Pretomanid and BPaL Regimen for Treatment of Highly-Resistant Tuberculosis

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TB Alliance

Antimicrobial Drugs Advisory Committee

Introduction and Overview of Pretomanid New Drug Application

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TB: Kills More People Than Any Other Infectious Disease

- Disease of poverty[1]
- > 2 billion people infected worldwide[2]
- 1.6 million deaths annually[2]
- Transmissible through person-to-person contact

1. World Health Organization Global TB Report, 2018 2. World Health Organization, 2016

Drug-Resistant Strains of TB Becoming More Common, Extremely Challenging to Treat

- Person-to-person transmission greatest source of drug resistant TB[1]
- Drug resistant TB largest single source of antimicrobial resistance globally[2]

1. Shah, 2017 2. O'Neill, 2016

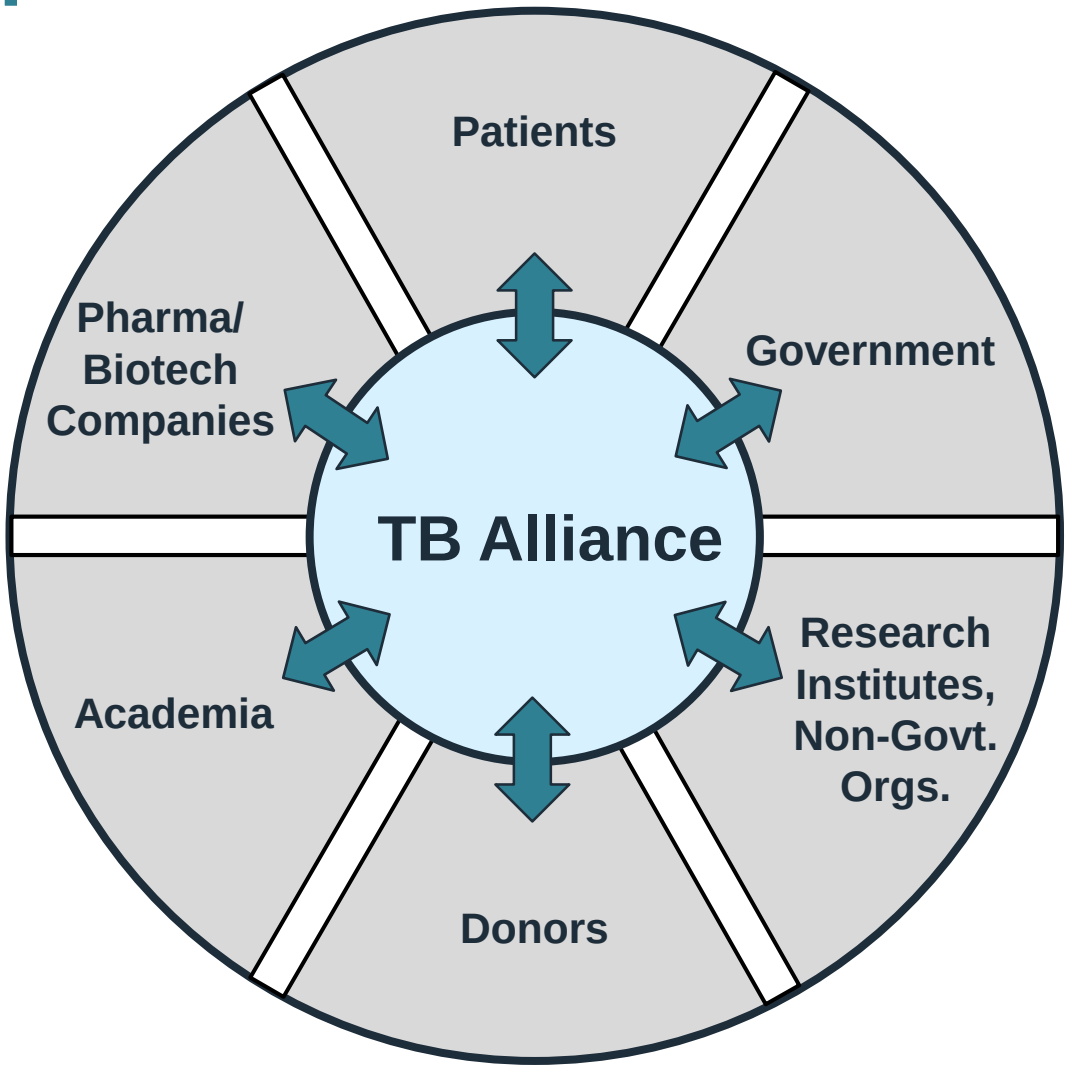
Challenges in Treatment of Extensively Drug-Resistant TB

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 rate

TB Alliance: Nonprofit, Product Development Partnership Developing Better, Faster TB Therapies

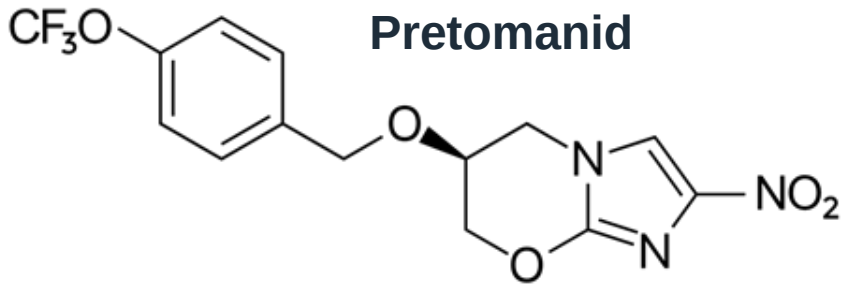
- Long-neglected field of tuberculosis
- Founded in 2000 at meeting in South Africa
  - Convened by Rockefeller Foundation
  - Hosted by Medical Research Council of South Africa, NIH, Bill and Melinda Gates Foundation, Wellcome Trust, UK Department for International Development
  - 120 representatives primarily from academia, government, non-governmental organizations, donors

Work with and Leverage Global Network of Public, Private Partners



- Only develop products that will be adopted, available, affordable
- Largest pipeline of potential new TB drug candidates

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
- Studied in 1168 individuals, 19 clinical studies
- FDA granted Priority Review, Qualified Infectious Disease Product, and Orphan Drug status

Nix-TB Pivotal Study Presented Opportunity to Evaluate 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

BPaL: All-Oral, Short, Fixed Regimen

- Breakthrough cure for extensively drug resistant or treatment intolerant or nonresponsive multidrug resistant pulmonary TB
  - “Highly-resistant TB”
  - Cure = no clinical or bacteriologic evidence of TB ≥ 6 months after completion of treatment
- 6-month BPaL regimen cured approximately 90% of patients
- AEs manageable and as expected with regimen
  - Majority able to complete therapy, achieve therapeutic success

Overcoming Challenges in Treatment of Highly-Resistant TB

Treatment Challenges	Opportunities with BPaL
Too long: 18+ months	6-month regimen
Too complicated: ≥ 5 drugs, some IM / IV, no defined regimen	3 drug, all oral, set regimen
Highly toxic, leading to discontinuations	Manageable tolerability, few discontinuations
Poor efficacy: ~20% cure rate pre-bedaquiline era in South Africa	90% cure rate

Indication

- *Pretomanid is a nitroimidazooxazine antimycobacterial drug indicated, as part of a combination regimen with bedaquiline and linezolid, in adults for the treatment of pulmonary extensively drug resistant (XDR) or treatment-intolerant or nonresponsive multidrug resistant (MDR) tuberculosis.*

- Represents select group of most severe, worst-prognosis patients with XDR-TB or MDR-TB

Nix-TB: Ongoing Study Initiated in 2015, Completed Enrollment in 2017

- 109 patients enrolled
- FDA agreed safety / efficacy data on first 45 patients acceptable to support NDA
- Presentation will include
  - Primary efficacy analysis: 81 patients
  - NDA safety analysis: 109 patients
  - 120-day efficacy update: 104 patients
- Patient follow-up ongoing to 24 months post end of treatment

Agenda

Unmet Need	**Neil Schluger, MD** Chief of the Division of Pulmonary, Allergy and Critical Care Medicine, Columbia University Department of Medicine
Nix-TB Results Efficacy and Safety	**Daniel Everitt, MD** Vice President and Senior Medical Officer TB Alliance
Clinical Perspective	**Francesca Conradie, MD** Deputy Director, Clinical HIV Research Unit University of the Witwatersrand Department of Medicine Johannesburg, South Africa
Q&A Moderator	**Daniel Everitt, MD**

Additional External Experts

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Chief Strategist, Regulatory Biostatistics/Data Standards at Rho

Unmet Need for Treatment of Highly-Resistant Tuberculosis

Neil Schluger, MD

Chief of the Division of Pulmonary, Allergy and Critical Care Medicine
Columbia University Department of Medicine

TB is World's Leading Cause of Death From an Infectious Disease

- WHO estimates 10 million developed TB in 2017
- > 4,000 people die every day
- Significant concern for people living with HIV
  - TB is greatest killer of people with HIV

World Health Organization Global TB Report, 2018

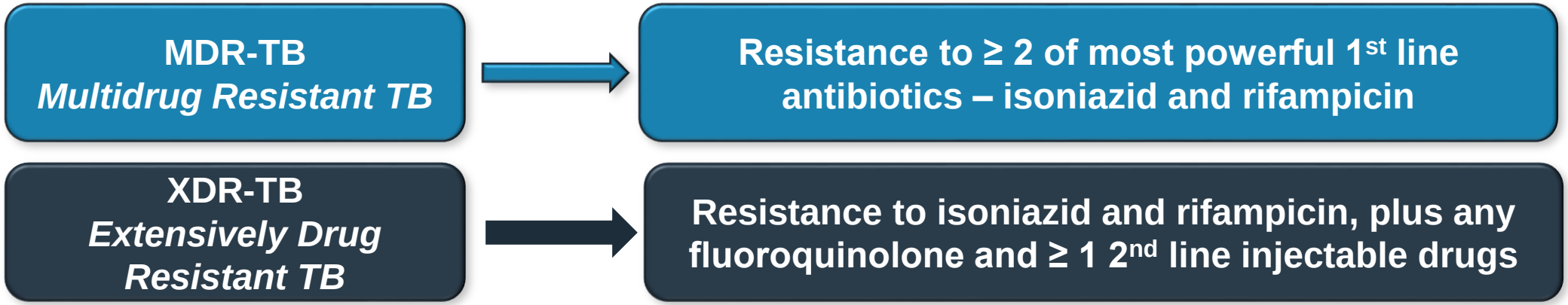
TB is Debilitating, Systemic Disease

- Fever, cough, weight loss, sputum, and hemoptysis
- Social isolation and stigma
- Treatment delays increase risk for
  - Permanent lung damage
  - Bacteria spreading to other organs
  - Transmission to others in community
  - Death

Effectively Treating Simplest Forms of TB Takes Between 6-9 Months

- Complex, difficult regimens present challenge in parts of world where access to care is limited
- Untreated or improperly treated patients remain sick, may die
- If drugs taken incorrectly, TB may become drug resistant

TB that is Resistant to Drugs is More Difficult to Treat



- Resistant TB can result from either
  - Transmission from one person to another
  - Failure of previous treatment
- Anti-microbial resistance is increasing
  - Likelihood of epidemic with difficult-to-treat strains

Growing Threat of Drug-Resistant TB

- Recognized in New York City in early 1990s, now globally[1]
- XDR-TB confirmed in 127 countries[2]
- In 2017, ~460,000 cases of MDR-TB globally[2]
  - ~39,000 estimated XDR-TB cases
  - ~8700 patients treated for XDR-TB

1. Frieden, 1993 2. World Health Organization Global TB Report, 2018

Treatment for Highly-Resistant TB is Burdensome, Prolonged, and Toxic

- Typical treatment consists of up to 8 drugs[1]
  - 6 months of daily injections
  - Followed by 12 to 18 months of 5 drugs daily
- Often requires hospitalization
- Drugs difficult to take, side effects include permanent hearing loss and kidney damage from injectable drugs[1]
- ~20 to 25% of patients with MDR-TB and XDR-TB treated[2]

1. World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 2. World Health Organization Global TB Report, 2018

Very Few Trials to Guide Treatment for Drug-Resistant TB

- Design regimens by creating lists, crossing off drugs that show resistance
- STREAM trial of patients with MDR-TB[1]
  - Under best conditions, treatment shortened to 9 months
  - Required administration of ≥ 7 drugs
  - Side effects as common as longer treatment regimens
  - Patients susceptible to 2nd line injectable or fluoroquinolone
- Improved outcomes with new drugs recommended by WHO[2]
  - Little data on ***how*** to use – in what combinations, for how long

