LIFTB
Leveraging Innovation for Faster Treatment of Tuberculosis

International Tuberculosis Research Center

KNCV TUBERCULOSIS FOUNDATION

TB Alliance

Rationale for the BPaL regimen:

Update on Nix-TB Trial Results & the ZeNix and SimpliciTB Trials, TB-PRACTECAL

Training of Trainers for the BPaL Operational Research
Philippines, 19-21 May 2021

Mamel Quelapio, MD
Consultant, KNCV

Acknowledgment: Daniel Everitt, MD
VP and Chief Medical Officer, TB Alliance

TB Alliance is a not-for-profit organization dedicated to the discovery, development and delivery of better, faster-acting and affordable tuberculosis drugs that are available to those in need.

TB Alliance

Disclaimer

- Please note that this information is intended purely for the purpose of scientific exchange for those working in global public health. This may include references to information outside of the approved US FDA or the European Commission label but that has already been put into the public domain through previous publications and/or presentations.

Outline

- Background
- The Nix TB Trial
  - Efficacy
  - Safety
- The BPaL Operational Research
- Other trials
  - Zenix TB Trial
  - SimpliciTB
  - TB Practecal

Challenges in the treatment of extensively drug-resistant TB

Treatment challenges	
Too long	18+ months
Too complicated	≥ 5 drugs, some IM / IV, no defined regimen
Highly toxic, leading to discontinuations	Side effects: deafness, renal failure, psychosis
Poor efficacy	In South Africa, pre-bedaquiline era (~20% cure) With bedaquiline and linezolid* (~67% cure)

**Olayanju et al, 2018:* https://www.ncbi.nlm.nih.gov/pubmed/29700106

Shorter, Simpler Treatment for Highly Drug-Resistant Forms of TB

NixTB

Please see Full Prescribing Information at: www.accessdata.fda.gov

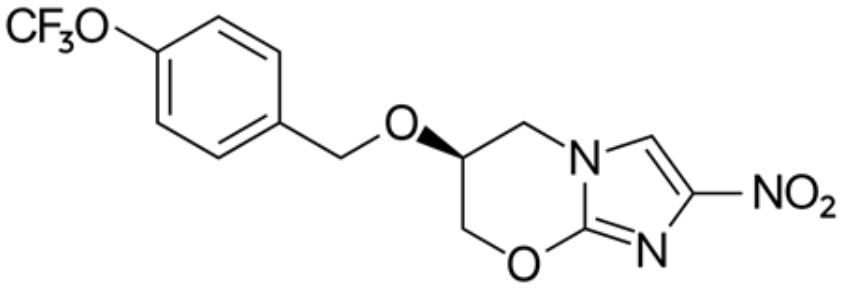
Nix-TB pivotal study presented opportunity to evaluate a novel regimen with transformative potential

- BPaL = bedaquiline **(B)** + pretomanid **(Pa)** + linezolid **(L)**
  - Each drug has potent preclinical and clinical anti-TB activity
  - Minimal pre-existing resistance
- All 3 drugs contribute to bactericidal and curative activity
  - In animal models, efficacy better than 1st line treatment for drug-susceptible TB and each drug contributed activity

Pretomanid: New chemical entity developed specifically to treat TB

- Class of nitroimidazooxazine (nitroimidazole, same chemical class as Delamanid)
- An oral antimycobacterial drug with novel mechanisms of action
  - Nonclinical and clinical studies showed anti-TB activity against drug-susceptible and drug-resistant *M. tuberculosis*
  - Possesses bactericidal and curative activities
- Studied in 1168 individuals, 19 clinical studies

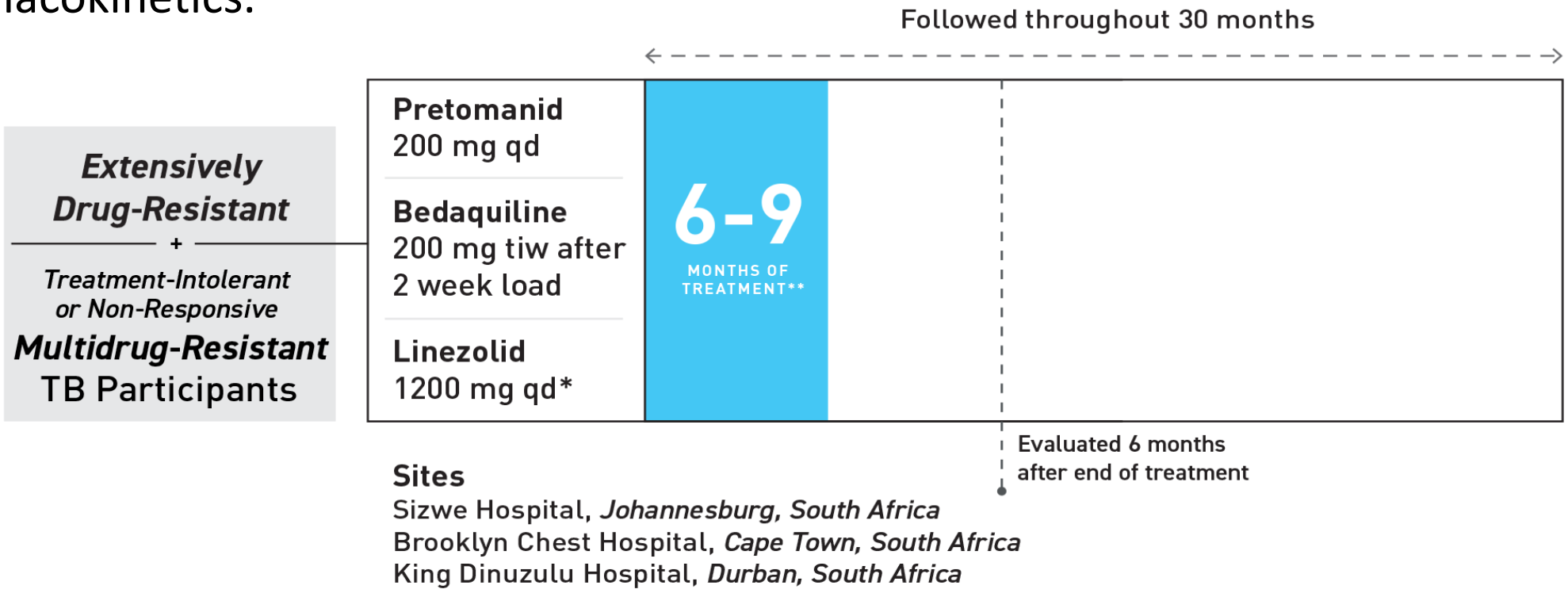
Pretomanid



The Nix-TB Trial with the BPaL Regimen

Nix-TB Phase 3 open-label single-arm trial

Assessed the safety and efficacy of patients with pulmonary XDR-TB or MDR-TB treatment-intolerant or non-responsive MDR-TB. Also assessed the tolerability and pharmacokinetics.



