BPaL Regimen

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RIGHT DIAGNOSIS RIGHT TREATMENT

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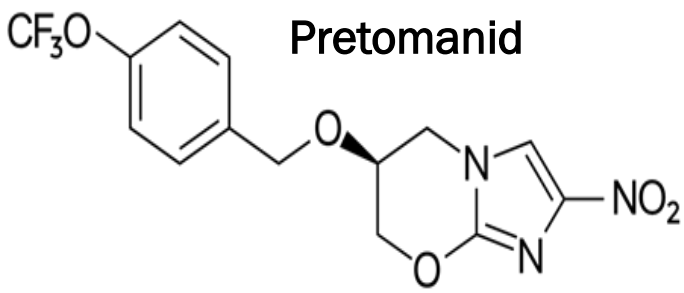
Presentation Outline

1. Overview of pretomanid & key info for use of BPaL
2. Overview of Nix-TB study & rationale
3. Efficacy results of the study
4. Overview of safety results from Nix-TB
5. WHO Guidance & generic OR protocol developed by KNCV
6. Pretomanid in other studies

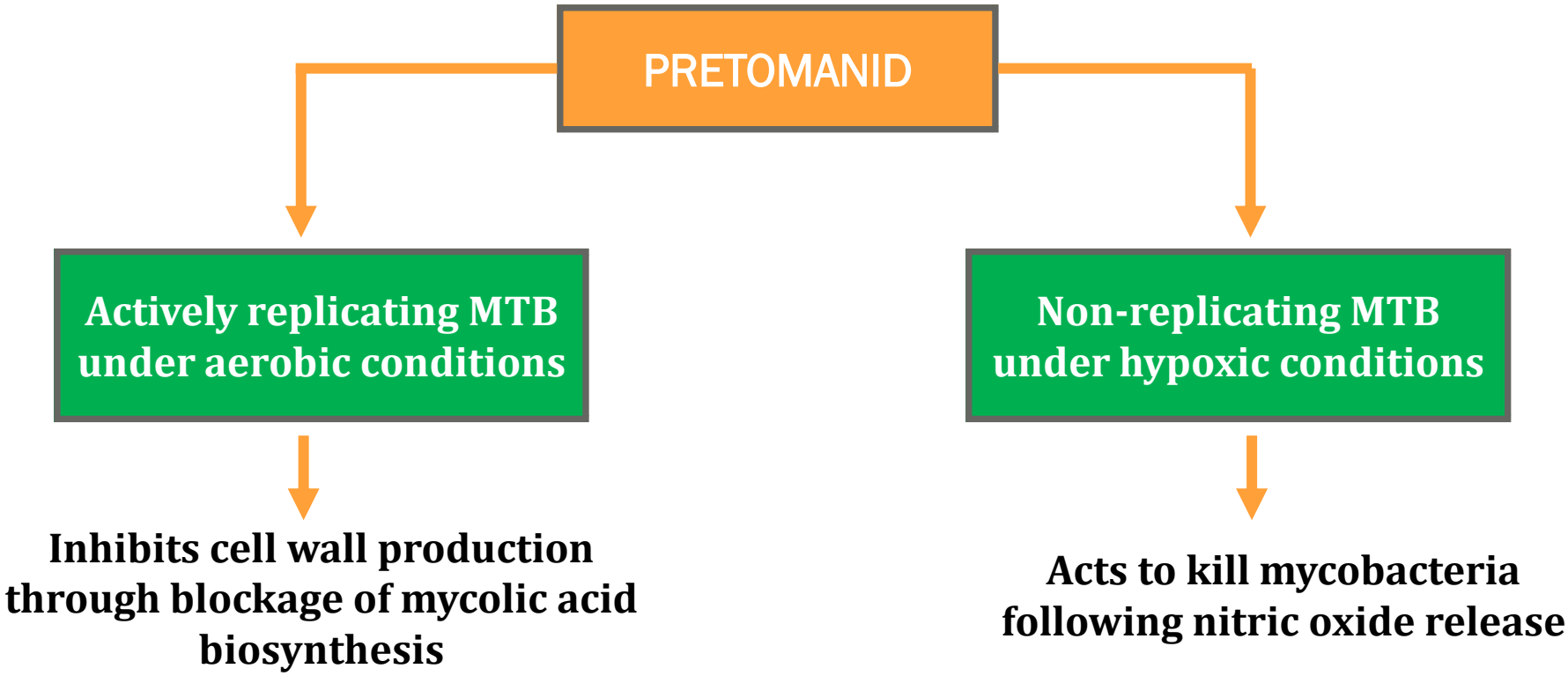
Pretomanid: New Chemical Entity Developed Specifically to Treat TB

- Nitroimidazooxazine 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



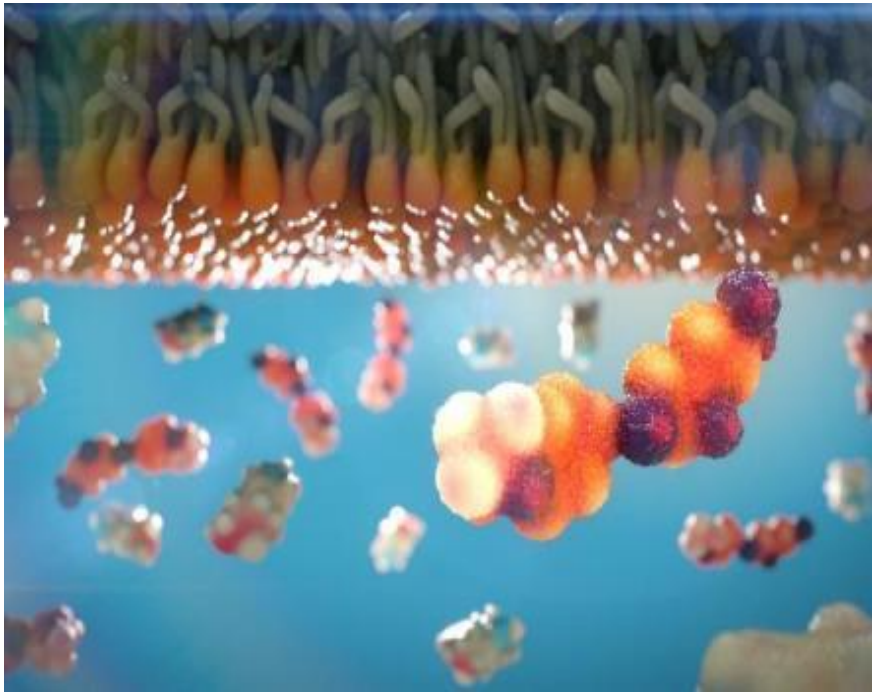
Pretomanid: New Chemical Entity Developed Specifically to Treat TB

- *Pretomanid kills replicating and non-replicating* drug-susceptible and drug-resistant *M. tuberculosis bacteria*



Pretomanid

- Pretomanid is the third new anti-TB drug approved for use by U.S. FDA, after rifapentine and bedaquiline
- Pretomanid is the first anti-TB drug to be developed and registered by a not-for-profit organization
- Approved as part of a discrete regimen