1. Moodley, 2016 2. World Health Organization, 2018

Need New, Defined Regimen for Highly-Resistant TB with Little to No Resistance

New regimen should

- Shorten treatment duration
- Allow quick culture conversion to interrupt transmission
- Simplify administration
- Improve tolerability and adverse event management
- Improve cure rates

Nix-TB Results

Daniel Everitt, MD
Vice President and Senior Medical Officer
TB Alliance

Pretomanid with Bedaquiline and Linezolid Cured ~90% of Patients with Highly-Resistant TB

- 3-drug, all-oral, 6-month regimen
- Patients converted to culture negative status very quickly
  - Median time of < 6 weeks
- Patients improved clinically
  - Reduction of TB symptoms
  - Overall improvement in patient-reported health status

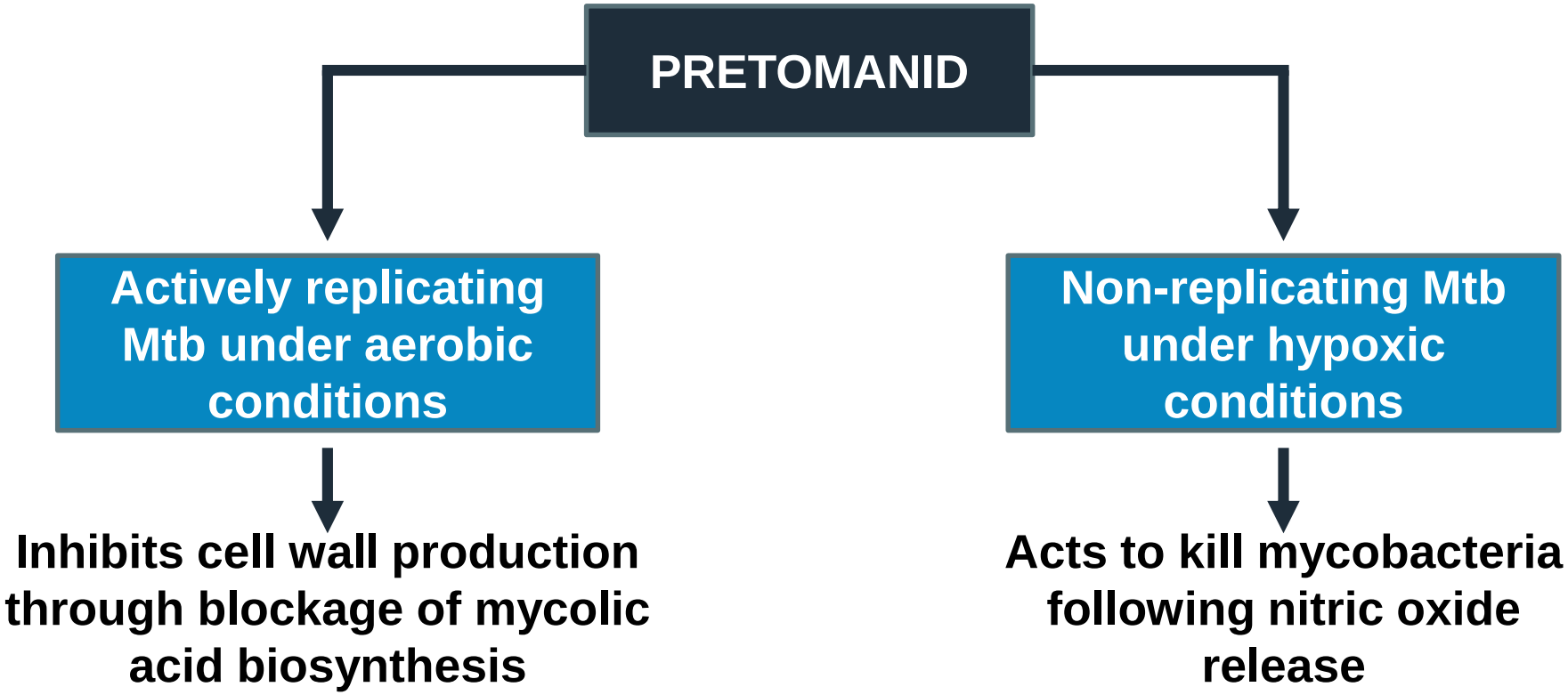
Nix-TB is First Clinical Trial of Fully New Regimen for Highly-Resistant TB

- Includes pretomanid, new chemical entity
- Focus: developing new drug within specific drug regimen
- Pivotal phase 3, multicenter, open-label, single-arm study
- Assesses efficacy, safety, tolerability of BPaL in patients with
  - XDR-TB or
  - TI/NR MDR-TB
- 109 patients enrolled and treated at 3 centers in South Africa

XDR-TB: Extensively Drug Resistant-TB
TI/NR MDR-TB: Treatment Intolerant or Non-responsive Multi-Drug Resistant-TB

Pretomanid Mode of Action Complex, Requires Metabolism of Drug to Active Form

- Pretomanid kills replicating and non-replicating *M. tuberculosis* bacteria



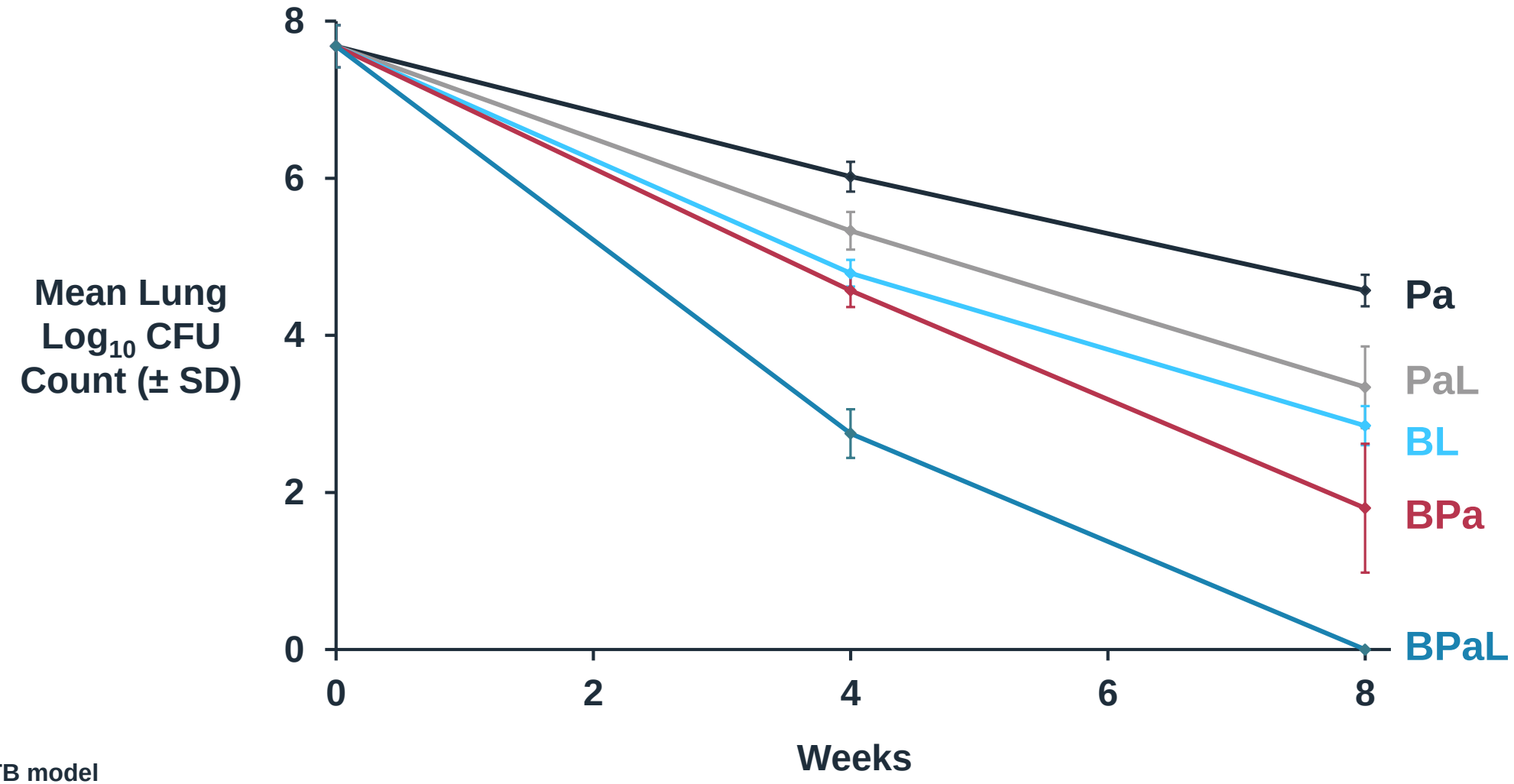
Minimum of 3 Drugs Required to Treat TB Infection

- Monotherapy with streptomycin and isoniazid led to unacceptable resistance
- 2-drug therapy showed some success, but required long durations
- Concerns of resistance led to consensus of 3-drug minimum to effectively treat 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
  - Clinically relevant doses demonstrated impressive results
  - TB bacteria in mouse lungs are quantified to assess bactericidal and curative activity

Potent Bactericidal Activity with Pretomanid Alone, Greatest with Full BPaL Regimen



Mouse TB model
5 mice / time-point / group

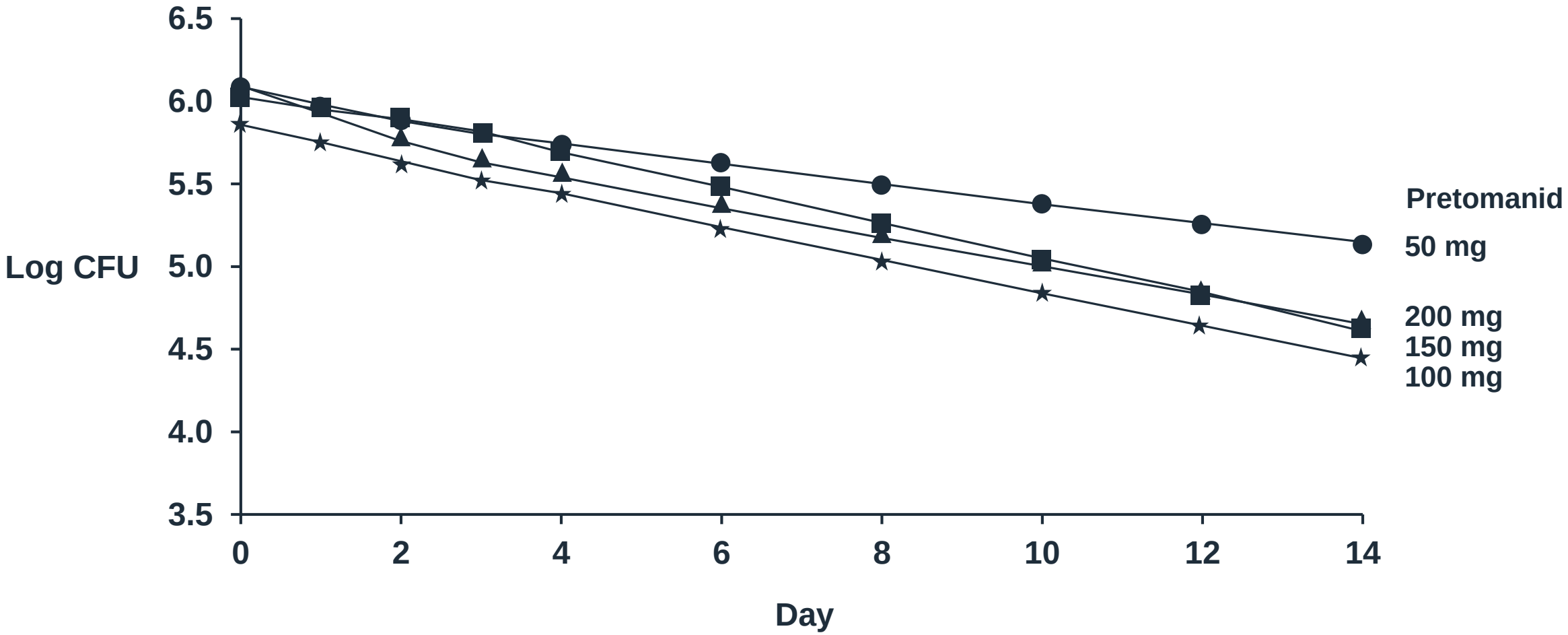
Pretomanid's Contribution to Curative Activity of BPaL in Mouse TB Model