*Amended from 600 mg bid strategy

**If sputum culture is positive at 4 months, patients received an additional 3 months of treatment

Primary endpoint is measured at six months of post-treatment follow up

Novel treatment regimen – BPaL regimen

BPaL regimen: 6(–9) Bdq- Pa-Lzd

Medicine	Preparation	Dose	Total number of tablets
Bedaquiline (Bdq)	100 mg /tab	400 mg daily for 2 weeks, then 200 mg thrice weekly for 24 weeks	200
Pretomanid (Pa)	200 mg /tab	200 mg daily	182
Linezolid (Lzd)	600 mg/tab	1200 mg daily	264-364*

*Based on Nix TB trial

Primary endpoint: Clinical endpoint

- **Primary endpoint** – clinical and bacteriologic status 6 months after end of treatment
- Patient outcome categorized as either
  - **Unfavorable outcome**
    - Clinical or bacteriologic failure during treatment
    - Bacterial relapse post-treatment
    - Patients requiring alternative treatment at any point, withdrawal, or any death in ITT analysis, unless prior relapse
  - **Favorable outcome**
- **Secondary endpoint** – 2 years after end of treatment

Study protocol allowed dose modifications for adverse events

- **Linezolid**
  - Could be reduced or temporarily interrupted
    - Restarted at same or lower dose
  - Could be discontinued after first month
- **Pretomanid, bedaquiline**
  - No dose modifications allowed
- **BPaL regimen**
  - Regimen could be interrupted for up to 35 consecutive days
  - Missed doses of regimen made up at end of treatment

Key results: efficacy

Status of follow-up

- 109 participants enrolled between April 2015 and November 2017
- All have been followed to primary endpoint 6 months after completion of regimen therapy
  - 47 have been followed to the secondary endpoint 24 months after completion of therapy

	BPaL Regimen N=109
Age, years, mean (range)	35 (17 – 60)
Male	52%
Race	
Black	76%
White	1%
Mixed Race	23%
BMI, kg/m^2, mean (range)	20.6 (12.4 – 41.1)

Patient disease characteristics in Nix-TB

	BPaL Regimen N=109
Current TB diagnosis	
XDR-TB	65%
MDR-TB non-responsive	17%
MDR-TB treatment intolerant	17%
Duration since original TB diagnosis, months, median (range)	12 (<1 – 141)
HIV Positive	51%
Duration since HIV diagnosis, years, median (range)	4.0 (0.2 – 14.3)
Chest cavity x-ray results compatible with TB	
Unilateral	47%
Bilateral	38%
None	16%

* https://www.nejm.org/doi/full/10.1056/NEJMoa1901814

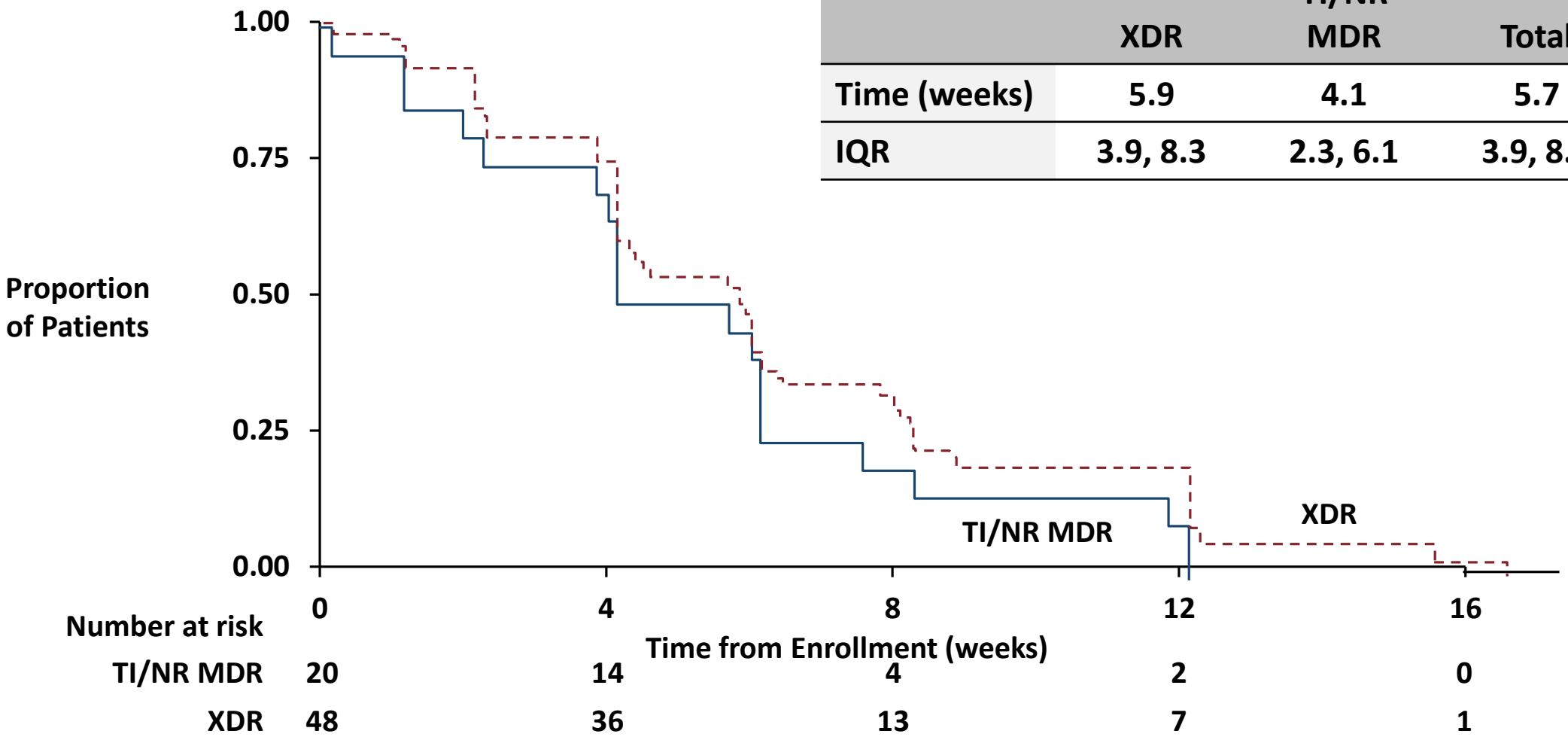
Updated efficacy in the ITT analysis with all 109 Patients*