Nix-TB: Trial Overview & Efficacy of BPaL

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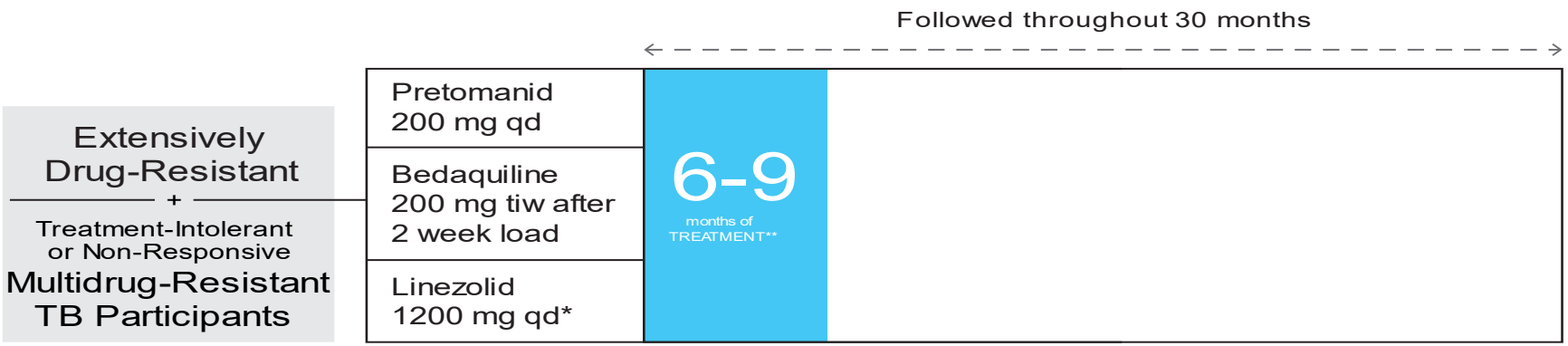
Introduction to Nix-TB study

A Phase 3 open-label trial assessing the **safety and efficacy of bedaquiline (Bdq) + pretomanid (Pa) + linezolid (Lzd)** in patients with either extensively drug-resistant PTB (XDR-TB) or treatment intolerant / non-responsive multi-drug resistant PTB (MDR-TB)



Sites
Sizwe Hospital, Johannesburg, South Africa
Brooklyn Chest Hospital, Cape Town, South Africa
King Dinuzulu Hospital, Durban, South Africa

*Amended from 600 mg bid strategy

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

Aim of study

The purpose of the study was to evaluate the **efficacy, safety, tolerability** and pharmacokinetics of Bdq plus Pa plus Lzd after **6 months of treatment (option for 9 months for subjects who remain culture positive at month 4)** in patients with either pulmonary XDR-TB, or treatment intolerant and non-responsive pulmonary MDR-TB

Rationale for BPaL Regimen

- BPaL
  - *3 drugs with little pre-existing resistance*
  - *Each with different mechanisms of anti-TB activity*

- Mouse model of TB predictive of bactericidal activity and cure in humans
  - *Preclinical results demonstrated strong bactericidal and curative activity for the regimen*

- Patients with highly-resistant TB have limited treatment options
- No standard of care for highly-resistant TB
- Challenges in DR TB treatment regimens
  - *Many side effects, poor treatment outcomes, long and complex, requiring ≥ 5 medicines including injectables*

Primary Endpoint: Clinical Endpoint, Not Biomarker or Surrogate

- **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

    OR
  - Favorable outcome

- **Secondary endpoint – 2 years after end of treatment**

Treatment duration and follow up

- 6 months
- Culture positive subjects at month 4, had their treatment extended to 9 months or withdrawn from study
- Follow-up:
  - Patients who completed treatment to return for follow-up visits 1 and 2 months after end of treatment and every 3 months for 24 months after end of treatment
  - Patients who were withdrawn <14 days of IMP administration to return for an Early Withdrawal visit only
  - Patients who were withdrawn after >15 days of IMP to return for the Early Withdrawal visit, and for the 3, 12 and 24 month follow up visits after their last dose of IMP

Assigned treatment regimen

- Treatment regimen was administered orally for 6 months (possibly 9 months) at the following doses and intervals:
  - Bedaquiline 400 mg once daily for 2 weeks, then 200 mg 3 times per week
  - Pretomanid 200mg once daily
  - Linezolid 600mg twice daily. Permitted changes included:
    - ❑ Reduction in the dose of Lzd (to either 600 mg od, 300 mg bd or 300 mg od)
    - ❑ Temporary cessation of Lzd (due to a Lzd-specific toxicity)
    - ❑ Re-introduction of Lzd (at the same or at a lower dose), or the full regimen, could be considered after an interruption not greater than 35 consecutive days

Patient numbers

- Planned: up to 200 male or female patients aged 14 and over with confirmed sputum culture-positive pulmonary XDR-TB or pulmonary MDR-TB with a documented treatment intolerance or non-response
- Total enrolled 109 patients between April 2015 and November 2017 from 3 sites in South Africa

	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%

BPaL Efficacy in Nix-TB

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Results of the Nix-TB study

- Nix-TB data demonstrated a **favourable outcome in 98 of 109 (90%)** enrolled patients after 6 -9 months of treatment with BPaL and 6 months of post-treatment follow-up
- All patients have been followed to primary endpoint 6 months after completion of regimen treatment
  - 47 have been followed to the secondary endpoint 24 months after completion of therapy
    - *Only 1 patient relapsed after the primary endpoint*
    - *15 months after completion of study regimen*
- Formal analyses presented on the first 80 participants at the FDA Advisory Committee Meeting
  - Based on these results:
    - Pretomanid (Pa) approved by US FDA and EMA for the treatment of pulmonary XDR-TB or treatment-intolerant or non-responsive MDR-TB, in a combination with Bdq and Lzd
    - In December 2019, WHO endorsed use of the BPaL regimen **under OR conditions**

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

Culture Conversion Status at 4 Weeks Determined from Time to Event Analysis for Those Positive at Baseline (All Enrolled)

	Total	XDR	TI/NR MDR
Total enrolled	109	71	38
Not positive at baseline	16	9	7
Analysis population	93	62	31
Negative	40 (43%)	27 (44%)	13 (42%)
Positive	53 (57%)	35 (56%)	18 (58%)
Died	0	0	0

Culture Conversion Status at 6 Weeks Determined from Time to Event Analysis for Those Positive at Baseline (All Enrolled)

	Total	XDR	TI/NR MDR
Total enrolled	109	71	38
Not positive at baseline	16	9	7
Analysis population	93	62	31
Negative	60 (65%)	39 (63%)	21 (68%)
Positive	32 (34%)	22 (35%)	10 (32%)
Died	1 (1%)	1 (2%)	0

Culture Conversion Status at 8 Weeks Determined from Time to Event Analysis for Those Positive at Baseline (All Enrolled)