Regimen	Proportion of Mice Relapsing		
	Treatment Duration		
	2 Months	3 Months	4 Months
BL	15/15	15/15	14/15
BPaL	7/15	0/15	0/15

- BL: almost all mice relapsed 3 months after ending therapy
- BPaL: all mice were cured after 3 months of therapy
- Pa: prevented B resistance compared to BL

B: bedaquiline; Pa: pretomanid; L: linezolid

Phase 2a Study of Early Bactericidal Activity of Pretomanid in Patients with TB



N=15 per group

Nix-TB: Single-Arm Study

- Patients with highly-resistant TB have limited treatment options
- No standard of care for highly-resistant TB
- Challenges in randomizing patients to BPaL vs historical ad-hoc regimens
  - Many side effects, poor treatment outcomes, long and complex, requiring ≥ 5 medicines including injectables

Nix-TB Conducted in South Africa

- Location ideal for this trial
  - High XDR-TB prevalence
  - Excellent investigators and trial infrastructure
  - Reliable regulatory environment

Nix-TB Dosing of BPaL Regimen

Pretomanid
200 mg QD for 26 weeks

+

Bedaquiline
400 mg QD for 2 weeks, followed by 200 mg 3 times per week for a total of 26 weeks

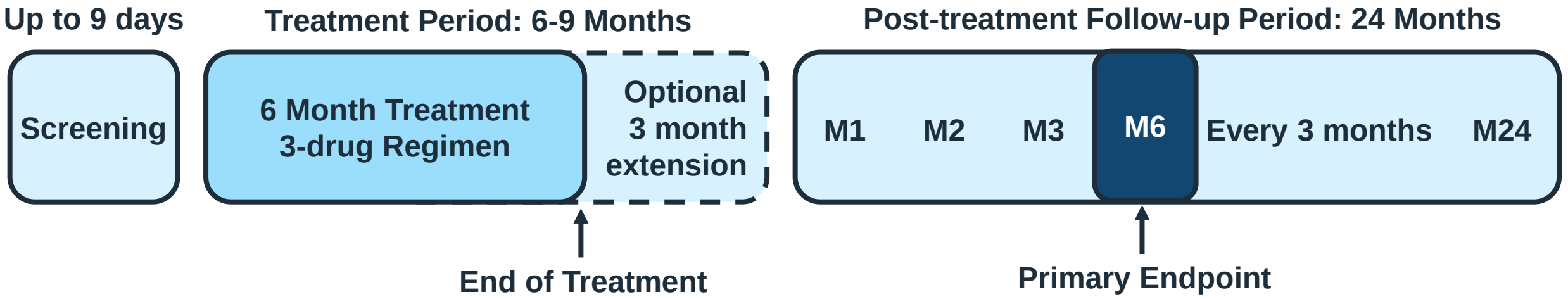
+

Linezolid
1200 mg daily for 26 weeks

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

Nix-TB Study Design: 6-Month Treatment Period Same as Time to Treat Standard TB



- Patients who were culture positive between months 4 and 6 could continue treatment for additional 3 months
- Study medication administered orally, with food
- Primary endpoint at 6 months post-treatment supported by literature

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, cured

Nix-TB Key Inclusion Criteria

- XDR-TB or TI/NR MDR-TB
  - Documented by culture or molecular test within 3 months of enrollment
  - Documented drug resistance
- Body weight ≥ 30 kg
- Chest X-ray consistent with pulmonary TB, taken within 1 year prior to screening

Nix-TB Key Exclusion Criteria

- HIV-infected patients with a CD4+ count of ≤ 50 cells/μL
- Patients needing drugs such as strong CYP450 hepatic enzyme inducers/inhibitors, drugs causing neuropathy, or drugs prolonging QT interval
- Abnormalities of concern for linezolid toxicity or hepatic safety
  - Hemoglobin < 8.0 g/dL
  - Platelets < 75,000/mm^3
  - Absolute neutrophil count < 1,000/mm^3
  - AST or ALT ≥ 3X ULN
  - Total bilirubin > 1.5X ULN

Primary Efficacy Analysis

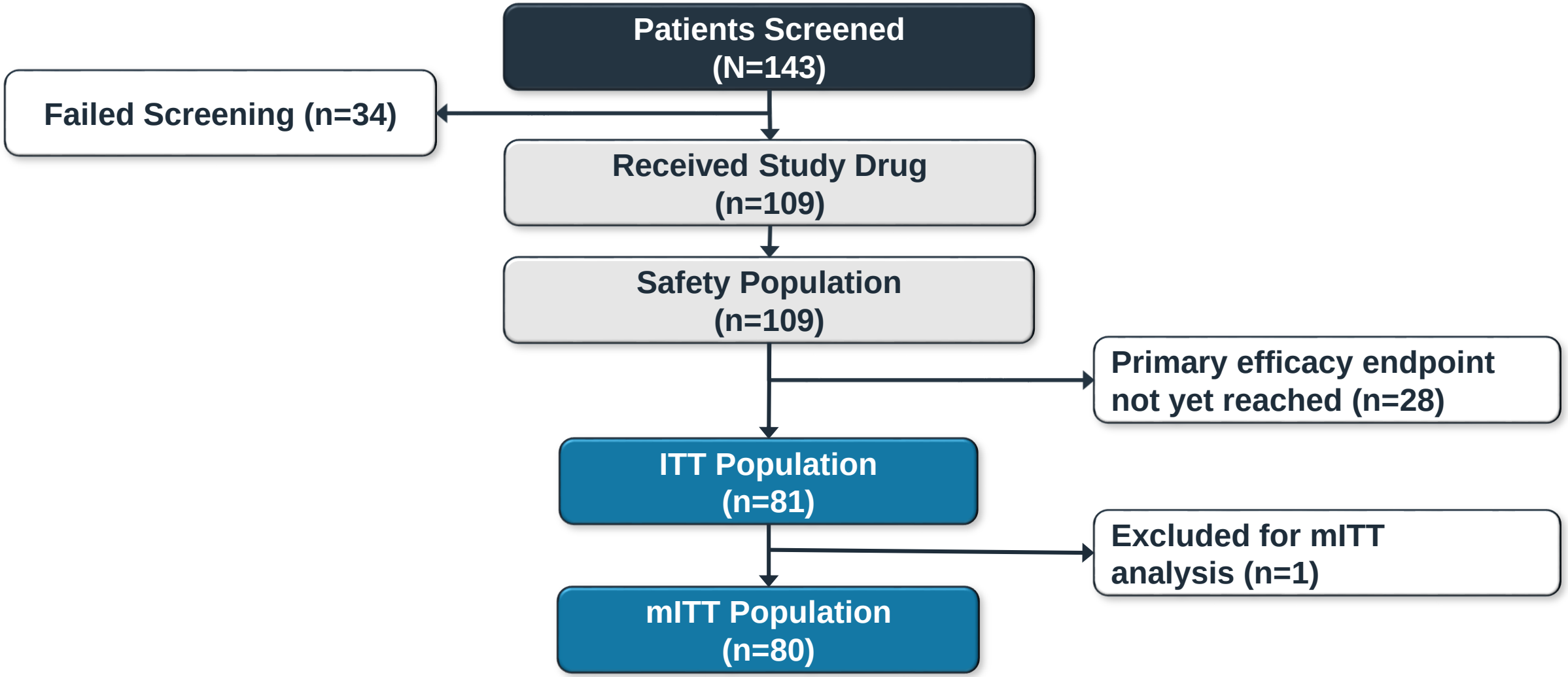
- Primary endpoint analysis
  - Percent of favorable outcomes
- Success of trial
  - Lower bound of 95% CI > 50% favorable rate
  - Higher than prior reported experience at time of trial design

Key Secondary Endpoints

- Time to sputum culture conversion to negative status
- Changes in TB symptoms
- Patient status at 24 months after end of treatment

Nix-TB Efficacy Results

93% of Patients Successfully Completed Treatment (ITT Population)



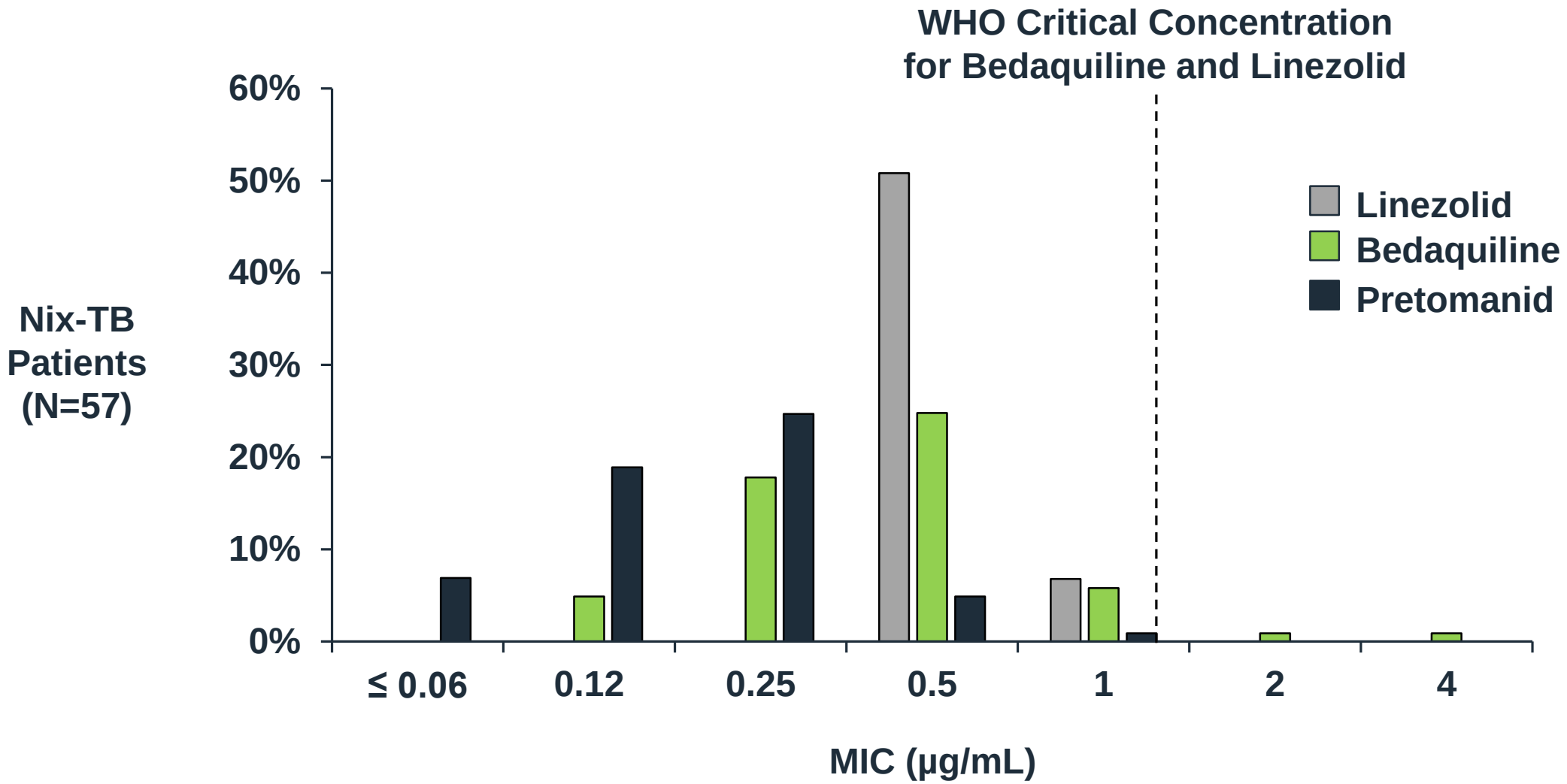
Demographics in Nix-TB

	BPaL Regimen N=109
Age, years, mean (range)	35.6 (17 – 60)
Male	52.3%
Race	
Black	76.1%
White	0.90%
Mixed race	22.9%
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	65.1%
MDR-TB non-responsive	17.4%
MDR-TB treatment intolerant	17.4%
Duration since original TB diagnosis, months, median (range)	12.1 (0.5 – 141.0)
HIV Positive	51.4%
Duration since HIV diagnosis, years, mean (range)	4.7 (0.2 – 14.3)
Chest cavity X-ray results compatible with TB	
Unilateral	46.8%
Bilateral	37.6%
None	15.6%

