25.3%)	5 (6%)
(b)	26 (29.2%)	19 (21.3%)	2 (2%)

Mok J, Lee M, Kim DK, et al. 9 months of delamanid, linezolid, levofloxacin, and pyrazinamide versus conventional therapy for treatment of fluoroquinolone-sensitive multidrug-resistant tuberculosis (MDR-END): a multicentre, randomised, open-label phase 2/3 non-inferiority trial in South Korea. Lancet. 2022 Oct 29;400(10362):1522–1530. doi: 10.1016/S0140-6736(22)01883-9.

SimpliciTB - RIPE versus 4 months (drug susceptible) or 6 months BPaMZ(drug resistant)

Study Name (Type of TB; Sample Size)	Study Arms Experimental Regimens [Control Regimen]	Key Findings
SimpliciTB NCT03338621 (DS-TB; N=303) *Arm c was enrolled as an exploratory cohort (MDR-TB; N=152)	(a) 4BPaMZ (b) [2HRZE/4HR] (c) 6BPaMZ*	**Efficacy Outcomes:** **The four-month BPaMZ regimen failed to demonstrate noninferiority to the six-month SOC for DS-TB (mITT).** The NI margin was 12%.

Did not meet non-inferiority compared to HREZ

Highly potent but unfavorable outcomes
Hope when LZD not tolerated

Favorable outcomes:			Risk difference, experimental - control (95% confidence interval)
(a)	118/144 (81.9%)	81.9	10.27 (3.06 to 17.48)
(b)	134/144 (93.1%)	93.1	NA
(c)	111/133 (83.5%)	83.5	NA

Primary Safety Outcome:

The incidence of AEs was higher with 4BPaMZ compared to the 6-month standard of care regimen for DS-TB. A higher proportion of participants withdrew from treatment due to AEs (predominantly hepatotoxicity) in the 4BPaMZ arm.

	Any grade 3 or 4 AEs	Any serious AEs	Deaths
(a)	68 (45.3%)	17 (11.3%)	3 (2.0%)
(b)	61 (39.9%)	7 (4.6%)	1 (0.6%)
(c)	47 (31.5%)	16 (10.7%)	2 (1.3%)

Eristavi M, Variava E, Haraka F, et al. SimpliciTB Results and Hepatic Safety of Pretomanid Regimens +/1 Pyrazinamide [OA-109]. Presented at: 2023 Conference on Retroviruses and Opportunistic Infections during Oral Abstracts Session-02 TB and Hepatitis. 2023 February 20; Seattle, Washington.

- AE = adverse event; DS-TB = drug-sensitive TB; mITT = modified intention to treat; MDR-TB = multidrug-resistant TB; N = sample size; NA = not applicable; NI = noninferiority; PP = per protocol; RR-TB = rifampicin-resistant TB; SOC = standard of care
- Numbers at the beginning of each regimen or after the forward slash (for regimens with intensive and continuation phases) represent the duration of treatment in months, unless otherwise specified
- Letters represent the individual drugs comprising each regimen: B = bedaquiline, C = clofazimine, D = delamanid, E = ethambutol, H = isoniazid, Lx = levofloxacin, Lz = linezolid, M = moxifloxacin, Pa = pretomanid, R = rifampicin, Z = pyrazinamide

SimpliciTB - RIPE versus 4 months (drug susceptible) or 6 months BPaMZ(drug resistant)

- Method was to study in drug susceptible TB to get initial information and to look for alternative 4 month regimen
  - Regimen **highly potent - 2.93 x more likely to reach culture conversion at 56 days but….**
  - Failed to meet non-inferiority due to unfavorable outcomes
    - 10% withdrew
    - Hepatotoxicity – likely due to combination of PZA and Pretomanid
      - **Stand Trial** Pretomanid/Moxifloxacin/PZA stopped due to safety. Restart allowed but TB Alliance decided to move forward with **NIX Trial** instead (BPaL).
- Drug resistant group added for safety analysis
  - Not powered for efficacy

CRUSH TB (CDC TB Trial Consortium)

drug sensitive TB but MDR type regimens

TBTC Study 38 / CRUSH-TB NCT05766267	4BMZRb 4BMZD [2HRZE/4HR]	DS-TB	288	IIc	Recruiting [Dec 2026]