	Total	XDR	TI/NR MDR
Total enrolled	109	71	38
Not positive at baseline	16	9	7
Analysis population	93	62	31
Negative	74 (80%)	48 (77%)	26 (84%)
Positive	15 (16%)	10 (16%)	5 (16%)
Died	4 (4%)	4 (6%)	0

Culture Conversion Status at 12 Weeks Determined from Time to Event Analysis for Those Positive at Baseline (All Enrolled)

	Total	XDR	TI/NR MDR
Total enrolled	109	71	38
Not positive at baseline	16	9	7
Analysis population	93	62	31
Negative	85 (91%)	55 (89%)	30 (97%)
Positive	3 (3%)	2 (3%)	1 (3%)
Died	5 (5%)	5 (8%)	0

Culture Conversion Status at 16 Weeks Determined from Time to Event Analysis for Those Positive at Baseline (All Enrolled)

	Total	XDR	TI/NR MDR
Total enrolled	109	71	38
Not positive at baseline	16	9	7
Analysis population	93	62	31
Negative	86 (92%)	57 (92%)	29 (94%)
Positive	1 (1%)	0	1 (3%)
Died	6 (6%)	5 (8%)	1 (3%)

Culture Conversion Status at End of Treatment Determined from Time to Event Analysis for Those Positive at Baseline (All Enrolled)

	Total	XDR	TI/NR MDR
Total enrolled	109	71	38
Not positive at baseline	16	9	7
Analysis population	93	62	31
Negative	87 (94%)	57 (92%)	30 (97%)
Positive	0	0	0
Died	6 (6%)	5 (8%)	1 (3%)

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
- 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

Nix-TB: Safety of BPaL

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Nix-TB: Interruptions of BPaL Regimen

- All surviving patients completed the full course of treatment with >90% success rate, regardless of changes in linezolid dosing

- Trial was designed to start at the full approved dose of 1200mmg daily
  - Full flexibility after the first month to modify the dose as needed

  - Dose reductions, interruptions or discontinuation
    - *34 patients had no linezolid dose interruptions*
    - *50 patients interrupted and resumed treatment at same or lower dose*
    - *33 patients permanently discontinued linezolid*

- Entire regimen interrupted in 20 patients due to adverse events

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.

Nix-TB: Adverse Events Occurring in > 15% of Patients

Adverse Events	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)

Nix-TB: Deaths Generally Occurred with Severe Underlying Disease

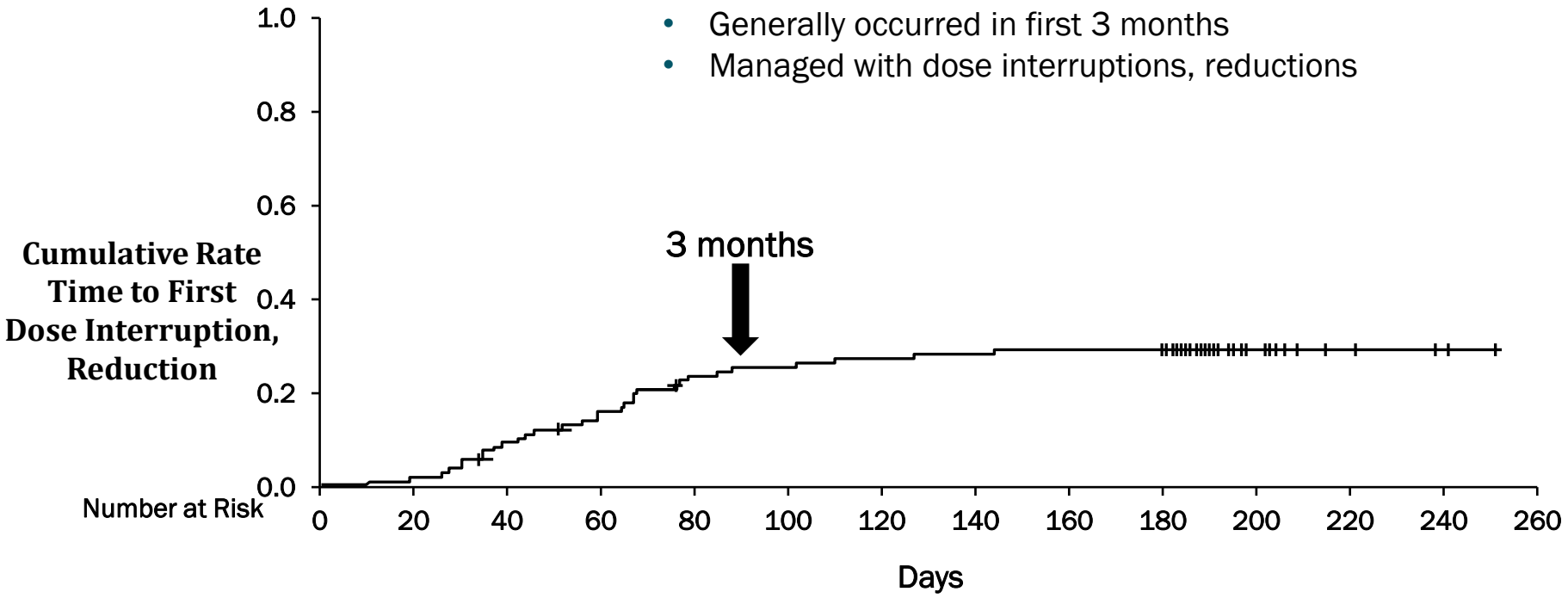
	Day of Death	Preferred Term for AEs Associated with Deaths	HIV Status
Patient 1	35	Pulmonary tuberculosis, disseminated tuberculosis	Positive
Patient 2	51	Upper gastrointestinal hemorrhage	Negative
Patient 3	55	Pulmonary tuberculosis	Positive
Patient 4	53	Pancreatitis hemorrhagic, multiple organ dysfunction 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

CD4 Count in HIV+ and Linezolid AEs

- 8 patients had HIV with CD4<200
- None with CD4<200 had early discontinuations of linezolid
- These patients had greater incidence of anemia requiring linezolid interruptions or reductions, but not of neuropathy

	HIV with CD4 <200	Total Population
Anemia requiring interruption or reduction of linezolid	5/8 = 63%	16/109 = 15%
Neuropathy requiring interruption, reduction or discontinuation of linezolid	2 of 8 = 25%	33/109 = 30%