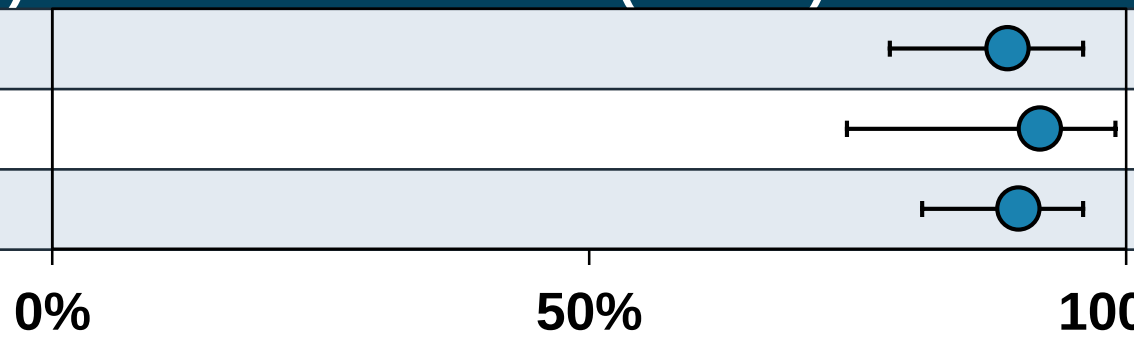
Retrospective Baseline MICs of Available Isolates Shows Susceptibility to BPaL



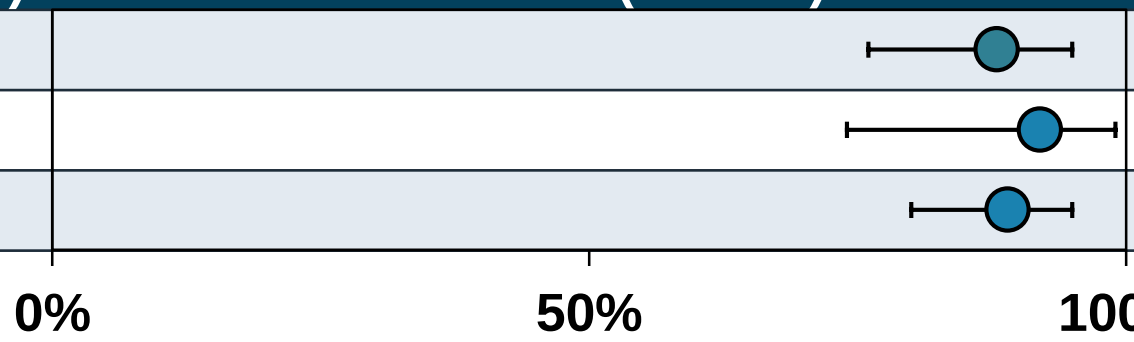
WHO: World Health Organization

Primary Endpoint Met by Majority of Patients

mITT Population	Patients (n)	Favorable (95% CI)	Favorable (95% CI)
XDR-TB	55		**89%** (78, 96)
TI/NR MDR-TB	25		**92%** (74, 99)
Total	80		**90%** (81, 96)

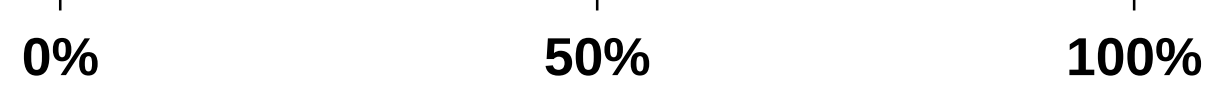


ITT Population	Patients (n)	Favorable (95% CI)	Favorable (95% CI)
XDR-TB	56		**88%** (76, 95)
TI/NR MDR-TB	25		**92%** (74, 99)
Total	81		**89%** (80, 95)



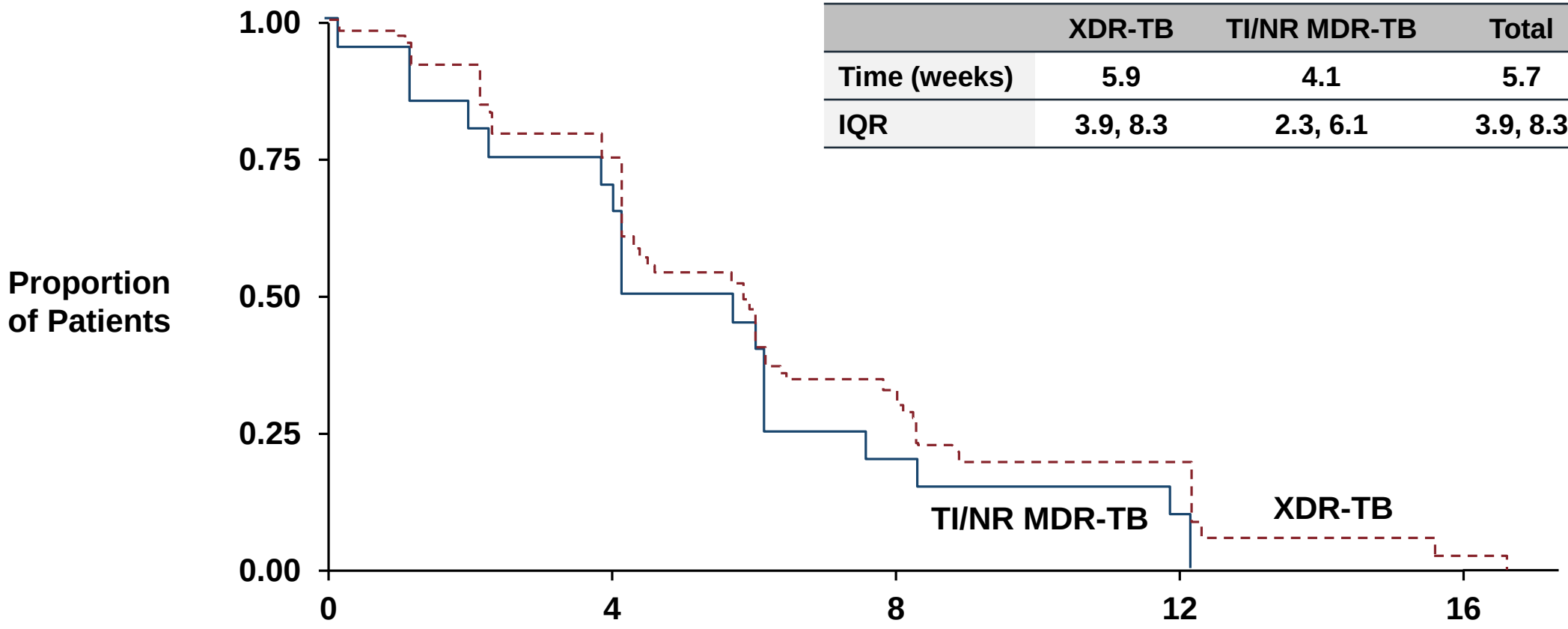
Similar Outcomes by HIV Status

HIV Status, mITT Population	Patients (n)	Favorable (95% CI)	Proportion Favorable (95% CI)
HIV-positive	39		**90%** (76, 97)
HIV-negative	41		**90%** (77, 97)
Total	80		**90%** (81, 96)



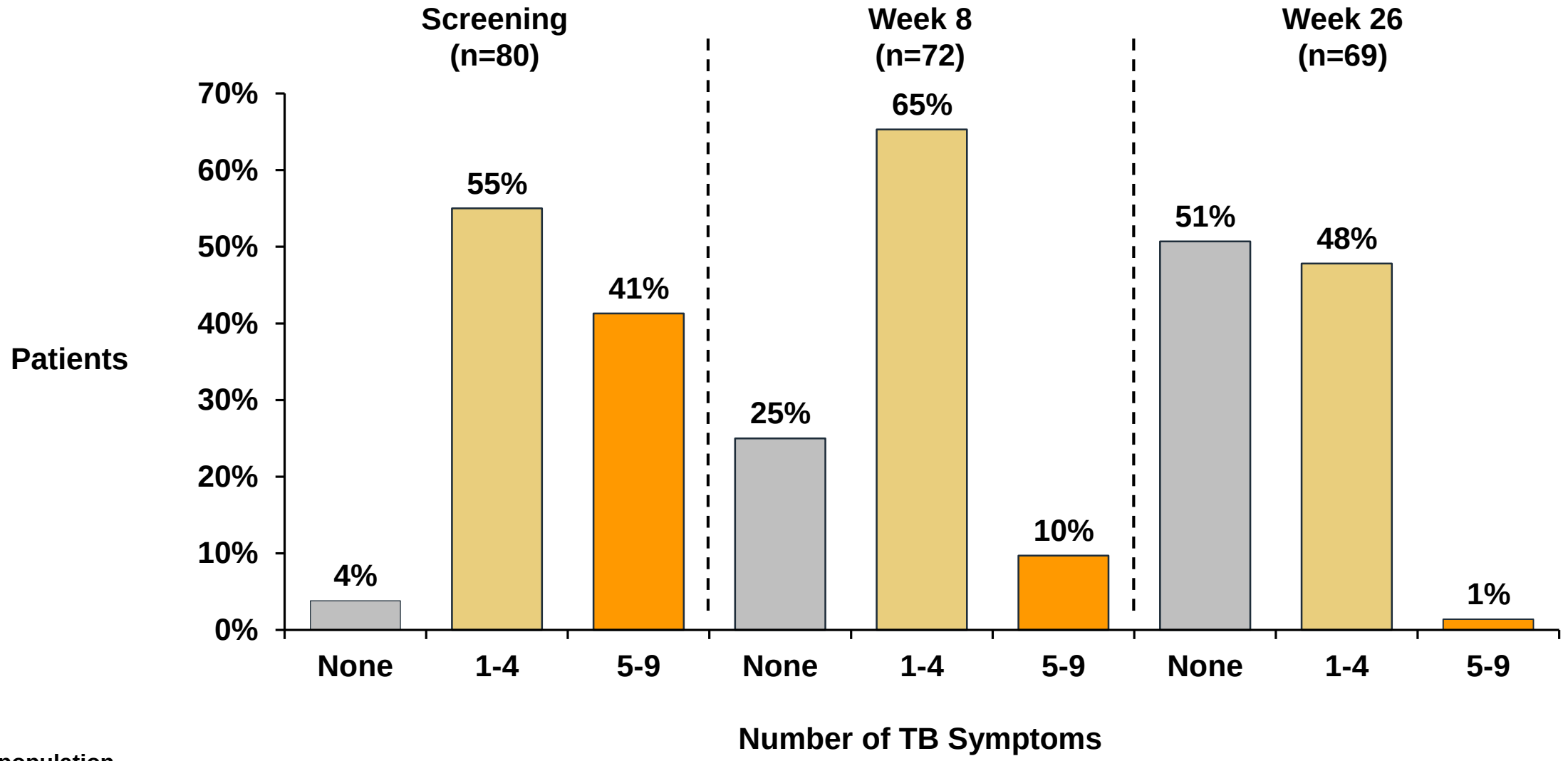
Secondary Endpoint: Median Time to Sputum Culture Conversion < 6 Weeks

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



Number at Risk					
TI/NR MDR-TB	20	14	4	2	0
XDR-TB	48	36	13	7	1

Secondary Endpoint: Patients Achieved Reduction of TB Symptoms by End of Treatment



mITT population

Secondary: Bacteriologic Failure or Relapse at 24 Months Post-Treatment Supports Long-Term Success

- 23 patients enrolled at least 30 months before NDA data cut-off
  - 3 died during treatment
  - 1 relapsed 15 months after completion of study regimen

Primary Efficacy Analysis from 120-Day Update Shows Favorable Rate of 91%

mITT Population	Patients (n)	Favorable (95% CI)	Proportion Favorable (95% CI)
XDR-TB	70		**90%** (80, 96)
TI/NR MDR-TB	34		**94%** (80, 99)
Total	104		**91%** (84, 96)

Matched Historical Control Comparator Supports Benefit of BPaL Treatment

- 84 patients in historical control compared with first 44 patients in Nix-TB
  - Control group patient data from one Nix-TB site
  - Same region, individually matched for age, sex, body weight, and HIV status
- Control group treated between 2008 and 2014 with various drug combinations
  - Did not include bedaquiline or linezolid
- Results either favorable or unfavorable