Table 2. Primary Efficacy Analysis.*

Outcome	XDR	MDR	Overall
Intention-to-treat population†			
No. of patients	71	38	109
Favorable outcome			
No. of patients	63	35	98
Percent of patients (95% CI)	89 (79–95)	92 (79–98)	90 (83–95)
Unfavorable outcome — no. (%)	8 (11)	3 (8)	11 (10)
Deaths — no.	6	1	7
Withdrawal during treatment — no.	1	0	1
Lost to follow-up after end of treatment — no.	0	1	1
Relapse — no.	1	1	2‡

Secondary endpoint: median time to sputum culture conversion ~ 6 weeks

	XDR	TI/NR MDR	Total
Time (weeks)	5.9	4.1	5.7
IQR	3.9, 8.3	2.3, 6.1	3.9, 8.3



Bacteriologic failure or relapse at 24 months post-treatment supports long-term success

- 47 patients have been followed for a full 24 months after treatment with final clinical and culture results
  - Only 1 patient relapsed after the primary endpoint

    (15 months after completion of study regimen)

Efficacy conclusion

- 90% of patients with highly-resistant TB achieved relapse-free cure status 6 months after end of treatment
  - Lower bound far exceeded prespecified threshold
- Patients converted to culture negative status very quickly
  - Median time < 6 weeks
- Preliminary 24-month data indicate long-term cure
- Short, simple, and effective BPaL regimen can cure large majority of patients with highly-resistant TB

Data on File. Pretomanid- sponsor briefing document. TB Alliance. April 28, 2019

Key results: safety

Nix-TB: interruptions of BPaL regimen

- All but 6 patients tolerated therapy and completed treatment
- All permanent discontinuations on BPaL were due to death
- Entire regimen interrupted in 20 patients for adverse events
  - All patients who interrupted (excluding deaths) able to complete full treatment course or were ongoing

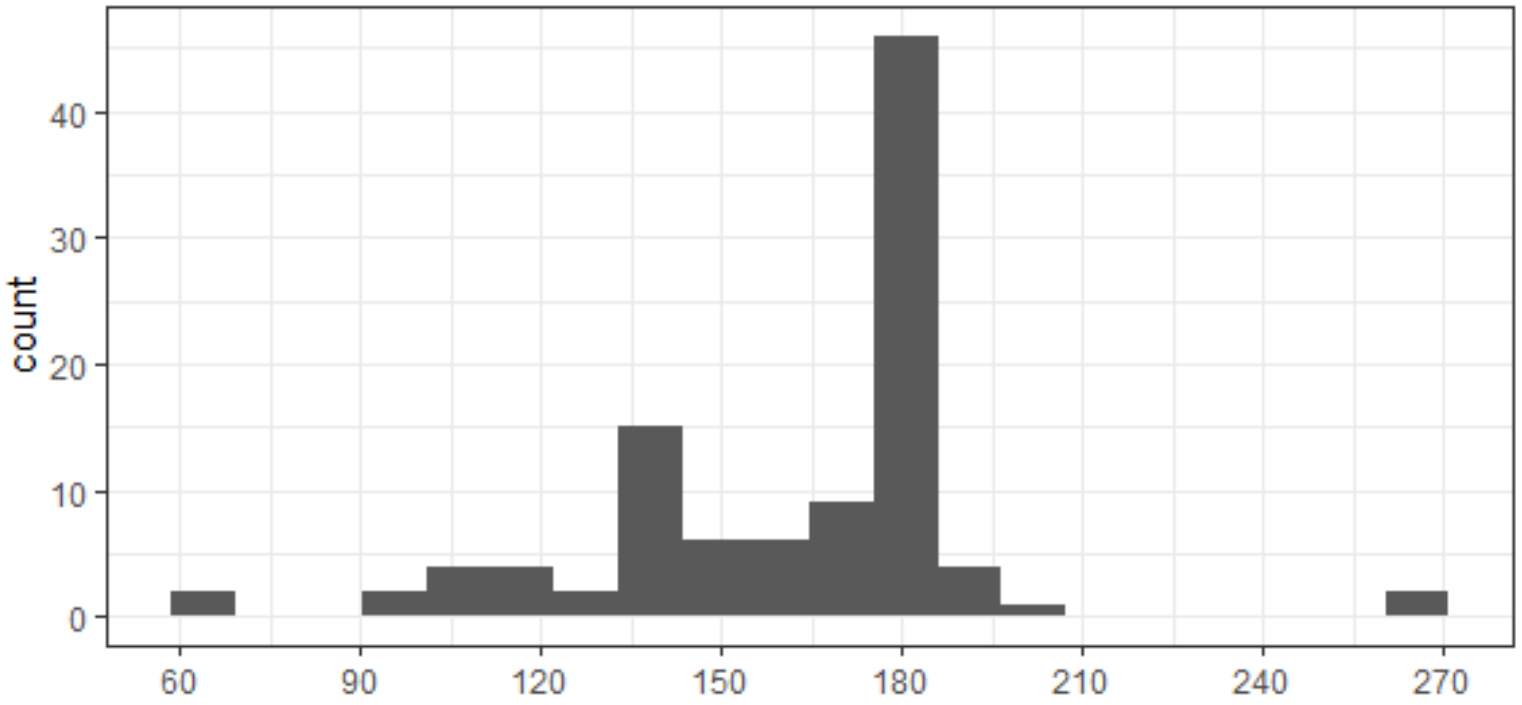
Linezolid dosing flexibility

Trial was designed to start at the full approved dose of 1200 mg daily

- Full flexibility after the first month to modify the dose as needed:
  - Dose reductions, interruptions or discontinuation

- All surviving patients completed the full course of treatment with >90% success rate, regardless of changes in linezolid dosing
  - 34 patients had no linezolid dose interruptions
  - 50 patients interrupted and resumed treatment at same or lower dose
  - 33 patients permanently discontinued linezolid