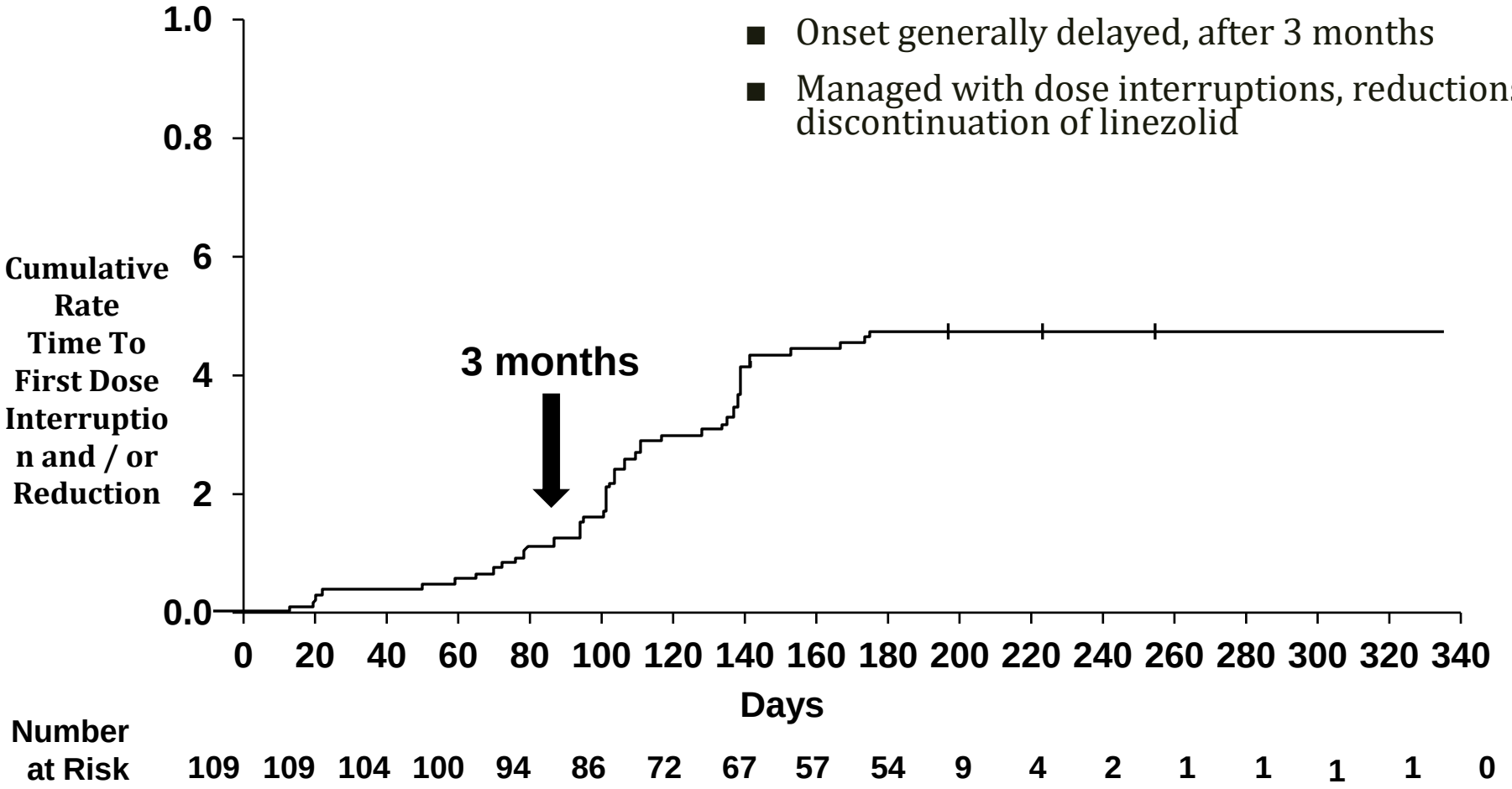
Onset of myelosuppression during Nix-TB study



Source: Dr. F. Conradie: NiX-TB trial experience: safety reporting and recommendations for programmatic implementation of the regimen. The 50th Union World Conference on Lung Health; 2019 Nov 1; Hyderabad India.

Peripheral Neuropathy: Delayed Onset, Managed with Dose Modifications

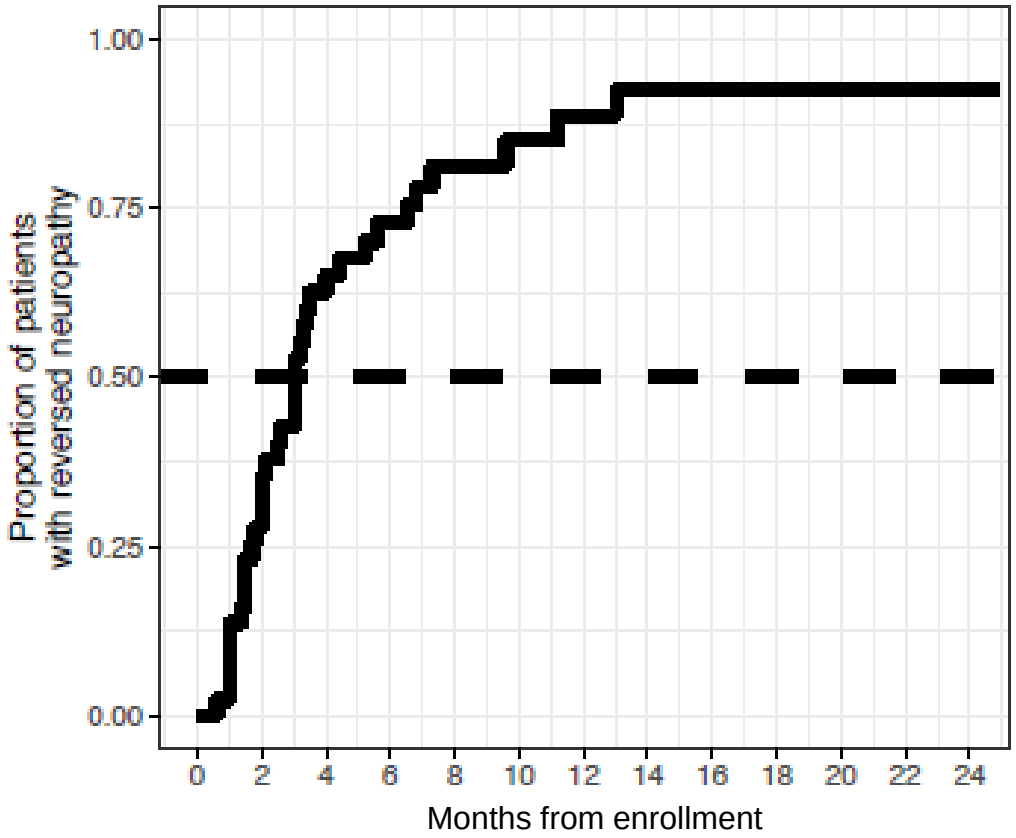
- Onset generally delayed, after 3 months
- Managed with dose interruptions, reductions, discontinuation of linezolid



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

Presented at 2020 CROI, Savic et al.



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

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 exam 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

What Adverse Drug Reactions are Attributable to Pretomanid?

- In patients, 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 pretomanid 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*

Final results of NIX TB

- 109 participants (65% XDR-TB, 35% MDR-TB; 51% HIV+) were enrolled and comprised the ITT population (MITT population = 107)
- All surviving participants, except 1 withdrawal, completed the full course of treatment
- At the primary endpoint six months after treatment, as previously reported, there were 98 with favorable outcomes (90% ITT, 92% mITT)
- After the primary endpoint one participant relapsed 15 months after treatment and one was lost to follow up
- Favorable outcomes 24 months post completion of treatment were sustained (88% ITT, 91% mITT) independent of sex or HIV status.