Higher Proportion of Patients in Nix-TB Study Had Favorable Outcomes vs Control

	Nix-TB Population N=44	Control Population N=84
Favorable	88.6%	10.7%
Unfavorable	11.4%	89.3%
Odds ratio (95% CI)	64.5 (8.8 – 472)	

BPaL Regimen Can Transform Treatment of Highly-Resistant TB – Short, Simplified, Effective

- 90% of patients with highly-resistant TB achieved relapse-free cure status 6 months after end of treatment
  - Lower bound far exceeded prespecified threshold
  - Same results with HIV co-infection
- Patients converted to culture negative status very quickly
  - Median time < 6 weeks
- Preliminary 24-month data indicate long-term cure

Safety

Nix-TB Safety Database: 109 Patients to be Followed for 24 Months Post-Therapy

- AEs as expected with treatment regimen
- AEs generally manageable through dose modifications
- Only patients who did not complete therapy were 6 who died
- 10 patients still on treatment at time of NDA submission

Larger Safety Database of Patients Exposed to Pretomanid

- 1168 patients across 19 studies
- Pretomanid studied alone and in different regimens

Phase 1: Adverse Events Occurring in ≥ 5% of Healthy Volunteers

Adverse Events	All Pretomanid N=289 n (%)	Placebo N=35 n (%)
Any AE	186 (64)	14 (40)
Headache	91 (32)	8 (23)
Nausea	34 (12)	0
Dermatitis contact	33 (11)	0
Hemoglobin decreased	31 (11)	0
Diarrhea	25 (9)	0
Dizziness	24 (8)	1 (3)

Phase 2: Adverse Events Occurring in ≥ 2% of Patients

Adverse Events	Pretomanid N=122 n (%)	HRZE N=16 n (%)
Any AE	47 (39)	7 (44)
Nausea	5 (4)	1 (6)
Vomiting	4 (3)	1 (6)
Pruritus generalized	4 (3)	0
Rash	4 (3)	0
Rash papular	4 (3)	0
Pruritus	3 (3)	2 (13)
Hemoptysis	3 (3)	1 (6)
Headache	3 (3)	0

Nix-TB: 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

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)

Nix-TB: Interruptions of BPaL Regimen

- All but the 6 patients who died 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 6 months of therapy or were ongoing

Nix-TB: Dose Modifications of Linezolid Enabled Patients to Complete BPaL Regimen

- Linezolid likely responsible for most adverse events and all dose modifications
  - 50 patients interrupted and resumed treatment at same or lower dose
  - 33 patients permanently discontinued linezolid, with all surviving patients (27) completing treatment
    - Peripheral neuropathy most common reason for discontinuing linezolid
  - 34 patients had no linezolid dose interruptions

Nix-TB: Serious Adverse Events Occurring in ≥ 2% of Patients

Serious Adverse Events	BPaL Regimen N=109 n (%)
Patients with at least 1 SAE	19 (17)
Pneumonia	3 (3)
Pulmonary TB	3 (3)
Sepsis	2 (2)
Hypoglycemia	2 (2)
Anemia	2 (2)

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

* Term for non-violent death in South Africa
EOT: end of treatment

Nix-TB Adverse Events of Special Interest

AEs of Special Interest Prospectively Identified

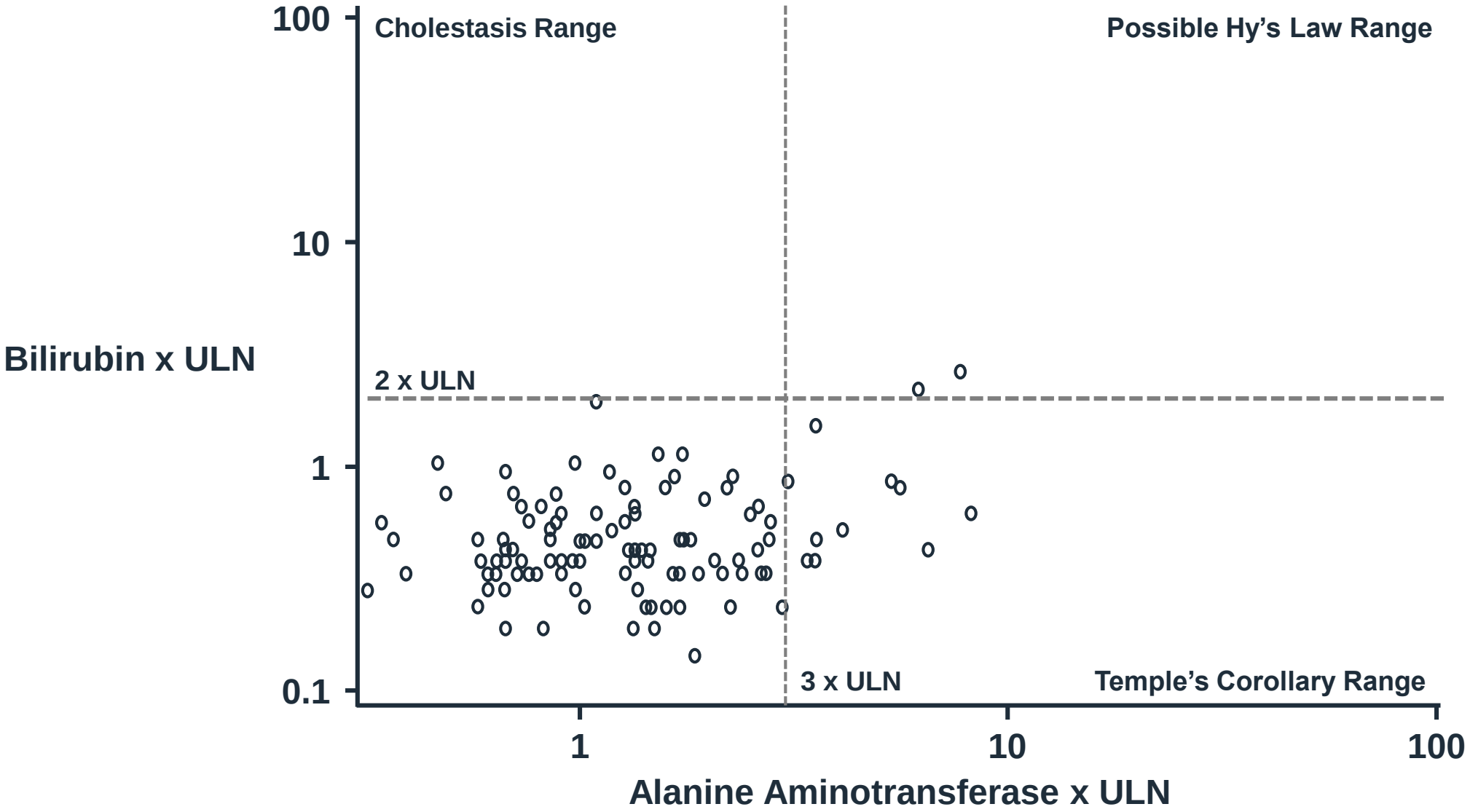
	Pretomanid	Bedaquiline	Linezolid
Lens disorders	X*		
Testicular toxicity	X*		
Convulsions	X*		X
ECG QT prolongation	X*	X	
Hepatic toxicity	X	X	
Myopathy / Rhabdomyolysis		X*	
Pancreatitis		X*	
Neuropathy (inc. optic)			X
Myelosuppression			X
Lactic acidosis			X

* Based on animal toxicology findings

Nix-TB: Hepatic Safety

Parameter x ULN	BPaL Regimen N=109 n (%)	
	All Elevations	Elevations when Normal at Baseline
ALT		
> 3 and ≤ 5 x ULN	6 (5.5)	2 (1.8)
> 5 and ≤ 8 x ULN	5 (4.6)	3 (2.8)
> 8 x ULN	1 (0.9)	0
Total bilirubin		
> 1 x ULN and ≤ 2 x ULN	6 (5.5)	6 (5.5)
> 2 x ULN	2 (1.8)	2 (1.8)

Potential Hy's Law Observed in 2 Cases



Potential Hy's Law in Phase 1–3 Studies of Varying Duration

	Pretomanid Alone N=411 n (%)	Pretomanid Combinations N=633 n (%)	HRZE N=229 n (%)	Nix-TB N=109 n (%)
Study participants	Healthy volunteers DS-TB	DS-TB MDR-TB	DS-TB	TI/NR MDR-TB XDR-TB
Patient years of exposure	18.2	124.4	50.2	51.9
ALT or AST > 3 x ULN and total bilirubin > 2 ULN (Potential Hy's Law)	0	4 (0.6)	3 (1.3)	2 (1.8)

- Both potential cases in Nix-TB resolved and patients resumed and completed treatment

DS: drug susceptible

AEs Potentially Related to Pancreas

	BPaL Regimen N=109 n (%)
Patients with AEs potentially related to pancreas	**22 (20)**
Amylase increased	**9 (8)**
Hyperamylasemia	**8 (7)**
Lipase increased	**5 (5)**
Pancreatitis	**2 (2)**
Hyperlipasemia	**1 (1)**
Pancreatitis hemorrhagic	**1 (1)**

- Many events were Grade 3 or 4, and 2 considered SAEs
- No withdrawals (aside from deaths) from Nix-TB due to these events
  - 2 patients who died had pancreatitis on autopsy

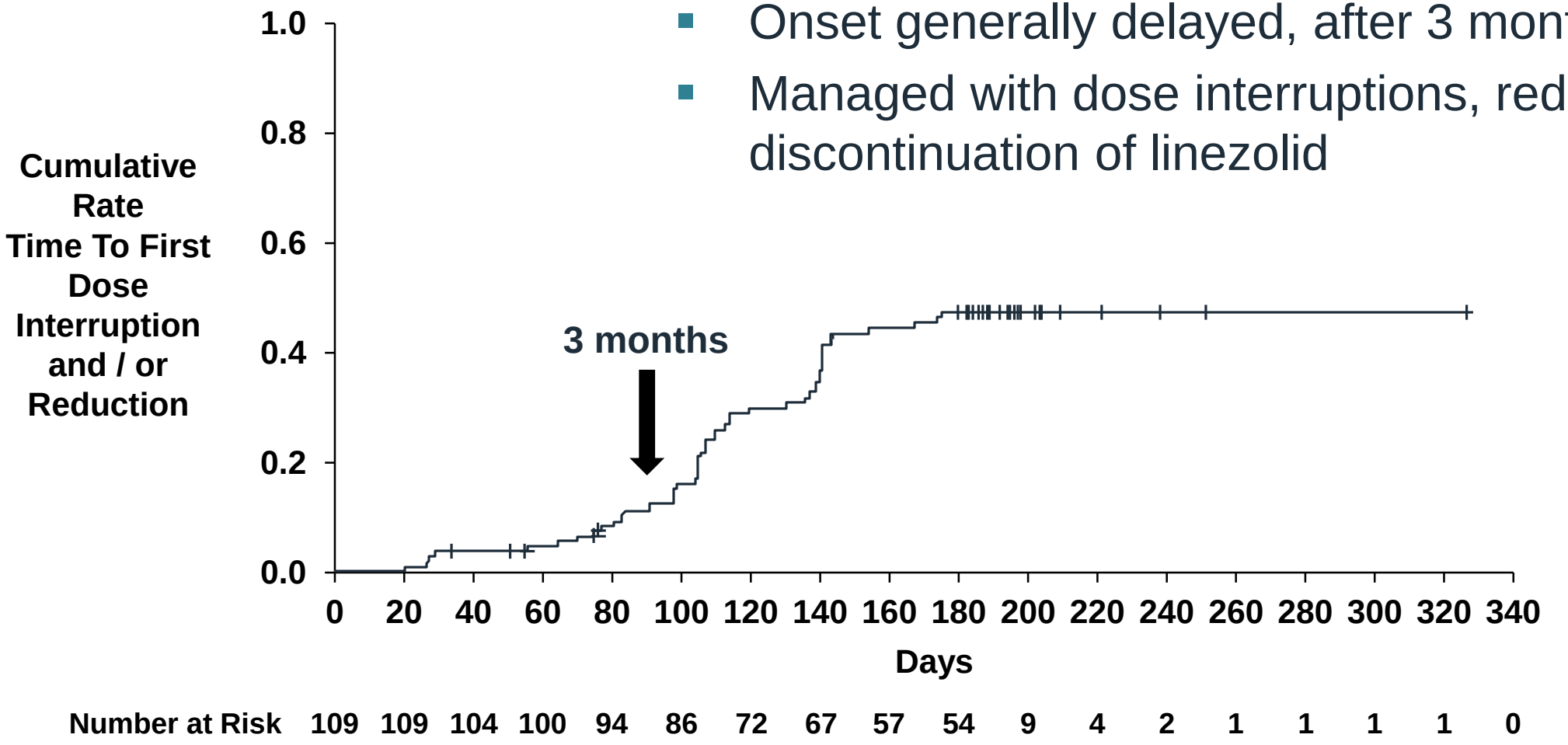
Peripheral Neuropathy Associated with Linezolid, Most Common Adverse Event