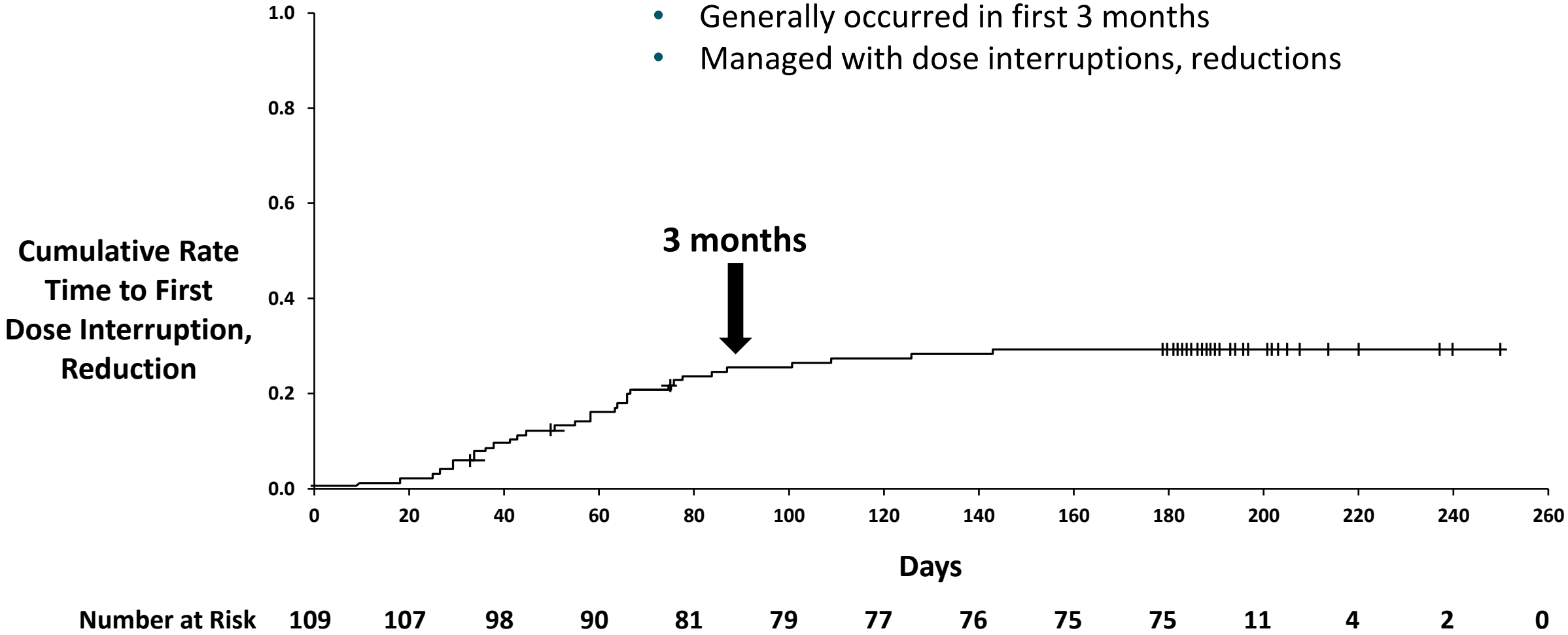
Total number of days of Linezolid administration




```
##    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
##    64.0   140.5   176.0   163.0   182.0   266
```

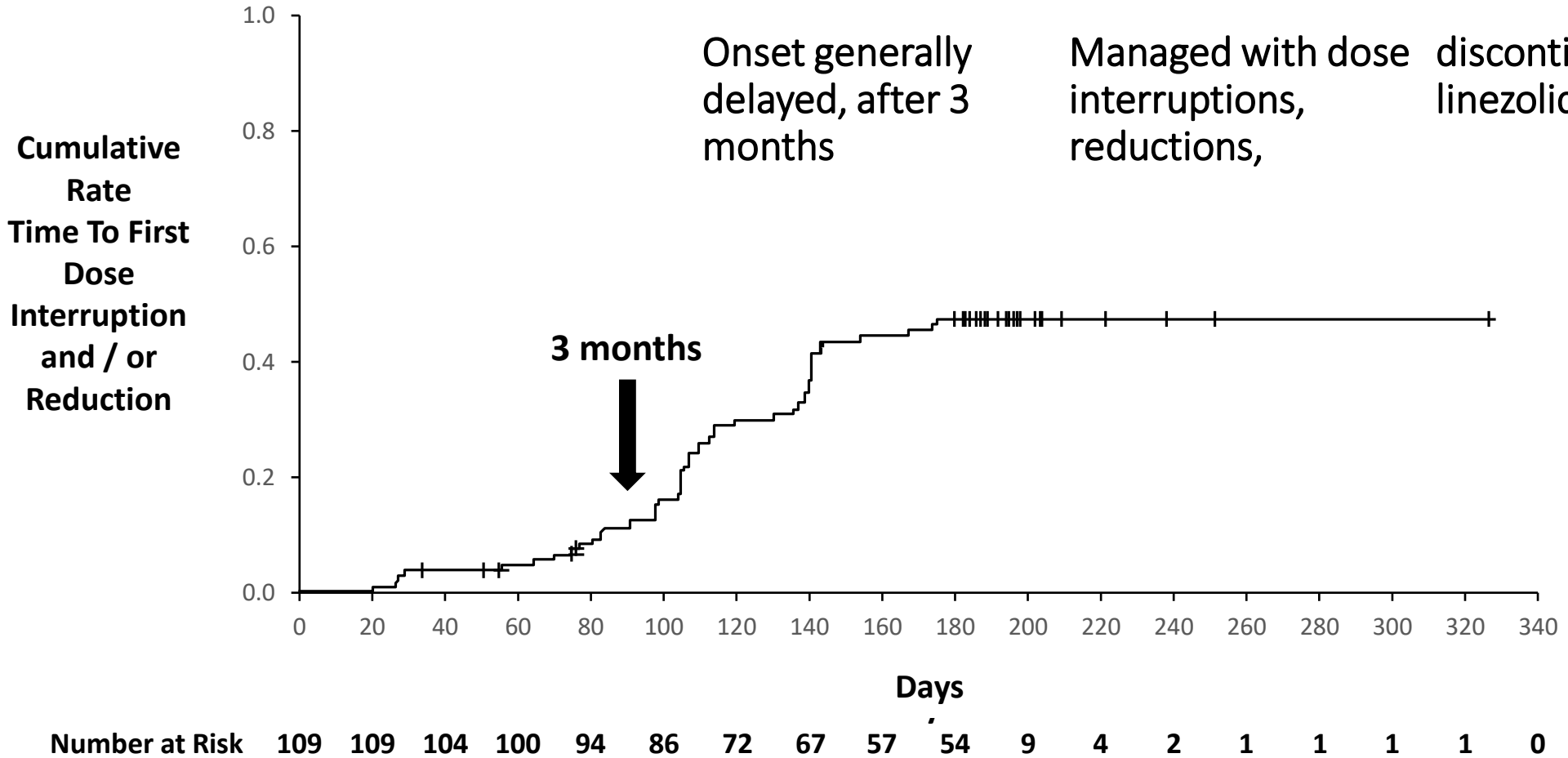
Myelosuppression: Early onset, managed with dose modifications