Pauline Howell MD
University of Witwatersrand, Wits Health Consortium Clinical HIV Research Unit, Johannesburg, South Africa
CROC 2021

https://www.croiconference.org/abstract/final-results-of-the-nix-tb-clinical-study-of-bpal-regimen-for-highly-resistant-tb/

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WHO Guidance & KNCV Generic Protocol

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Novel treatment regimen - BPaL

- A treatment regimen lasting 6–9 months, composed of bedaquiline, pretomanid and linezolid (BPaL)

BPaL regimen: 6–9 Bdq- Pa-Lzd

- WHO recommended BPaL to be used under operational research conditions in MDR-TB patients with resistant to fluoroquinolones, no previous exposure to bedaquiline and linezolid or not more than 2 weeks

  Conditional recommendation, very low certainty in the estimates of effect

- WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment 2020

Requirements for operational research

01

Establish operational research committee and agree on roles and responsibilities

02

Establish functional National DR-TB Consilium/Expert TB Committee

03

Ensure functional aDSM framework

04

Ensure procurement and availability of drugs, including ancillary drugs

Requirements for operational research

01

Develop study protocol including:

- Study objectives
- Study population
- Study sites
- Eligibility criteria
- Enrollment period
- Follow-up

02

Develop data collection tools and monitoring framework

03

Develop training materials/ job aids/SOPs for HCWs and research staff

BPaL regimen eligibility criteria

- Bacteriologically confirmed pulmonary MDR-/RR-TB with additional FQ resistance (with or without resistance to second-line injectable agents)
- Aged at least 18 years at the time of enrolment
- Weighs 35 kg or more
- Willing to sign informed consent to be enrolled in an operational research (or sign by a witness consent if the patient is illiterate)
- Adhere to the follow-up schedule

BPaL regimen eligibility criteria

- Ready to used effective contraception (if the patient is a premenopausal woman, not pregnant or breastfeeding)
- No known allergy to any of the BPaL component drugs
- No evidence of resistance to any of the drugs by DST results
- No previous exposure to any of the drugs for more than 4 weeks or longer
- No extrapulmonary TB (including meningitis, other CNS TB, or TB osteomyelitis)

BPaL regimen exclusion criteria

- Known severe allergy to any of the BPaL component drugs
- DST showing infection with a strain resistant to any of the component drugs; or previous exposure to any of the component drugs for more than 4 weeks
- TB meningitis, other central nervous system TB, or TB osteomyelitis
- Pregnancy or breastfeeding
- Unable to take oral medications

KNCV's generic OR protocol for BPaL introduction and scale-up

Study Design: A prospective observational cohort study

Primary objectives:

- To estimate the effectiveness of the BPaL regimen by assessing the end of treatment outcome among patients treated with the regimen
- To estimate the safety of the BPaL regimen by determining the rates of serious adverse events

Secondary objectives:

- To determine the time to sputum culture conversion among patients treated with the BPaL regimen
- To determine the proportion of patients with recurrence-free cure 6 and 12 months after the successful treatment with the BPaL regimen.
- To determine the proportion of patients treated with the BPaL regimen who experience adverse events of special interest (include following AESI: QT-prolongation, peripheral neuropathy, myelosuppression, optic neuritis and hepatotoxicity).

Inclusion/Exclusion Criteria

Inclusion Criteria

A patient, who:

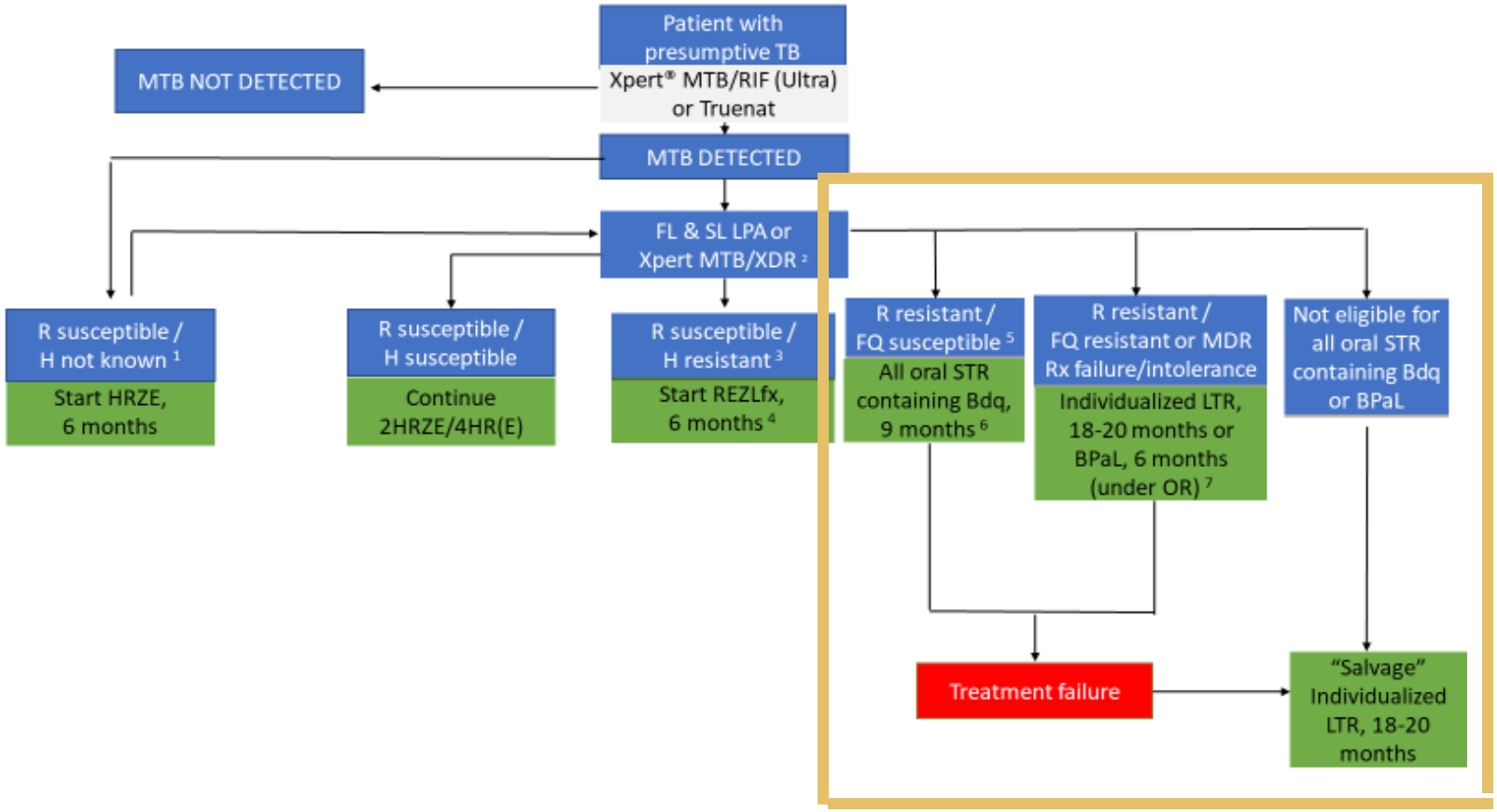
- is diagnosed with TB in any of the following circumstances:
  - has a laboratory-confirmed resistance to at least Rif and FQ; or
  - has strong clinical and radiological evidence of active TB and is a close household contact of a TB patient with a laboratory-confirmed resistance to at least Rif and FQ; or
  - Has been treated for MDR-/RR-TB and has documented non-response to treatment, and a decision has been made by the Expert Committee to shift the patient to the BPaL regimen; , or
  - Has been treated for MDR-/RR-TB and has documented intolerance, and a decision has been made by the Expert Committee to shift the patient to the BPaL regimen; and
- is willing and able to give informed consent to be enrolled in the OR and adhere to the OR procedures and the follow-up schedule (signed or witnessed consent if illiterate);
- is at least 18 years old at the time of enrolment; and
- is willing to use effective contraception if a pre-menopausal woman.