Figure 1. Global Pipeline of Medicines in Clinical Development for TB

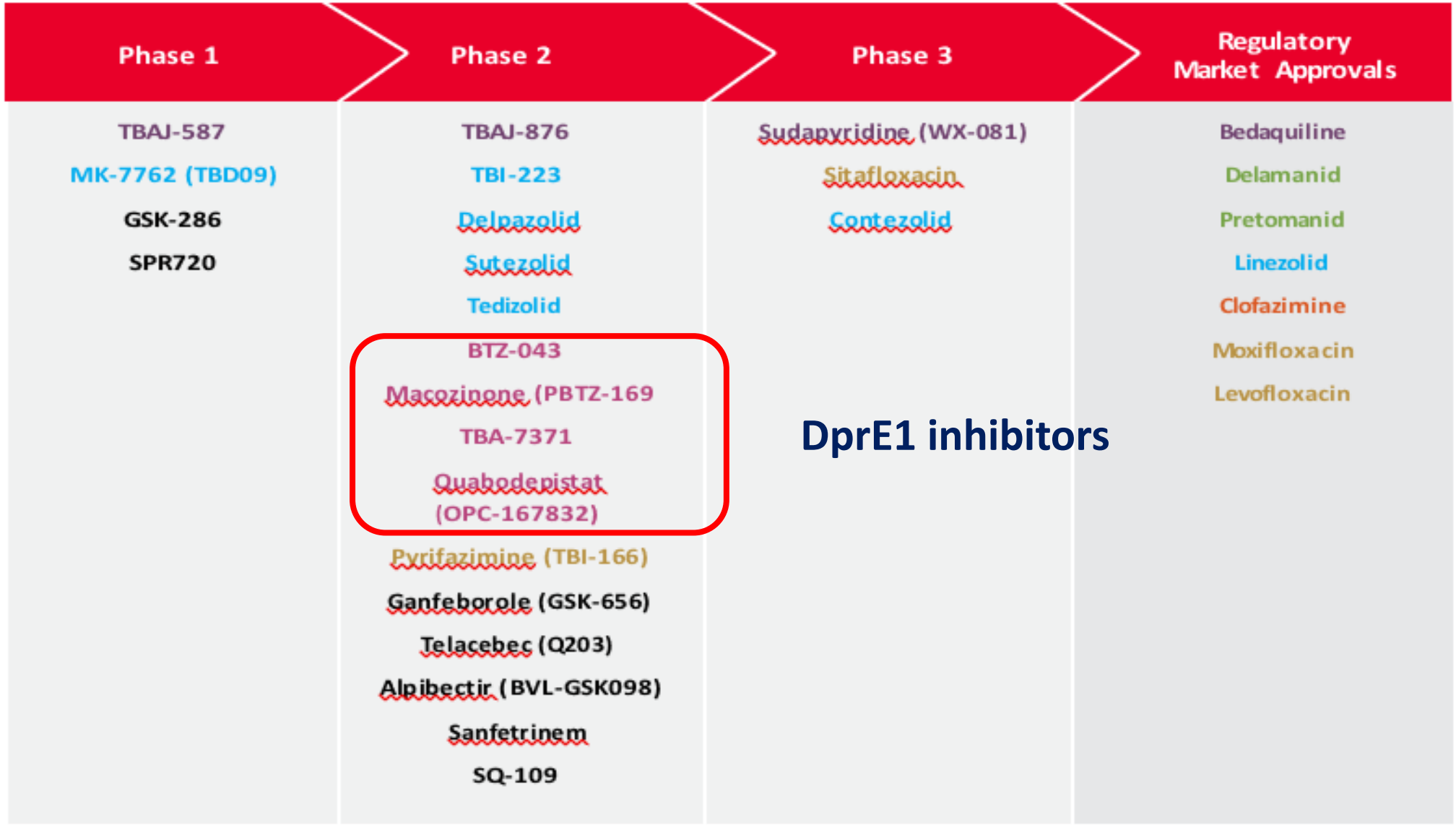


Figure adapted from Stop TB Partnership Working Group on New Drugs.
Diarylquinoline; Oxazolidinone; DprE1 inhibitor; Riminophenazine Nitroimidazole; Fluroquinolone.
Drugs that appear in black font are from classes and/or with mechanisms of action not otherwise represented by the other colors.

Pipeline Report 2023

Where should research be going? What does the TB Community Want?

- **Safety**

Efficacy

- **Tolerability**
  - Pill burden, side effects

Time

Duration, **home time**

One Size Does Not Fit All