- Generally occurred in first 3 months
- Managed with dose interruptions, reductions



Data on File. Pretomanid- sponsor briefing document. TB Alliance. April 28, 2019

Peripheral neuropathy: delayed onset, managed with dose modifications

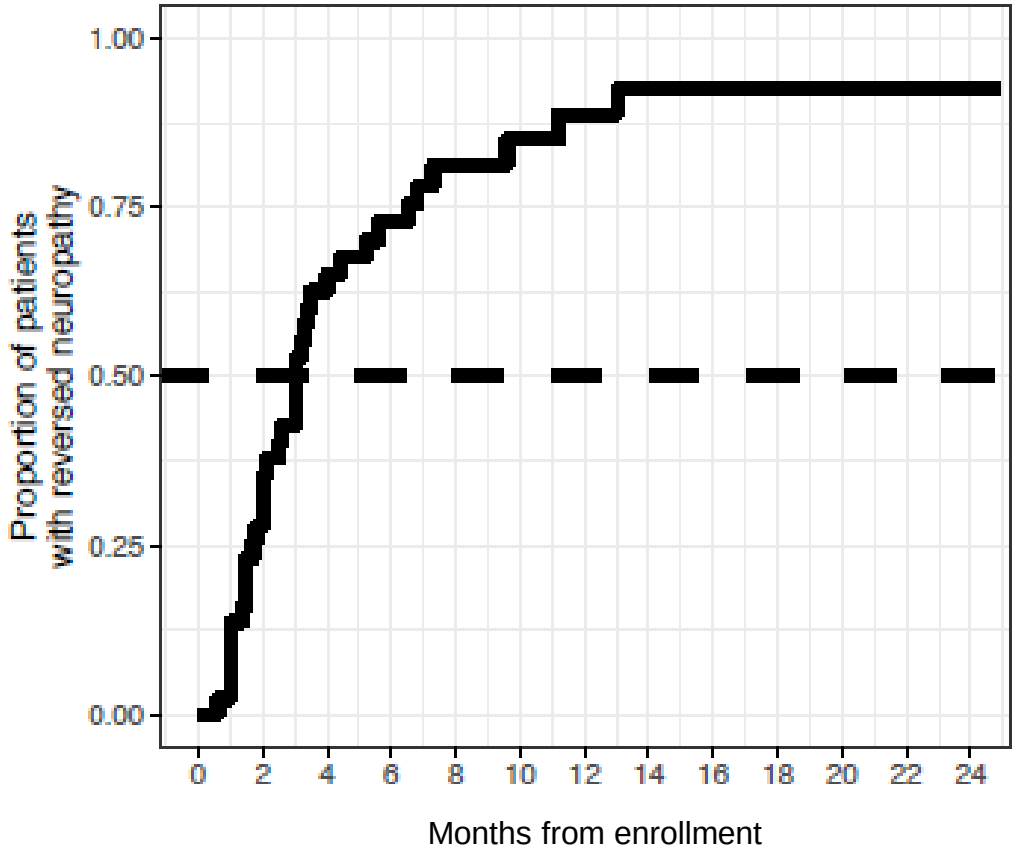


Onset generally delayed, after 3 months

Managed with dose interruptions, reductions, discontinuation of linezolid

Time-course for Improvement in Peripheral Neuropathy

Time from first visit when a mean score is moderate-severe (N=45)
to improvement to none or mild score



Score is the mean of scores of 0-10 for each of 4 questions on the Brief Peripheral Neuropathy Rating Scale. Mild is a mean score ≤2; Mod-severe is a mean score>2

Presented at 2020 CROI, Savic et al.

Based on symptom rating in the Brief Peripheral Neuropathy Rating Scale. *Note that follow up is ongoing*

Optic neuropathy

- 2 patients with optic neuropathy / neuritis
  - Both with symptoms of visual changes approximately 4.5 and 5 months after starting treatment with the regimen
  - Fundus examinatiom consistent with optic neuropathy

- Complete resolution of symptoms and findings with linezolid discontinuation

Data on File. Pretomanid-sponsor briefing document. TB Alliance. April 28, 2019

Adverse drug reactions are attributable to Pretomanid?

- The safety profile of Pretomanid alone is often **confounded** by other drugs in the regimen.
  - Outside of the 2 two-week EBA studies, patient studies have largely included combinations variably with moxifloxacin, pyrazinamide, bedaquiline and linezolid
- The safety of Ps has been evaluated across **19** trials and over **1100** patients and healthy volunteers
- Per the **Investigators Brochure**, the following may be attributable to pretomanid:
  - Mild to moderate nausea and vomiting
  - Mild to moderate rash
  - Transaminases increased
  - Headache

Nix-TB study: Adverse events overview

Adverse events	BPaL Regimen N=109 n (%)
Any AE	109 (100)
SAE	19 (17)
AEs by severity	
Grade 1	8 (7)
Grade 2	43 (39)
Grade 3	41 (38)
Grade 4	17 (16)

Grading according to DMID scale

Source: TB Alliance. BPaL Country planning meeting, 31 October 2019 Hyderabad India.

Adverse events occurring in > 15% of patients

Adverse Events	PĐ BPaL/ BPaL Regimen N=109 n (%)
Peripheral sensory neuropathy	75 (69)
Anemia	40 (37)
Nausea	40 (37)
Vomiting	37 (34)
Headache	28 (26)
Dermatitis acneiform	26 (24)
Dyspepsia	26 (24)
Decreased appetite	24 (22)
Pleuritic pain	20 (18)
Upper respiratory tract infection	20 (18)
Gamma-glutamyltransferase increased	18 (17)
Rash	17 (16)

Source: TB Alliance. BPaL Country planning meeting, 31 October 2019 Hyderabad India.

