TB Alliance

Update on Pretomanid, in Combination with Bedaquiline and Linezolid (the BPaL Regimen) in Drug-Resistant TB

Salah Foraida, MD, MS
Head of Medical Affairs, 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.

Outline

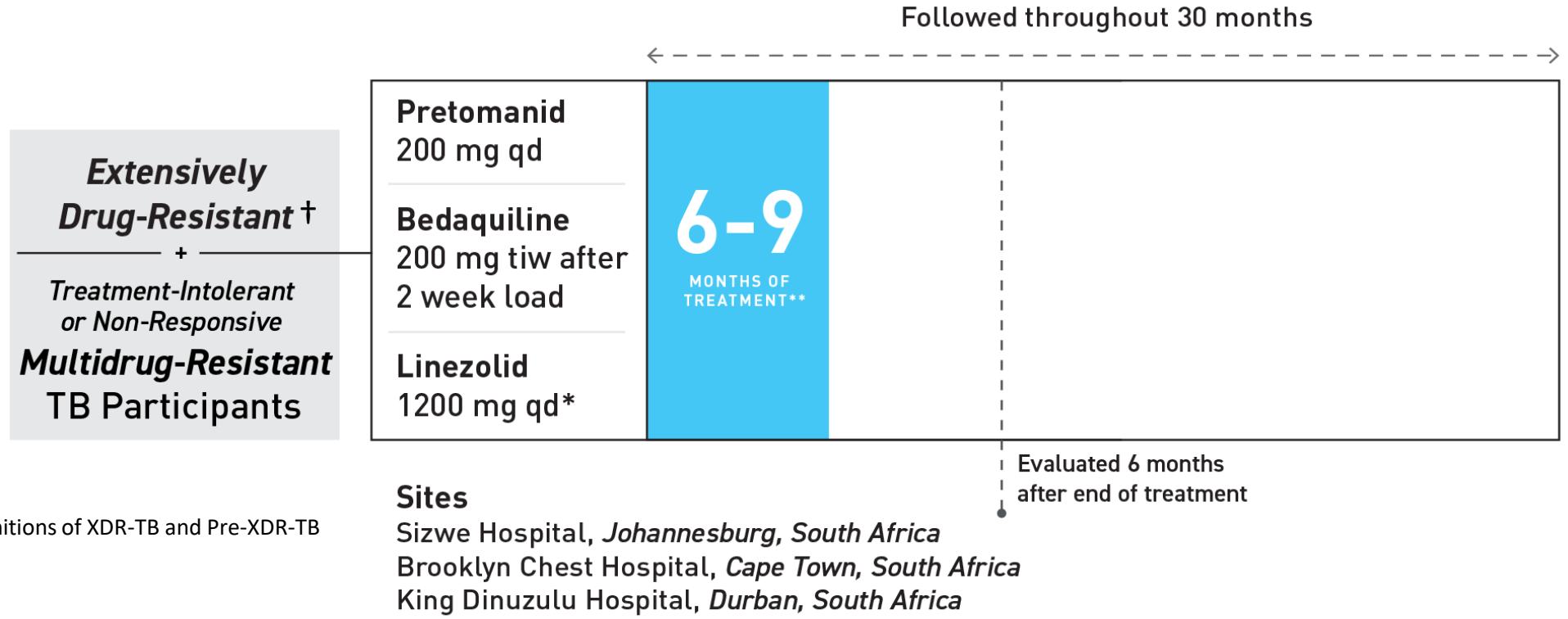
- The Nix TB Trial
- The ZeNix Trial to Optimize Linezolid in the BPaL Regimen
- TB-Practical Trial