Peripheral Neuropathy	BPaL Regimen N=109 n (%)
Patients with any peripheral neuropathy AESI	87 (80)
Peripheral sensory neuropathy	75 (69)
Neuropathy peripheral	10 (9)
Paraesthesia	5 (5)
Hypoaesthesia	3 (3)
Peripheral motor neuropathy	2 (2)
Burning sensation	1 (1)
Hyporeflexia	1 (1)
Peripheral sensorimotor neuropathy	1 (1)

- Majority Grade 1 or Grade 2, none serious
- Gradually diminished following treatment

Peripheral Neuropathy: Delayed Onset, Managed with Dose Modifications

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



Optic Neuropathy

- 2 patients with optic neuropathy / neuritis
  - Both with symptoms of visual changes approximately 4 and 5 months after starting BPaL
  - Fundus exam consistent with optic neuropathy
- Complete resolution of symptoms and findings with linezolid discontinuation

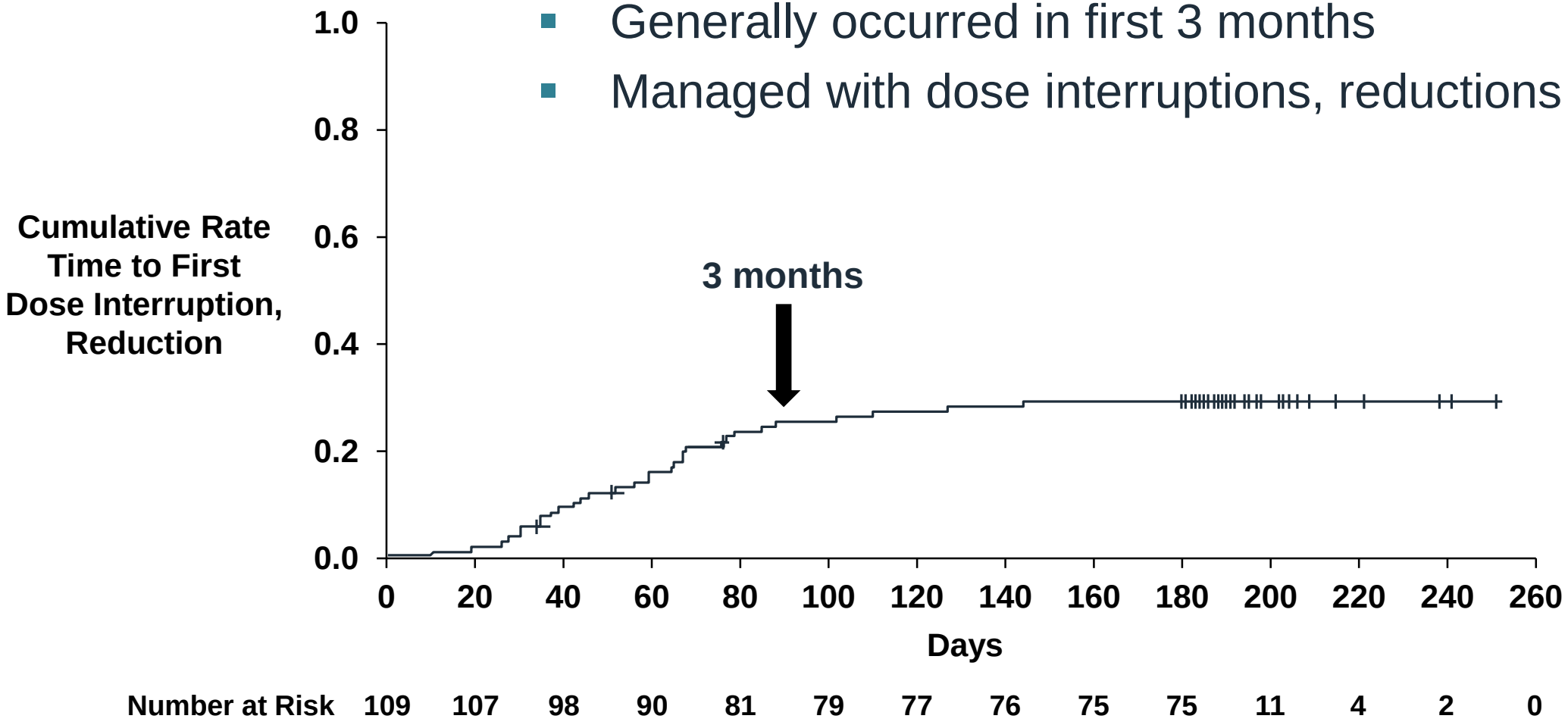
Myelosuppression is Known Linezolid Risk, Anemia Most Common

Hematopoietic Cytopenias	BPaL Regimen N=109 n (%)
Patients with any hematopoietic cytopenias AESI	51 (47)
Anemia	40 (37)
Neutropenia	9 (8)
Thrombocytopenia	5 (5)
Bone marrow failure	3 (3)
Leukopenia	2 (2)
Bicytopenia	1 (1)
Lymphopenia	1 (1)
Pancytopenia	1 (1)

- Majority Grade 1 or 2
- 3 SAEs (1 neutropenia, 2 anemia)
- 2 patients discontinued linezolid due to myelosuppression, but remained on B and Pa

Myelosuppression: Early Onset, Managed with Dose Modifications

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



Manageable Safety Allowed Majority of Patients to 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

Post-Marketing Activities

- Studies to further evaluate efficacy and safety of BPaL
  - ZeNix
  - SimpliciTB
  - Male reproductive study
  - Global pretomanid resistance surveillance study

Clinical Perspective on Treatment for Highly-Resistant Tuberculosis

Francesca Conradie, MD
Deputy Director, Clinical HIV Research Unit
University of the Witwatersrand Department of Medicine
Johannesburg, South Africa

Extensively Resistant to First- and Second-Line TB Treatment

- Try as many potentially effective drugs a patient can tolerate in hopes of killing resistant bacteria
- Can require ≥ 2 years of potentially debilitating treatment
- Haphazard approach of last resort

Evolutions in Treatment; Patients Still Face Long, Complicated Journey

- In 2009, first documented XDR-TB outbreak in South Africa[1]
  - 52 of 53 people died
- From 20% success rate pre-2014, to 65% with bedaquiline and linezolid[2]
- Treatment still requires ≥ 5 drugs, and ≥ 18 months[3]
  - Continue adding in medicines in hopes of success
- Lab tests can establish drug susceptibility
  - Not widely available, reliable
- Still no proven “set regimen” or standard of care[3]

1. Gandhi, 2006; Cohen, 2015 2. Olayanju, 2018 3. World Health Organization, 2019

Nix-TB Could Cure Highly-Resistant TB in Same Amount of Time as Susceptible TB

- Launched Nix-TB in 2015 with BPaL
  - Bedaquiline – in 2012, first new anti-TB drug in 50 years
  - Linezolid – a repurposed drug for resistant infections
  - Pretomanid – investigational drug developed by TB Alliance
- Not working to advance additional ***individual*** medicines
- Provide evidence for effectively using the 3 drugs to simplify, shorten treatment with ***pre-defined combination***

Overcoming Highly-Resistant TB in Patients Vulnerable to Side Effects

- Nix-TB patients
  - TB infection for substantial period of time
    - Mean of 22 months
  - Half co-infected with HIV

Efficacy Results Exceeded Expectations

- Durable cure rate of nearly 90% far superior to any reported cure rate for highly-resistant TB
- Similar to cure rates for standard, drug-susceptible TB

Knew AEs to Expect and Counseled Patients Prior to Enrollment

- Weakness, numbness, tingling in feet from peripheral neuropathy most consistent side effect
- Neuropathy and other linezolid-associated AEs led > 60% patients to interrupt linezolid at least once
- Identified events early with clinical assessments, counseling
- Dose modification allowed patients to stay on therapy
- No surviving patient withdrew due to AE

Life-Changing Results

- Young female
  - Sister died from XDR-TB
  - Before Nix-TB, 1 year of treatment
- Young male
  - Contracted XDR-TB at 17
  - Before Nix-TB, 6-7 years of treatment
- Both patients cured of TB within 6 months, continue to do well
- Resume lives, re-enter communities, earlier than with previous therapies

TB is Highly-Transmissible Infection

- Drug-resistant TB is as infectious as drug-susceptible TB
- TB predominantly seen in areas with fewer resources
  - A global problem
- Other infectious illnesses cross borders
  - H1N1, SARS, MERS, Ebola

BPaL Regimen: Overall Benefit-Risk Ratio Highly Positive

- Nix-TB results are a watershed
- Field refers to treatment environment as “Pre- and Post-Nix”
  - Establishing new standard of care
- Major step towards achieving WHO goal to end TB means stopping emergence and spread of drug resistance

Simplified, effective, shorter, clearly-defined, all-oral: BPaL regimen transforms treatment for people with highly-resistant TB

Pretomanid and BPaL Regimen for Treatment of Highly-Resistant Tuberculosis

June 6, 2019

TB Alliance

Antimicrobial Drugs Advisory Committee

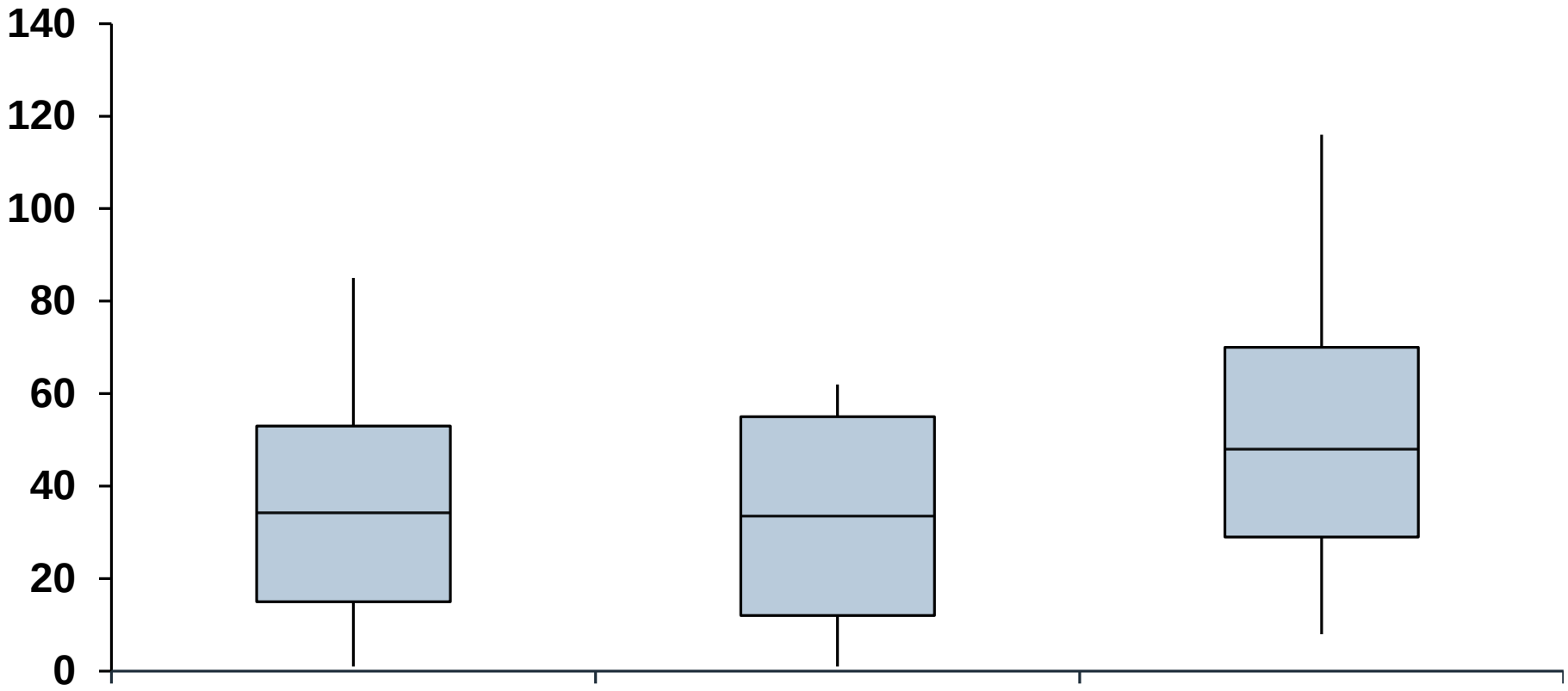
Q&A Slides

Data to Support Long Term Linezolid Use

- While not commonly used, when trial designed increasing publications of LT linezolid use in TB
- Key publication of linezolid on failing regimen in S. Korea where lin used long term – 600 mg/day[1]
  - 38 patients
  - 7 with optic neuropathy
- Overall AEs similar to product label, with neuropathies and optic neuropathies occurring with longer term exposure