Exclusion Criteria

A patient, who:

- has a known severe allergy to any of the BPaL component drugs; or
- has DST showing resistance to any of the component drugs; or
- has been previously exposed to any of the component drugs or DIm for more than two – four weeks; or
- has a form of extrapulmonary TB that would require treatment longer than usual for pulmonary TB (e.g. TB meningitis, other central nervous system TB, or TB osteomyelitis); or
- is pregnant or breastfeeding; or
- is unable to take oral medications.

Patient Triage Algorithm



Treatment initiation

- **A study enrolment form** should be completed once a patient has signed for informed consent

- Ensure all baseline tests, including clinical evaluation, bacteriological and laboratory testing, are done according to the monitoring schedule and **check results before treatment initiation**
  - Clinical evaluation to include physical examination (with brief peripheral neuropathy screening), weight/BMI, visual acuity and colour discrimination screen, and performance status assessed by Karnofsky Performance Status Screen

Schedule of baseline, routine and post-treatment monitoring evaluations

Table 5. Schedule of baseline, routine and post-treatment monitoring evaluations.					
	Baseline	**2 weeks**	**Monthly**	**End of treatment**	**6- and 12-months after treatment**
Sputum smear	X		X	X	X
Sputum culture[4]	X		X	X	X
Sputum drug susceptibility testing[5]	X		If smear or culture positive[6]		
Extrapulmonary samples (smear/culture/DST)	X		If possible and no documented response to treatment		
Radiology, ECG & laboratory evaluations					
Chest X-Ray	X			X	X
ECG	X	X	X	X	
Full blood count	X	X	X	X	
Liver function tests (AST, ALT, bilirubin)	X	X	X	X	
Thyroid stimulating hormone (TSH)	X		As indicated		
Serum electrolytes [7]	X		X	X	
Urea, creatinine	X				
Pregnancy test	X				
HIV / HBV / HCV tests	X				
Baseline Sugar level / HbA1c [8]	X				

[1] Vital signs, TB symptom screen, pain, nausea, appetite and nutrition, diarrhoea, candidiasis. Clinical assessment should focus on a) monitoring response to treatment and b) addressing common symptoms associated with TB treatment and long-term antibiotic use, with the goal of supporting adherence.

[2] Food security, housing, mental state, substance use. Psychosocial assessment should offer an opportunity to assess supportive factors for treatment adherence and should be directly linked to relevant interventions wherever possible, per country specific questionnaires

[3] Assessed by Karnofsky Performance Status Scale, see Annex 9.

[4] Isolates from all positive cultures collected during every visit, including pre-treatment, will be stored separately for future research.

[5] Xpert MTB/RIF, second-line LPA, culture based second-line DST, if available, this should include Xpert/XDR and DST for the BPaL component drugs and next generation sequencing. A culture collected prior to start of BPaL treatment should be frozen for each enrolled patient for further analysis once pDST methods for Bdq, Pa and Lzd are available and for comparison of genotype and resistance conferring mutations in case of possible relapse.

[6] Repeat DST if culture still positive at month 4, end of treatment or post-treatment follow-up

[7] Includes K, Na and Ca. Add Mg if hypokalaemic.

[8] If abnormal at baseline, diabetes mellitus should first be ruled out. If patient is found to have diabetes mellitus, he should be treated and followed up accordingly.

Relative contraindications for the BPaL regimen

- Concurrent use of medications that have known interactions or overlapping toxicities with BPaL component drugs
- Baseline QTcF > 500ms
- Severe myelosuppression; haemoglobin level < 8.0 g/dL, platelet count <75,000/mm3, absolute neutrophil count < 1000/ mm3
- Severe peripheral neuropathy; Grade 3 or Grade 4
- Moderate hepatic or renal failure
- ART regimen including Zidovudine or Efavirenz (need to modify the regimen)

Treatment initiation

- Treatment initiation can be either hospital or ambulatory based on country requirement
- DOT should be administered **seven days** a week throughout the full length of treatment, either facility-based or community-based
- Treatment should be taken **with food** for better absorption
- Adherence support (Eg. Health facility or community based DOT / VOT)should be initiated based on country specifications
- **Enablers/incentives** to cover travel expenditures (and food supplements if relevant) should be provided base on country policy

Treatment duration

- The standard treatment duration is 6 months = 26 weeks.

- If the sputum culture taken at 4 months of treatment (or later) is still positive, patients can receive an additional 3 months of treatment (total 9 months = 39 weeks).

Drug	Dose	Total number of tablets
Bedaquiline (100 mg tablet)	400 mg once daily for 2 weeks, then 200 mg 3 times per week	200
Pretomanid (200 mg tablet)	200 mg once daily	182
Linezolid (600 mg tablet)	1200 mg once daily (adjustable)	264 - 364 (based on Nix trial)

Treatment modification

- The following modifications in the management of adverse events may be considered based on experience in the Nix-TB study:
  - Can be temporarily interrupted or the dosage can be reduced to 600 mg or 300 mg after the first 4 weeks of treatment at full dose of 1200 mg
  - Can be restarted at same or lower dose (not < 300 mg once daily)
  - Can be permanently discontinued after **at least 4 weeks** of 1200 mg daily dose, while smear negative and clinically improving; if total exposure less than 4 months, discuss with National Consilium / Expert TB committee
  - An interruption of the FULL BPaL REGIMEN is allowed for a **maximum of 14 days in the first 4 weeks** of treatment
  - Missed doses of Lzd due to adverse reactions are **to be made up** at the end of treatment

Treatment modification

- **Bedaquiline and/or Pretomanid**
  - **No** dose modifications or temporary interruptions are allowed
- **Full BPaL regimen**
  - Can be interrupted for maximum 35 consecutive days, thereafter the patient should be referred to the National Consilium / Expert TB Committee to decide on further management
  - Missed doses to be made up at the end (not for Lzd)

- **Any dose modification/interruption** of the BPaL regimen should be followed by a careful clinical assessment to observe the effect and managed accordingly and documented on the **study evaluation form**

- Interruptions/reductions **without clinical improvement** should be regarded with **additional caution**

- **In any doubt,** discuss patient with National Consilium / Expert TB Committee (regimen may need to be strengthened and patient withdrawn from study)