The Nix-TB Trial With the BPaL Regimen

TB Alliance

Nix-TB Phase 3 Trial in XDR-TB

Patients with XDR-TB or who have failed or are intolerant to MDR-TB Treatment



† Pre-2021 WHO Definitions of XDR-TB and Pre-XDR-TB

*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

Nix-TB Primary Efficacy Analysis

- 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

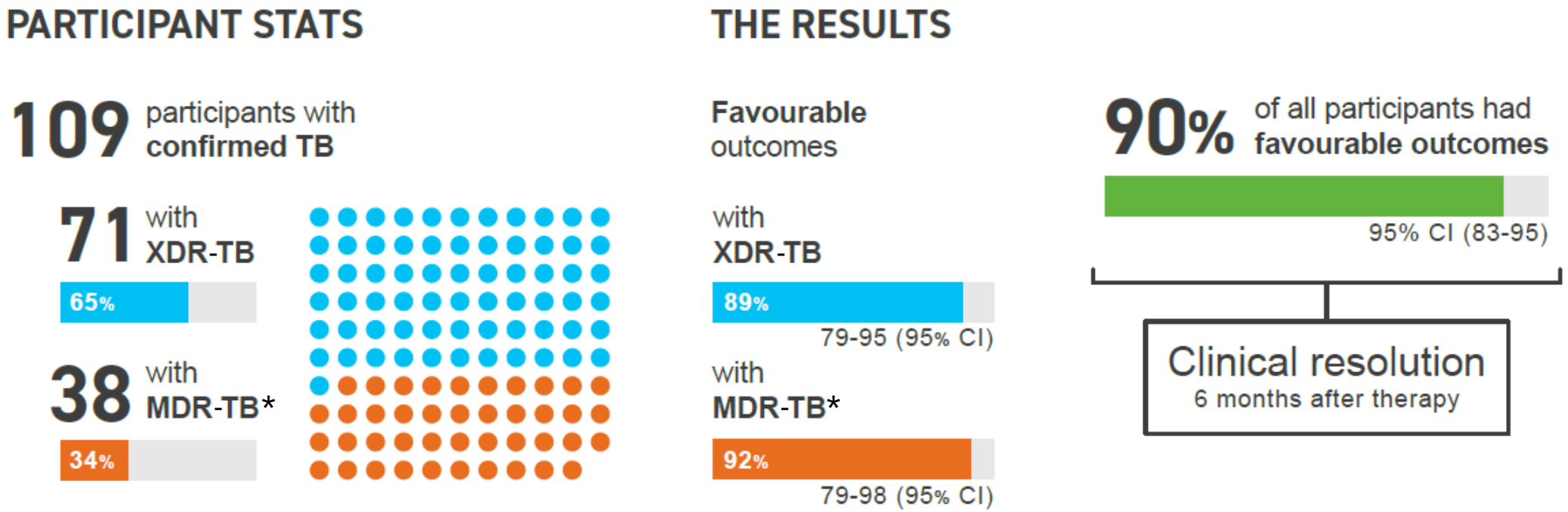
    OR

  - **Favorable outcome, cured**

Key Results

Nix-TB Results

New England Journal of Medicine, March 2020



*Treatment intolerant or non-responsive MDR-TB

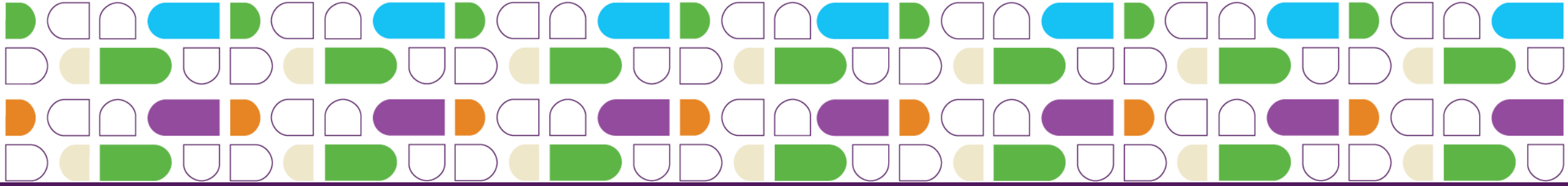
24 Months Post-treatment Follow-up Supports Long-Term Success

Presented at CROI, March 6-10, 2021

- Patients have been followed for a full 24 months after treatment
  - **After two years of follow up, the results of the Nix trial have held firm:**

90% of patients with highly drug resistant TB survived and remained healthy long after completing treatment.

Safety



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

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

Nix-TB Adverse Events of Special Interest

Key Safety Information

Key Concerns for Monitoring:

- Neuropathy
  - *Monitor visual function*
- Myelosuppression, especially anemia
  - *Monitor Complete Blood Counts*
- Hepatic enzyme elevations
  - *Monitor symptoms and signs and liver-related laboratory tests*

24-Month Nix Results: Peripheral Neuropathy

Presented at CROI, March 6-10, 2021

- Peripheral neuropathy (weakness, numbness and pain, usually in hands and feet) is a serious side effect that is associated with the use of linezolid.
- Of 84 patients who reported no symptoms of neuropathy upon enrollment:
  - 57 reported either moderate or severe symptoms of neuropathy (“pain, aching, or burning in feet or legs”) after six months of treatment with BPaL.
  - We followed up with these patients over two years and found that the neuropathy had significantly subsided, with about 80% of affected patients reporting no symptoms.
- Long-term follow up showed that neuropathy from the use of linezolid goes away for most patients.