1. Lee, 2012

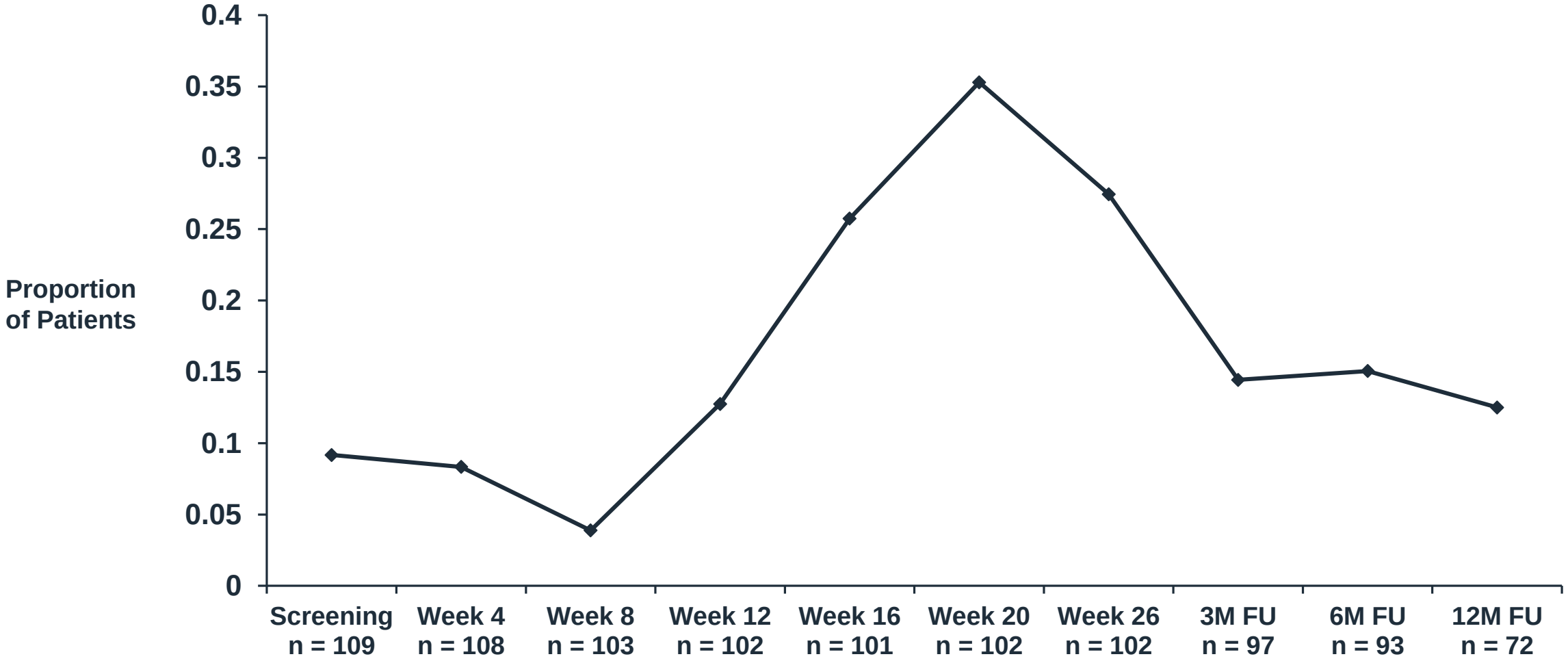
Favorability Rate and Time to Culture Conversion by Linezolid Treatment Status



	Patients who Interrupted	Patients who Discontinued	Patients who did not Interrupt or Discontinue
MTT Population: Favorable Rate n (%)	37/38 (97.4%)	22/28 (78.6%)	35/36 (97.2%)

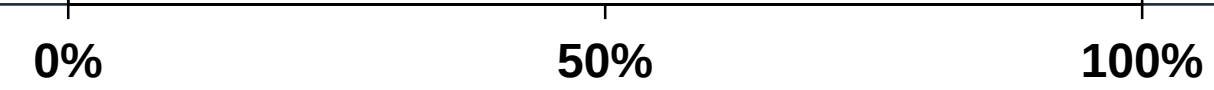
Note: Patients can appear in both the interrupted and discontinued rows

Patients Experiencing Pain, Aching or Burning in Feet



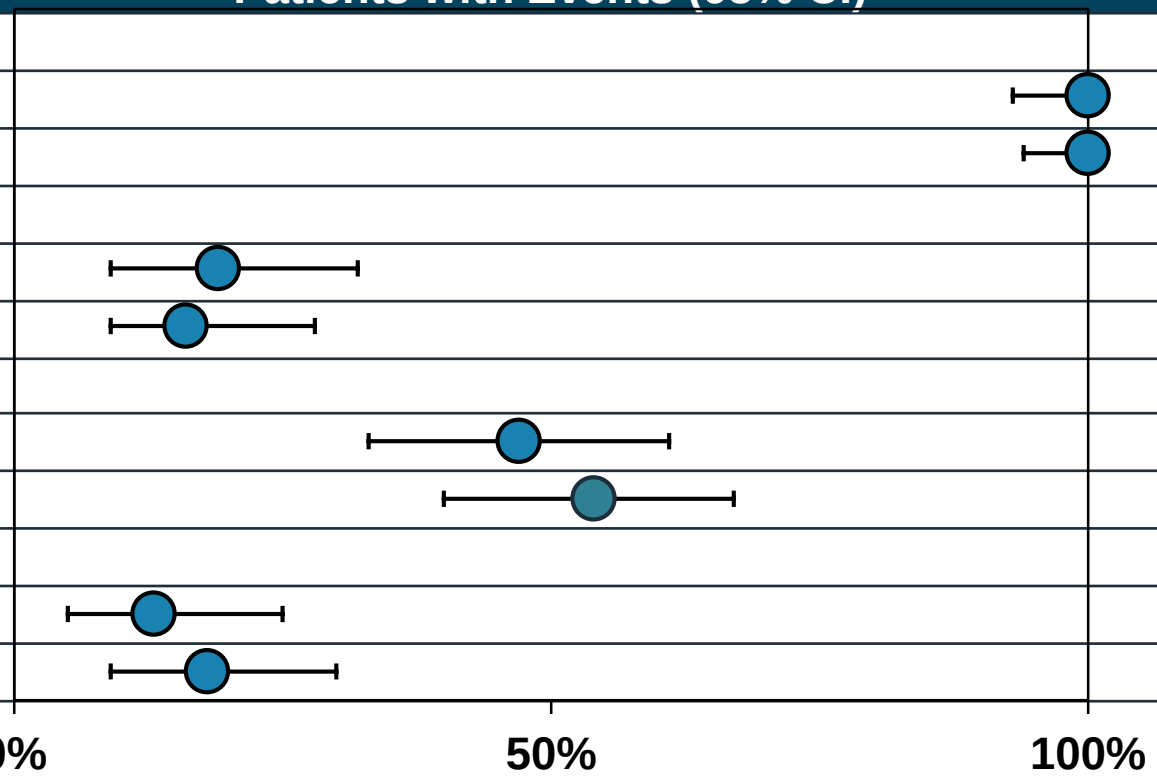
mITT Population: Primary Endpoint by HIV Status

mITT Population	Patients, n (%)	Favorable (95% CI)	Proportion Favorable (95% CI)
HIV Status			
Negative	41 (51.3%)		**90%** (77, 97)
Positive	39 (48.8%)		**90%** (76, 97)



Safety Population: Summary of AEs by HIV Status

Safety Population	Patients, n (%)	Patients with Events (95% CI)	Proportion with Events (95% CI)
Any AE			
HIV negative	53 (48.6%)		**100** (93, 100)
HIV positive	56 (51.4%)		**100** (94, 100)
Serious AE			
HIV negative	53 (48.6%)		**19** (9, 32)
HIV positive	56 (51.4%)		**16** (8, 28)
Grade 3 AE			
HIV negative	53 (48.6%)		**47** (33, 61)
HIV positive	56 (51.4%)		**54** (40, 67)
Grade 4 AE			
HIV negative	53 (48.6%)		**13** (5, 25)
HIV positive	56 (51.4%)		**18** (9, 30)



All-Cause Mortality in Nix-TB and Matched Historical Controls

		Alive n (%)	Died n (%)	Risk Ratio (Control/Nix-TB)
12 months	Control (N=190)[a]	135 (71.1)	55 (28.9)	3.3 95% CI (1.3-8.5)
	Nix-TB (N=45)[a]	41 (91.1)	4 (8.9)	
24 months	Control (N=182)[a]	113 (62.1)	69 (37.9)	3.4 95% CI (1.5-8.0)
	Nix-TB (N=45)[a]	40 (88.9)	5 (11.1)	

a. Only those with outcome data from the 204 patients were included in the analysis

Long-term bedaquiline-related treatment outcomes in patients with extensively drug-resistant tuberculosis from South Africa

Olatunde Olayanju, Jason Limberis, Aliasgar Esmail, Suzette Oelofse, Phindile Gina, Elize Pietersen, Mohammed Fadul, Rob Warren, Keertan Dheda

European Respiratory Journal 2018 51: 1800544; **DOI:** 10.1183/13993003.00544-2018

- 24-month favorable outcome rate substantially better in bedaquiline and linezolid vs non-bedaquiline and linezolid group[1]
  - 66.2% (45/68) vs 13.2% (27/204); $p < 0.001$
  - Treatment: median of 8 drugs (clofazimine, PAS, pyrazinamide, terizidone, linezolid (81%), levofloxacin)
  - Overall duration of treatment for 24 months
  - HIV positive: 51.5%

[1]**Olayanju, 2018.**

Baseline Characteristics of Nix-TB and Historical Control Populations

	Nix-TB Population N=45	Control Population N=202
Age at XDR-TB diagnosis, years (mean)	33.6	34.7
Male	55.6%	58.4%
Weight, kg	57.6	53.6
HIV status		
Negative	51.1%	51.2%
Positive	48.9%	48.0%
Refused	0	0.5%

Little Preexisting Resistance to Bedaquiline, Linezolid and Pretomanid

- Published data: preexisting resistance rates 0.5–2.3% for bedaquiline[1,2] and 0.2% for linezolid[3]
- Limited published data on pretomanid baseline resistance
- Surveys of strain collections showed pretomanid resistance rates near 1%
- Susceptibly testing of baseline isolates from >700 patients (phase 2 and 3 trials) identified only 1 resistant isolate
- In Nix-TB, only 2 isolates showed low-level resistance to bedaquiline

1. Villella *et al*, 2016; 2. Ismail *et al*, 2018; 3. Yang *et al*, 2018

Steady-State PK of Pretomanid Under Different Food Conditions

Study	Population	Regimen	Food Instructions	N	Mean $AUC_{0\text{-}24,ss}$ (µg*hr/mL)
Fasted					
CL-002	HS			6	**30**
CL-007	DS-TB			13	**31**
CL-010	DS-TB			16	**38**
NC-001	DS-TB	+Z		14	**36**
	DS-TB	+MZ		12	**40**
	DS-TB	+B		12	**28**
Fed					
NC-002	DS-TB	+MZ	"at least 2 hours after a meal (preferably the morning meal)"	12	**80**
	MDR-TB	+MZ		16	**58**
NC-003	DS-TB	+BCZ	"within 30 minutes after breakfast"	14	**59**
	DS-TB	+BZ		13	**72**
	DS-TB	+BC		14	**64**
NC-005	DS-TB	+BZ	"with a meal … preferably around breakfast time"	29	**55 – 59**
	MDR-TB	+BMZ		12	**78**
Nix-TB	XDR- & TI/NR MDR-TB	+BL	"with a meal"	21	**56**