Nix-TB: Grade 3 or 4 AEs occurring in > 2% of patients

Grade 3 or 4 AEs	BPaL Regimen N=109 n (%)
Patients with grade 3 or 4 AEs	58 (53)
Peripheral sensory neuropathy	19 (17)
Transaminases increased	7 (6)
Gamma-glutamyltransferase increased	7 (6)
Amylase increased	6 (6)
Anemia	**6 (6)**
Lipase increased	4 (4)
Hyperamylasemia	4 (4)
Hypoglycemia	**4 (4)**
Neutropenia	**4 (4)**
Neuropathy peripheral	**3 (3)**
Pneumonia	3 (3)

Deaths generally occurred with severe underlying disease

	Day of Death	Preferred Term for AEs Associated with Deaths	HIV Status
Patient 1	35	Pulmonary tuberculosis, disseminated tuberculosis	Positive
Patient 2	51	Upper gastrointestinal hemorrhage	Negative
Patient 3	55	Pulmonary tuberculosis	Positive
Patient 4	53	Pancreatitis hemorrhagic, multiple organ dysfunction syndrome	Positive
Patient 5	93	Sepsis, pneumonia	Negative
Patient 6	76	Septic shock, pneumonia	Negative
Patient 7	369 (185 days after EOT)	Due to natural causes*	Positive
Patient 8	486 (303 days after EOT)	Thrombotic thrombocytopenic purpura, sepsis, dry gangrene, peripheral vascular disorder, infected skin ulcer	Positive

Manageable safety allowed majority of patients on complete BPaL regimen

- All but 6 patients completed treatment
  - Similar completion rate as drug-susceptible TB
  - Higher completion rate than with other treatments in highly-resistant TB
- Adverse events expected, well-characterized, and managed by
  - Interrupting full regimen
  - Dose interruptions, reductions, or discontinuations of linezolid
- Patients on regimen to be followed carefully

Pretomanid Approved by the US FDA

August 14, 2019

(Limited Population Pathway for Antibacterial and Antifungal Drugs)

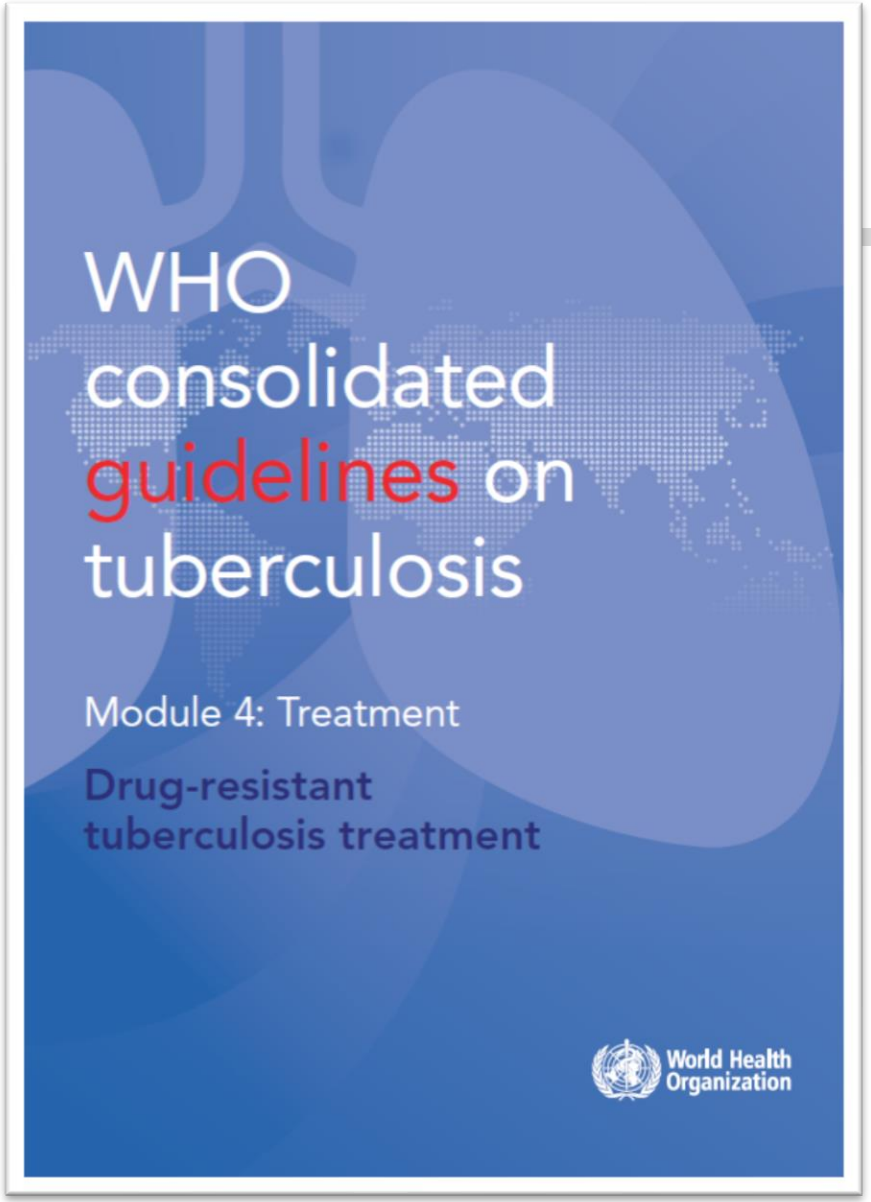
INDICATIONS AND USAGE

Limited Population: Pretomanid Tablet is an antimycobacterial indicated, as part of a combination regimen with bedaquiline and linezolid for the treatment of adults with pulmonary extensively drug resistant (XDR), treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB). Approval of this indication is based on limited clinical safety and efficacy data. This drug is indicated for use in a limited and specific population of patients. (1)

Pretomanid Approved by the European Medicines Agency (EMA)

June 2020

Similar label as US FDA's



WHO recommendation of the BPaL regimen

2020 WHO Consolidated Guidelines

Section 4. The bedaquiline, pretomanid and linezolid (BPaL) regimen for multidrug-resistant tuberculosis with additional fluoroquinolone resistance

4.1 Recommendation

NEW RECOMMENDATION

No.	Recommendation
4.1	A treatment regimen lasting 6–9 months, composed of bedaquiline, pretomanid and linezolid (BPaL), may be used under operational research conditions in multidrug-resistant tuberculosis (MDR-TB) patients with TB that is resistant to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for no more than 2 weeks. *(Conditional recommendation, very low certainty in the estimates of effect)*