Linezolid (LZD)		600mg BD (N = 44)	1200mg QD (N = 65)	Total (N = 109)
Nos of patients who completed Rx	n	40	63	103
Nos of patients who received a full uninterrupted 26 weeks of linezolid at any dose	n	10	27	37
Nos of patients who received 1200 mg total daily dose without interruption over the full 26 weeks of therapy	n	4	12	16
LZD duration in Rx completers	mean (weeks)			23.3

Baseline		After Baseline	Month 24 After End-of-Treatment			
Pain, aching and burning			None	Mild/Mod	Severe	N/A
None: 84	→	Always None: 27	→ 27	0	0	0
(Mild/Mod: 15)	→	Max. Mild/Mod: 34	→ 29	3	0	2
(Severe: 1)	→	Max. Severe: 23	→ 13	7	1	2
		84	→ 69	10	1	4
			82%	12%	1%	5%

NixTB Conclusions

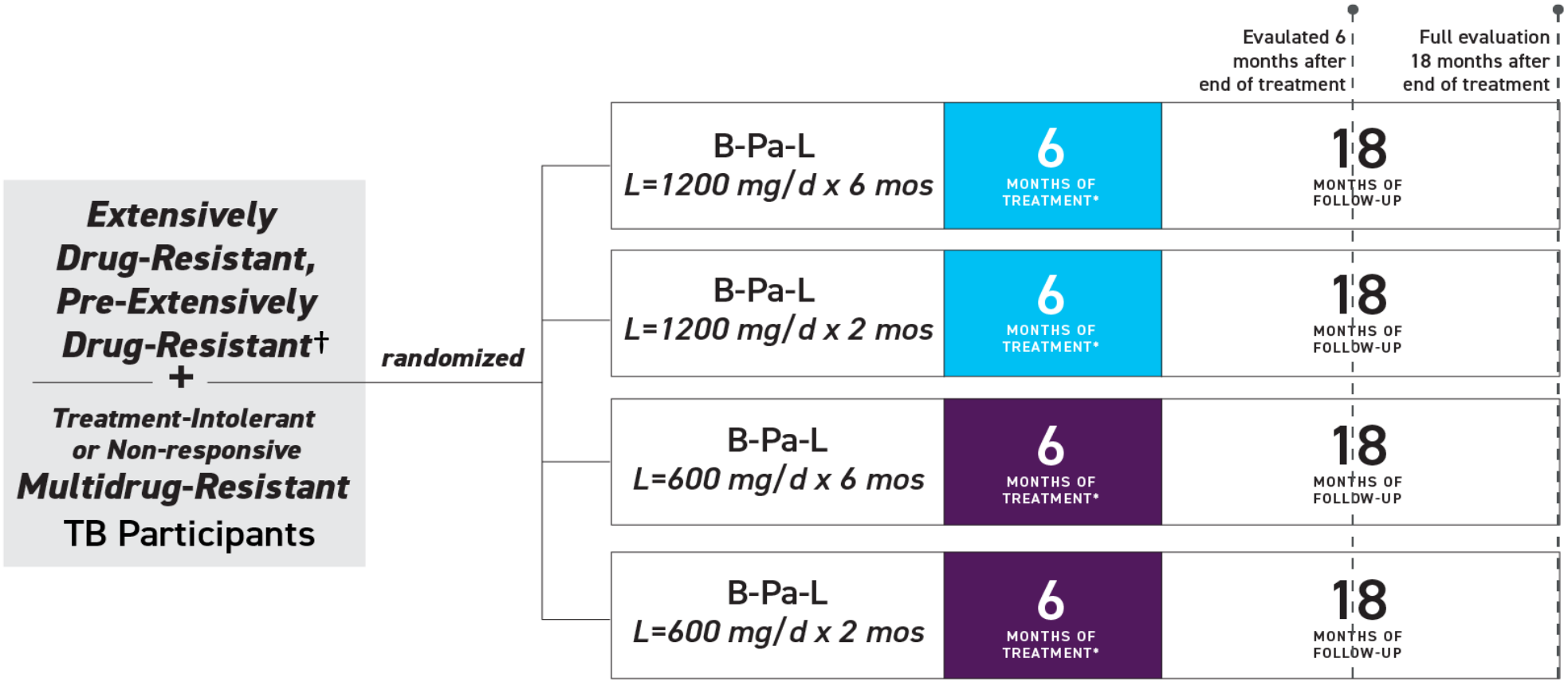
- Approximately 90% of subjects with highly resistant TB achieved relapse-free cure status 6 months after the end of treatment with this simplified, shortened all oral regimen.
- This high efficacy was sustained through 2-year follow-up.
- Peripheral neuropathy from linezolid was common, but manageable, and symptoms improved over 24 months of follow-up
- A follow-on trial, **ZeNix**, that investigates the optimal dose and duration of linezolid in the BPaL regimen: **Results of all patients followed to the primary endpoint 6 months after treatment completion were presented at IAS July 2021**