Fertility Study in Rats (Seq I Study)

Dose, mg/kg	Fertility Index (%)		
	Males doses: 10+3 wks Females doses: 2+3+1 wks	Males doses: 14 wks Pared with naïve females	Males +10 wks recovery Pared with naïve females
0	92	100	87
10	95	92	93
30	64	64	79

- **NOAEL** 10 mg/kg, **LOAEL** 30 mg/kg
- No conception at 100 mg/kg. The infertility was associated with male testicular atrophy, lower sperm counts, reduced sperm motility
- No significant effect on litter at 10 and 30 mg/kg: corpora lutea, implantations, viable and nonviable embryos

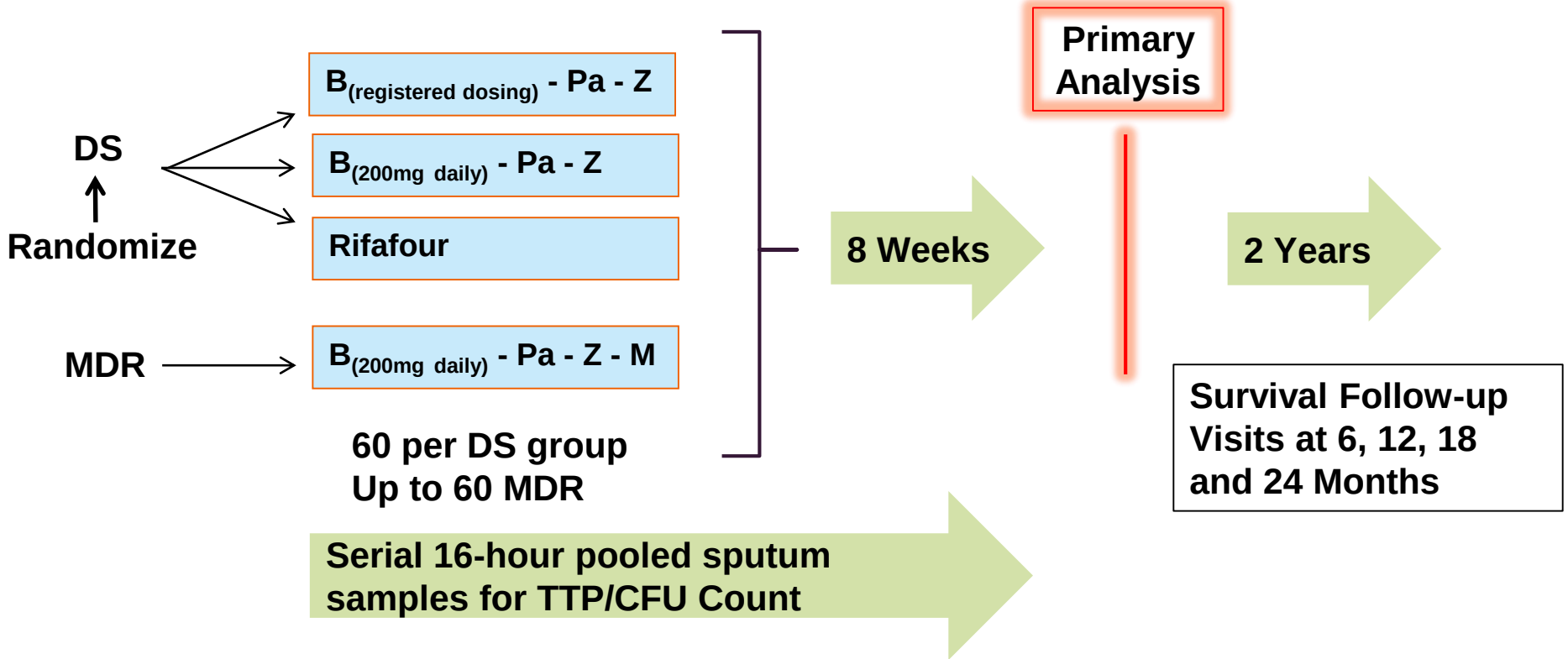
Patients who Interrupted BPaL Regimen Due to Hepatic Adverse Events

Duration of Interruption (Days)	AE	AE Grade
2	Transaminases increased	Grade 3
4	Transaminases increased	Grade 3
7	Transaminases increased	Grade 2
10	Hepatic enzyme increased	Grade 1
13	Transaminases increased	Grade 3
15	Drug-induced liver injury	Grade 2
16	Transaminases increased	Grade 3
18	Drug-induced liver injury	Grade 3
30	Transaminases increased	Grade 3

- **Unique N of patients:** 8 (1 patient had 2 interruptions of 4 and 16 days)
- **Median interruption time (days):** 13
- **IQR:** 7, 16
- **All resumed the BPaL regimen and completed treatment and were cured**

NC-005: 8-Week SSCC Study of B-Pa-Z-M

- B, Pa, Z and M containing regimens
- Participants with newly diagnosed smear positive DS- and MDR-TB



Z=pyrazinamide (1500mg daily), M = moxifloxacin 400mg daily, Pa = PA-824 200mg daily , $J_{(registered\ dosing)}$ = bedaquiline 400mg for 14 days then 200mg three times a week, $J_{(200mg\ daily)}$ = bedaquiline 200mg daily

Study NC-005: Hazard Ratios for Time to Liquid Media Sputum Culture Conversion

	Hazard Ratio		p-value
	Estimate	95% CI	
B (loading dose/t.i.w.) PaZ vs HRZE	1.782	(1.113, 2.852)	0.0160
B (200 mg) PaZ vs HRZE	2.044	(1.295, 3.228)	0.0021
B(200 mg) MPaZMDR vs HRZE	3.295	(2.096, 5.178)	< 0.0001
B(200 mg) PaZ vs B(loading dose/t.i.w.)PaZ	1.147	(0.742, 1.772)	0.5062
B(200 mg) MPaZMDR vs B(loading dose/t.i.w.)PaZ	1.849	(1.206, 2.834)	0.0279
B(200 mg) MPaZMDR vs B(200 mg)PaZ	1.612	(1.059, 2.452)	0.1430

NC-005: Patients Culture Negative at 2 Months

Liquid Culture	Overnight
B (loading) PaZ	67%
B (200 mg) PaZ	76%*
BPaZM (MDR) Z-sensitive	96%*
HRZE control	51%

*Statistically significant vs HRZE

24-month Follow-up at 120-day Efficacy Update

	Data cut	
	06/2018	01/2019
n for patients with 24-month follow-up	23	38
Deaths during treatment	3	4
Relapse	1	1
Culture negative	19	33

Patients who Interrupted BPaL Regimen Due to Hepatic Adverse Events

Duration of Interruption (Days)	Study Day of Interruption (Days)	AE	AE Grade
7	14	Transaminases increased	Grade 2
2	20	Transaminases increased	Grade 3
30	29	Transaminases increased	Grade 3
16	50	Transaminases increased	Grade 3
10	60	Hepatic enzyme increased	Grade 1
18	61	Drug-induced liver injury	Grade 3
15	88	Drug-induced liver injury	Grade 2
13	114	Transaminases increased	Grade 3
4	124	Transaminases increased	Grade 3

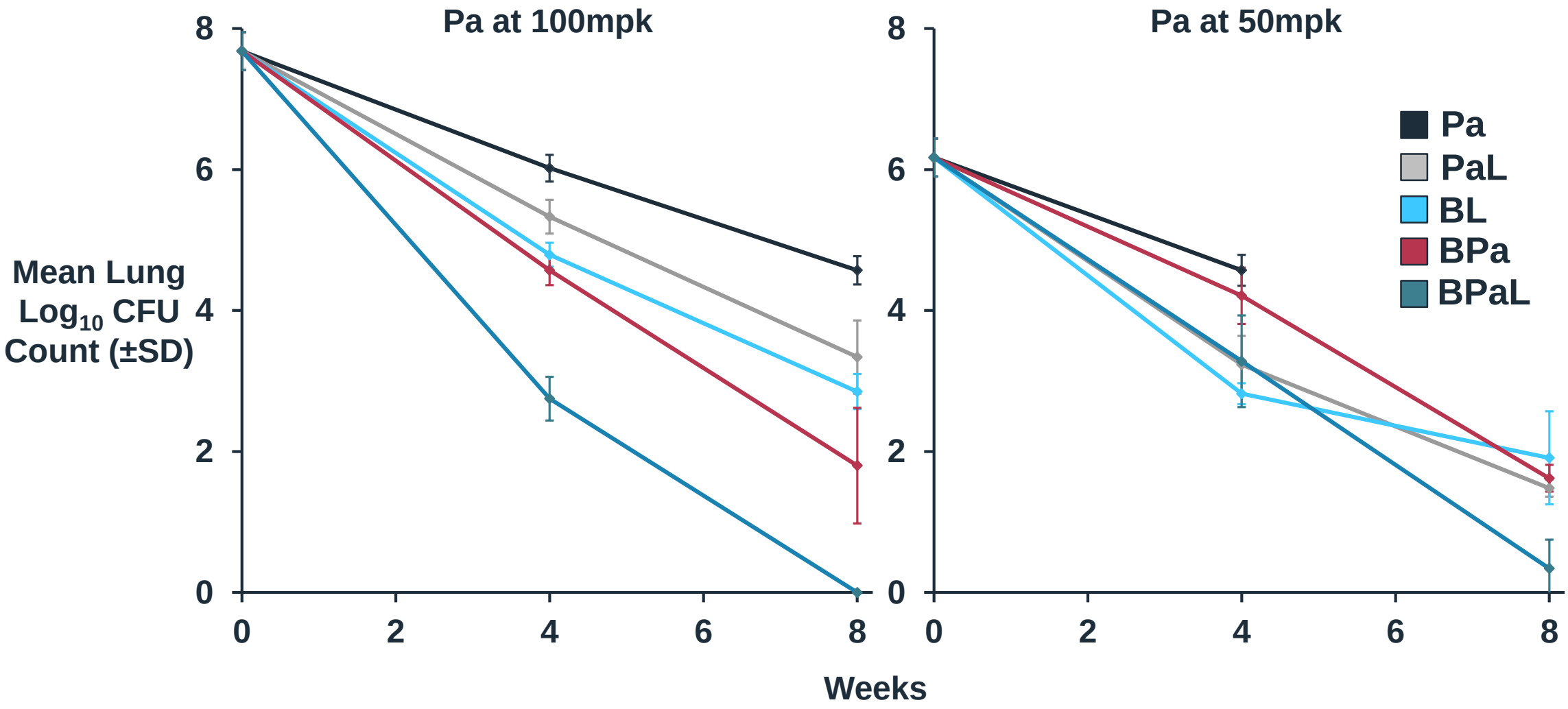
- All resumed the BPaL regimen and completed treatment and were cured
  - 2 interruptions resumed with lower linezolid dose
  - No dose modifications to BPa

STAND: Treatment-Emergent Lab Abnormalities

	PaMZ Regimen (STAND) N = 216 n (%)
ALT	
> 3 and ≤ 5 x ULN	12 (5.6)
> 5 and ≤ 8 x ULN	7 (3.2)
> 8 x ULN	17 (7.9)
AST	
> 3 and ≤ 5 x ULN	13 (6.0)
> 5 and ≤ 8 x ULN	6 (2.8)
> 8 x ULN	19 (8.8)
Total bilirubin	
> 1 x ULN and ≤ 2 x ULN	10 (4.6)
> 2 x ULN	4 (1.9)

*Percentages corrected from what was shown at meeting

Pretomanid Contributes to BPaL in Mice When Dosed at 50 mpk and at 100 mpk



Pa Exposures in Mice at Doses Where Pa's Contribution to BPaL Was Demonstrated

	Over 7 Days, with Dosing for First 5		24 Hours After 5th Dose	
Dose (mg/kg)	% Time Over MIC	Cavg (µg/mL)	% Time Over MIC	Cavg (µg/mL)
50	54	2.3	73	3.3
100	64	4.7	88	6.6

In humans, at 200 mg under fed conditions:

- **% Time Over MIC ≈ 100%**
- **Cavg ≈ 2.4 µg/mL**