Considerations for implementation

- a study protocol developed and submitted to a national ethics board for approval
- pre-specified inclusion and exclusion criteria in place
- an appropriate schedule of safety monitoring and reporting is in place (including aDSM)
- a pre-defined schedule of clinical and microbiologic monitoring is in place, preferably including post-treatment completion follow-up
- individual patient informed consent is obtained
- patient support is provided
- a standardized reporting and recording system is used, including for adverse events

2020 WHO Operational Handbook

Pretomanid and the BPaL Regimen – Additional Information

- Please see Full US Prescribing Information at: https://www.accessdata.fda.gov

- Full publication in the *New England Journal of Medicine*
  - https://www.nejm.org/doi/full/10.1056/NEJMoa1901814

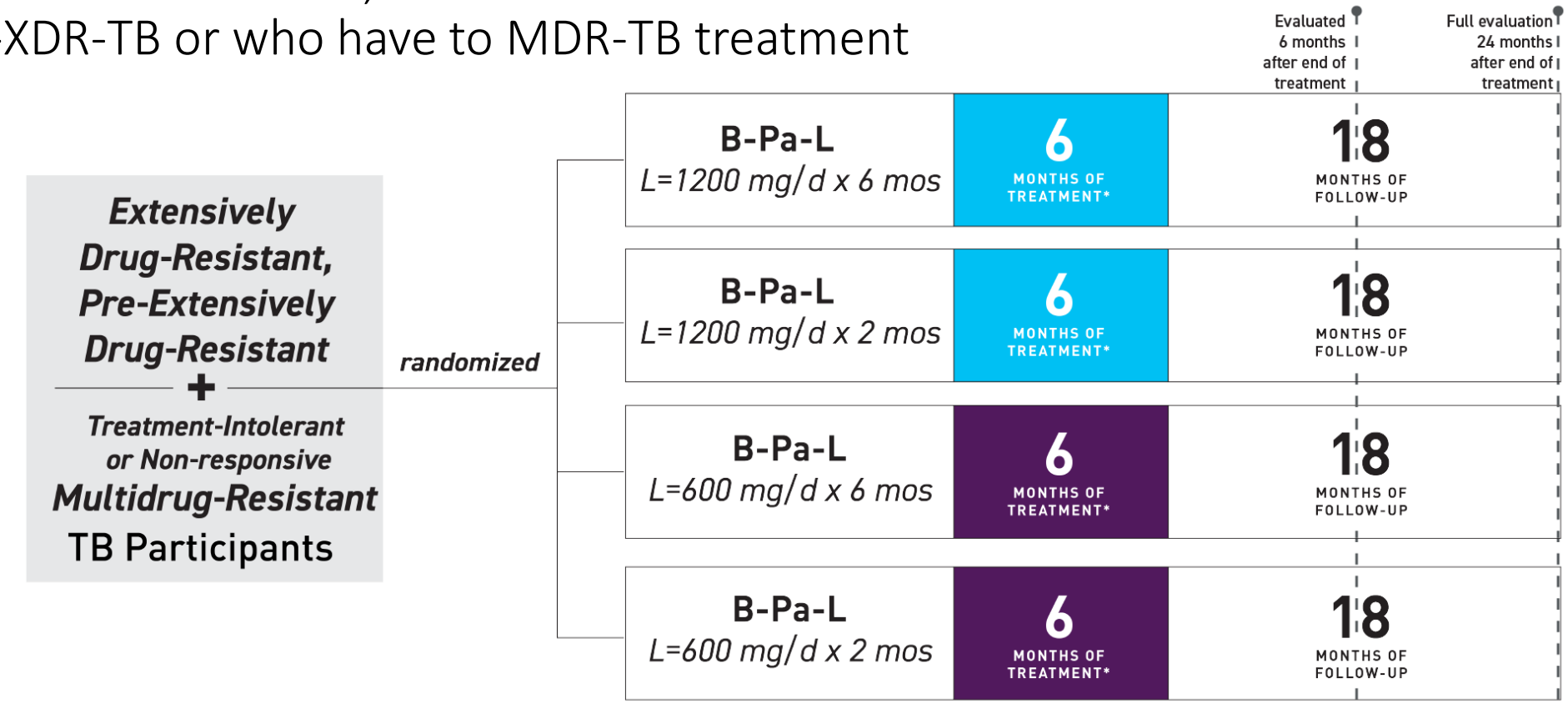
- Detailed Information from FDA Advisory Committee Briefing Documents:
  - *FDA:* https://www.fda.gov/media/127592/download
  - *TB Alliance:* https://www.fda.gov/media/127593/download

- European Marketing Authorization Information, Including the EPAR Assessment Report:
  - https://www.ema.europa.eu/en/medicines/human/EPAR/pretomanid-fgk

Improvements in the BPaL Benefit/Risk Value

ZeNix: Linezolid Optimization Trial

Patients with XDR-TB, failed or are intolerant
Pre-XDR-TB or who have to MDR-TB treatment



*Additional 3 months if sputum culture positive between week 16 and week 26 treatment visits

Pa pretomanid dose = 200 mg daily
B bedaquiline dose = 200 mg x 8 weeks, then 100 mg x 18 weeks

Status of the ZeNix Trial
March 2020

ZeNix

- Enrollment completed in South Africa, Russia, Georgia, Moldova

- 181 participants enrolled
  - All have completed dosing with the study regimens and are in follow up

- Results of all patients followed to the primary endpoint 6 months after treatment completion expected March, 2021