Discontinuation of the BPaL regimen

When:

- Permanent discontinuation of Lzd before completion of 1200 mg daily dose for at least the first 4 consecutive weeks of treatment

- Permanent discontinuation of Lzd after receiving 1200 mg daily for at least the first 4 consecutive weeks, without evidence of negative smear and clinical improvement

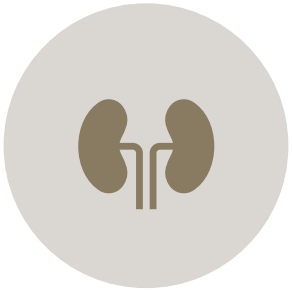
- Permanent discontinuation of either Bdq or Pa

- **Discontinuation** of the regimen should be documented on **the study evaluation form and treatment completion form**

In all the above cases, the patient should be referred to the National Consilium / Expert TB Committee to construct a new regimen by replacing BPaL component drugs and/or adding additional drugs

Treatment monitoring

Monitoring should be based on the clinical evaluation schedule



Increasing monitoring can be as a result of AEs or co-morbidities which require frequent follow ups

In significant laboratory or ECG abnormalities, more frequent monitoring should also be performed

A study evaluation form should be completed during every visit; indicate type of visit on the form (e.g. week 2, month 1, etc)

Post treatment follow up

- Important to assess patients for signs of recurrent TB

- At 6 and 12 months after completion of treatment
  - Clinical assessment, including follow-up on adverse events
  - Sputum smear and culture, CXR

- Need to complete a **Study evaluation form** and a **Follow-up completion form** at each follow-up visit

- To be incorporated in **routine** DR-TB treatment monitoring

- **pDST** should be done on **any positive culture** (including Bdq, Lzd); during follow-up; isolate to be forwarded to for sequencing and comparison with (frozen) baseline isolate

Assessment/Review

1. **Which are the required exams to be be conducted in order to monitor treatment response?**
   a. ECG, FBC and biochemistry
   b. Xpert MTB/Rif and LPA
   c. Physical examination, smear, culture, and Chest X-Ray
   d. Karnofsky score and visual test charts

2. Which statement is *correct* concerning discontinuation or modification of drugs in the BPaL regimen?

a. Bdq should be discontinued if QTcF > 500 ms; treatment can continue with Pa and Lzd for maximum 35 days
b. Lzd dosage can be reduced to 600 mg or 300 mg at any time during treatment
c. Missed doses of Lzd due to adverse reactions are not to be made up at the end of treatment
d. Interruption of the full BPaL regimen in case of adverse events is not allowed

ZeNix

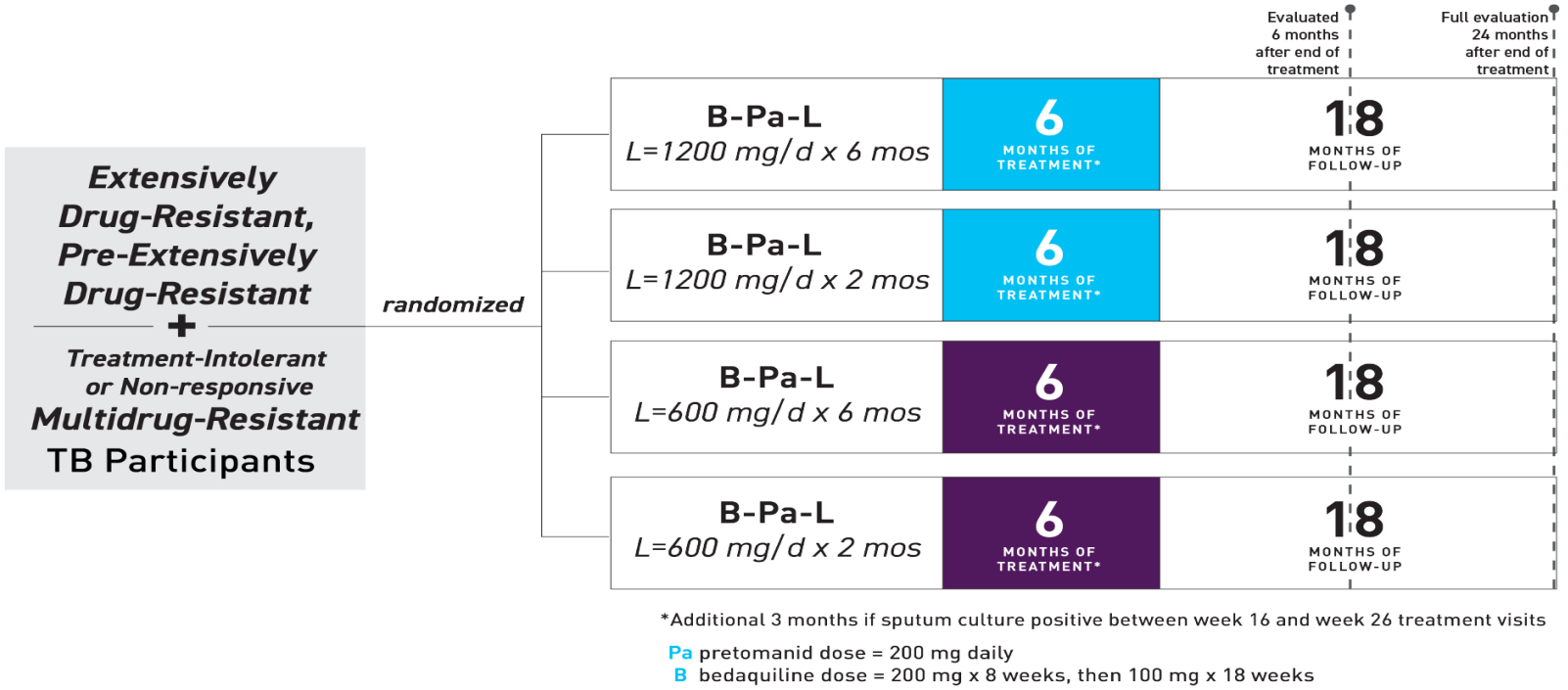
Improvements in the BPaL Benefit – Risk Value: The ZeNix Trial

TB Alliance

KNCV TUBERCULOSIS FOUNDATION

ZeNix: Linezolid Optimization Trial

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



- Enrollment completed in South Africa, Russia, Georgia, Moldova
- 181 participants enrolled
- Results of all patients followed to the primary endpoint 6 months after treatment completion expected in 2021