SIMPLICITB

The BPaMZ Regimen to Treat Patients with DS or DR Tuberculosis

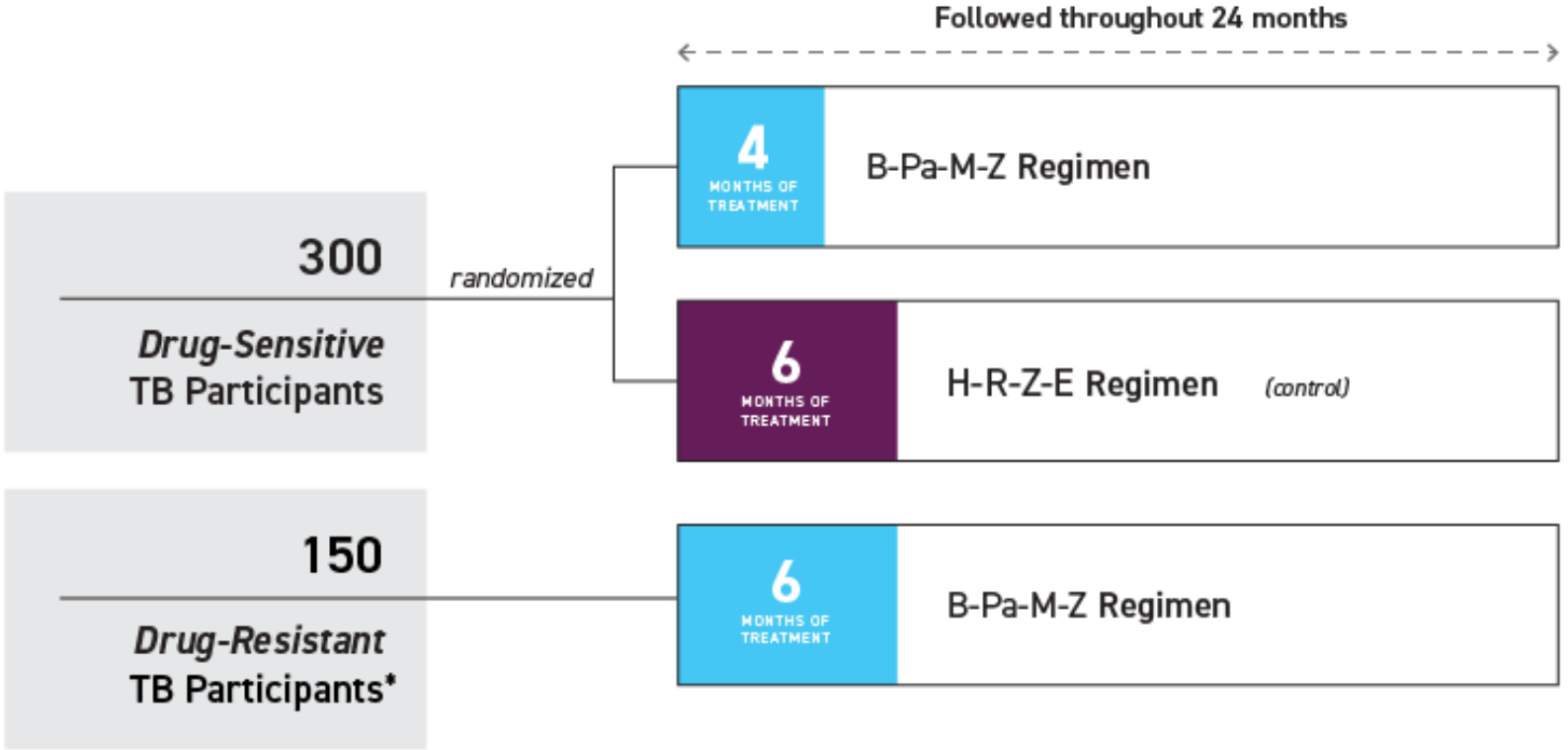
BPaMZ: Evaluating a new regimen for DS and DR-TB patients

SIMPLICITB

- BPaMZ = Bedaquiline (B), Pretomanid (Pa), Moxifloxacin (M) and Pyrazinamide (Z)
- Currently being tested in pivotal SimpliciTB trial
- Potential for BPaMZ to improve treatment for both DS-TB & DR-TB
- Enrollment commenced on 30 July 2018

SimpliciTB Trial: BPaMZ

- Participants with newly diagnosed DS- and MDR-TB



*Specifically MDR-TB and mono-resistance to isoniazid or rifampicin.

B bedaquiline 200 mg x 8 weeks, then 100 mg | Pa pretomanid 200 mg | M moxifloxacin 400 mg | Z pyrazinamide 1500 mg

H isoniazid | R rifampin | Z pyrazinamide | E ethambutol

SimpliciTB Status Update

- Enrolling countries (27 sites total):
  - Africa: South Africa, Tanzania, Uganda
  - Asia: Malaysia and **Philippines**
  - Eastern Europe: Georgia and Russia
  - South America: Brazil
- First participant randomised: 30 July 2018, Tbilisi, Georgia
- DS arms have completed enrolment (303 in total) on 12 August 2019
- DR arm enrolment completed on 2 March 2020 (152 in total)
- CSR in August 2021 (1-year post start of treatment)

TB PRACTECAL: Phase II/III clinical trial by MSF

➢**Investigational arms:** (24 weeks treatment which included 8 weeks of admission, follow-up 108 weeks):

Regimen 1

- Bdq, Pa and Lzd + Mfx – 400 mg OD

Regimen 2

- Bdq, Pa and Lzd + Cfz - 50 mg (less than 33 kg), 100 mg (more than 33 kg)

Regimen 3

- Bdq, Pa and Lzd – 600mg daily X 16 wks then 300mg daily for the remaining 8 wks

vs. locally accepted **standard of care (SOC)** of 18-20 months

N=242 in Belarus, SA and Uzbekistan (7 sites)
Data for peer review by WHO

https://www.msf.org/drug-resistant-tuberculosis-trial-ends-enrolment-after-positive-initial-data

Summary of clinical trials involving Bdq, Pa and Lzd

	Nix TB	TB Practecal	ZeNix
Aim	Safety, efficacy and tolerability	Safety, efficacy and tolerability	Safety, efficacy and tolerability
Type of study	Phase 3, open-label, single-group	Phase 2 and 3, open label, Multi-center, multi-arm, randomized, controlled	Partially blinded, Randomized controlled
Drugs	Bdq + Pa+ Lzd	Bdq +Pa + Lzd (Mfx and Cfz) Controlled arm (SoC)	Bdq + Pa + Lzd (Lzd placebo)
Study population	PTB (XDR-TB treatment intolerant / non-responsive MDR-TB)	PTB (XDR-TB. MDR-TB)	PTB (XDR-TB, pre-XDR-TB, treatment intolerant / non-responsive MDR-TB)
Treatment duration	26 or 39 weeks	24 weeks	26 or 39 weeks
Lzd dose modification	After 4 weeks of 1200mg	After 16 weeks of 600mg	Different doses

LIFTB
Leveraging Innovation for Faster Treatment of Tuberculosis

International Tuberculosis Research Center

KNCV TUBERCULOSIS FOUNDATION

TB Alliance

Thank you for your attention