TB Practecal

Innovating MDR-TB Treatment

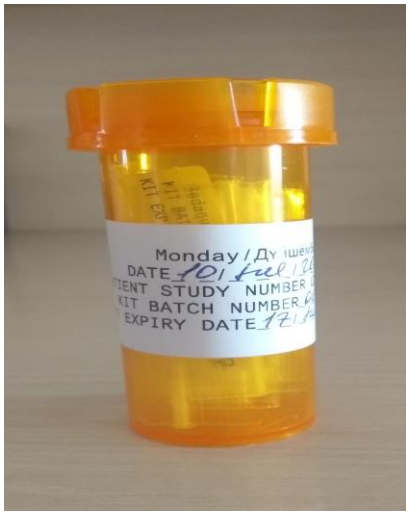
TB Practecal CT

TB PRACTECAL: Regimens

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

Regimen 1

- contains B , Pa and Lzd +
- Mfx – 4 00 mg once daily

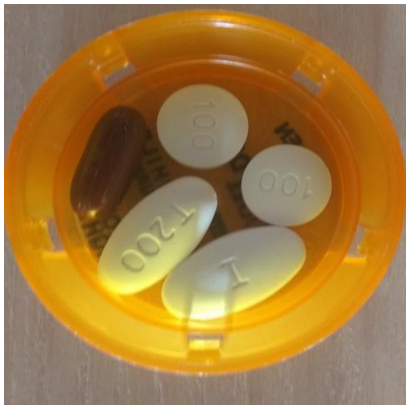


Regimen 2

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

Regimen 3

- B – 400 mg once daily for 2 weeks then 200 mg 3x p/w for 22 weeks
- Pa – 200mg once daily
- Lzd – 600mg daily for 16 weeks then 300mg daily for the remaining 8 weeks



TB PRACTECAL: Regimens

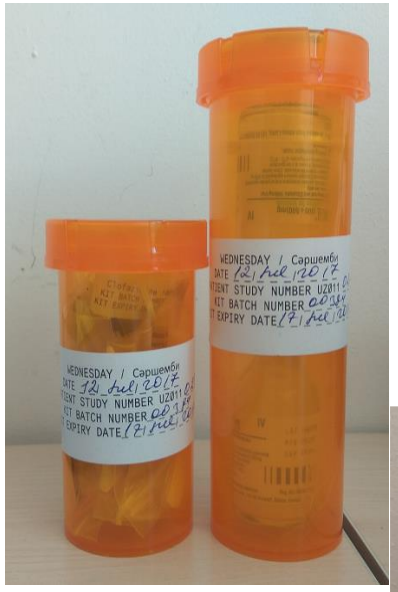
- **Standard of Care (SOC) Arm:** Locally accepted **Standard of Care (SOC)** based on the New WHO guidelines (May 2016).

SCR

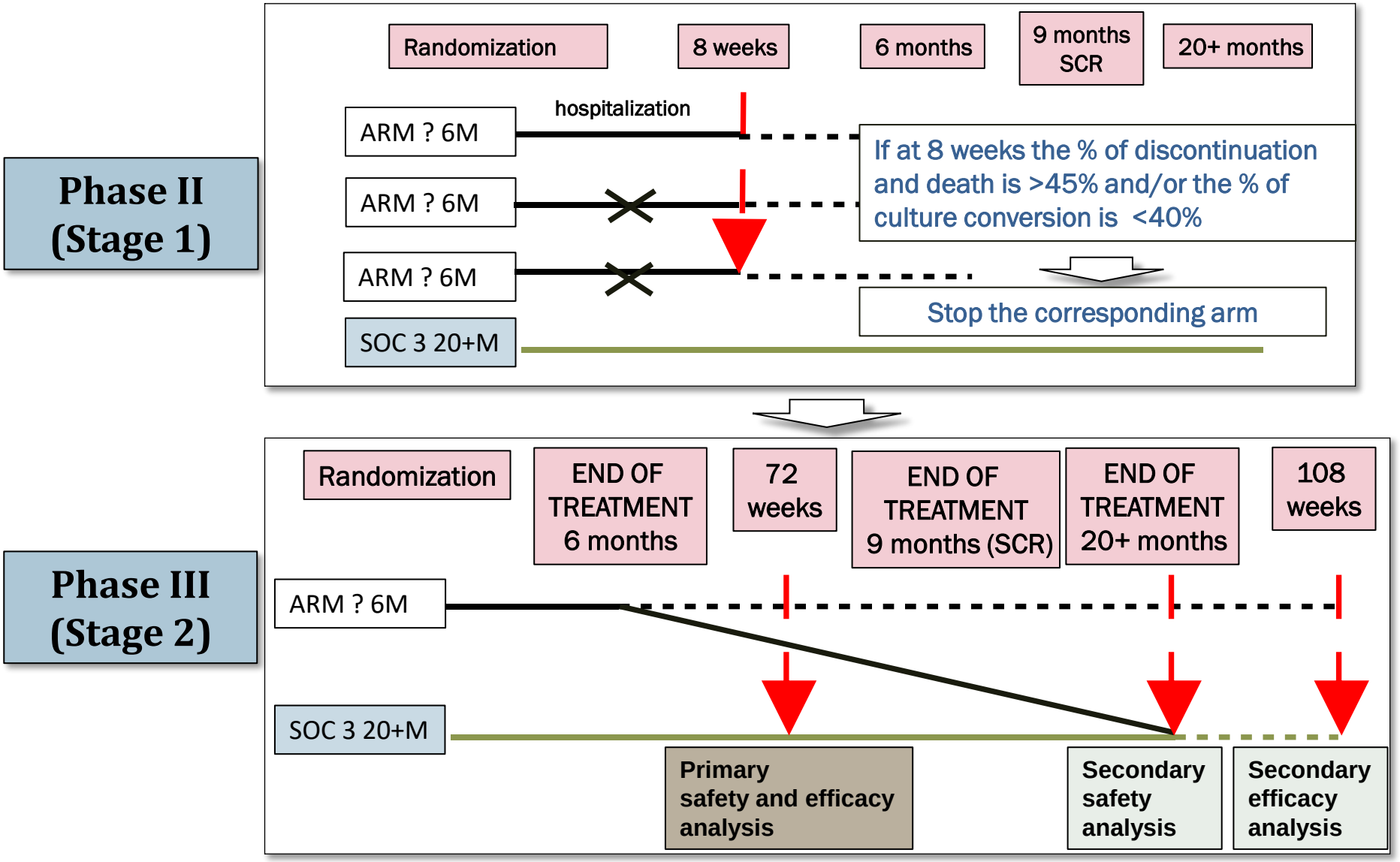
- Treatment last for a minimum of 36 weeks and maximum of 44 weeks then follow-up of 72 weeks or 64 weeks)

Conventional

- Treatment last for a minimum of 80 weeks for MDR and 96 weeks for XDR patients



TB PRACTECAL: stage I and II



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2. The protocol for the Nix-TB study is available at: https://clinicaltrials.gov/ct2/shw/NCT02333799.https://clinicaltrials.gov/ct2/show/ NCT02333799, and the results of the Nix-TB study have been published (90)

3. The NEJM article: https://www.nejm.org/doi/suppl/10.1056/NEJMoa1901814/suppl_file/nejmoa1901814_protocol.pdf

4. TB Practecal Clinical Trial protocol

ACKNOWLEDGEMENTS

Agnes Gebhard, Mamel Quelapio, Inge Koppelaar, Fraser Wares, Ieva Leimane, Mansa Mbenga

This presentation was developed by KNCV TB Foundation with support of the TB Alliance, and uses elements from new WHO policies guidance on the use of new drugs for the treatment of DR-TB

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