Improvements in the BPaL Benefit – Optimization of linezolid dosing & duration: The ZeNix Trial

ZeNix

TB Alliance

ZeNix: Linezolid Optimization Trial



*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

† Pre-2021 WHO Definitions of XDR-TB and Pre-XDR-TB

Total participants randomised by treatment arm and country

Country	Linezolid 1200mg 26 weeks(N=45) n	Linezolid 1200mg 9 weeks (N=46) n	Linezolid 600mg 26 weeks (N=45) n	Linezolid 600mg 9 weeks (N=45) n	Total (N=181) n
South Africa	11	18	21	16	66
Georgia	13	8	5	8	34
Russia	19	16	18	18	71
Moldova	2	4	1	3	10

Demographic and Baseline Characteristics

	Total (N=181) n (%)
Age (mean, years)	37.1
Sex (male)	122 (67.4%)
Race (white)	115 (63.5%)
Black or African American	66 (36.5%)
HIV Positive	36 (19.9%)
Current TB type MDR-TB (NR)	12 (6.6%)
MDR-TB (TI)	9 (5.0%)
Pre-XDR	85 (47.0%)
XDR	75 (41.4%)

Primary efficacy analysis (MITT)

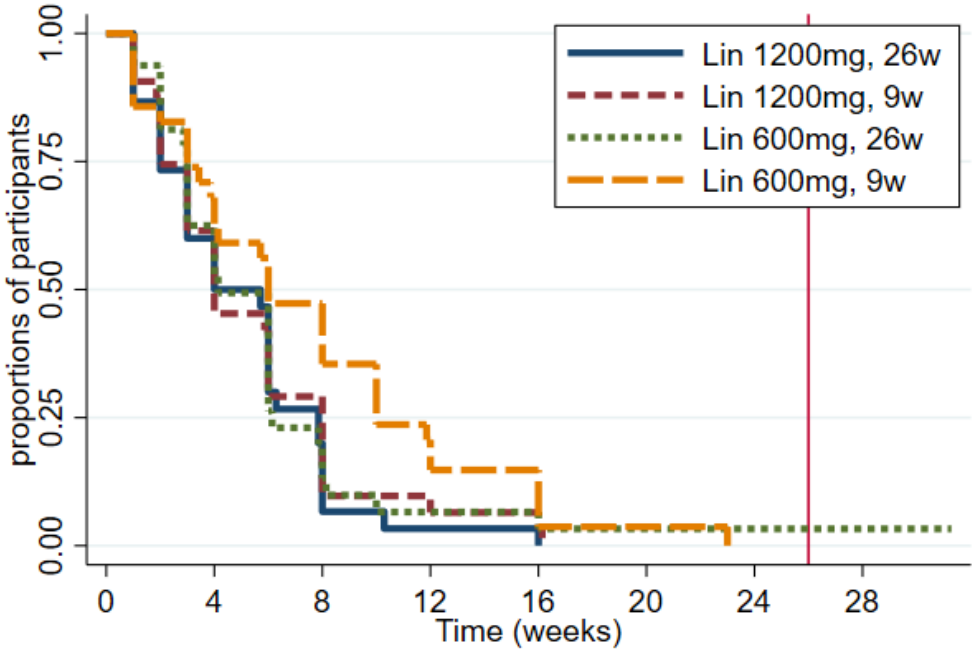
	Linezolid 1200mg 26 weeks (N=45) n (%)	Linezolid 1200mg 9 weeks (N=46) n (%)	Linezolid 600mg 26 weeks (N=45) n (%)	Linezolid 600mg 9 weeks (N=45) n (%)	Total (N=181) n (%)
Unassessable	1	1	1	1	4
Total assessable	44	45	44	44	177
Favourable	41 (93.2%)	40 (88.9%)	40 (90.9%)	37 (84.1%)	158 (89.3%)
Unfavourable	3 (6.8%)	5 (11.1%)	4 (9.1%)	7 (15.9%)	19 (10.7%)
95% CI for Favourable	81.3% to 98.6%	75.9% to 96.3%	78.3% to 97.5%	69.9% to 93.4%	83.7% to 93.4%

Details of primary efficacy endpoint classification (MITT)

Status	Outcome		Linezolid 1200mg 26 weeks (N=45) n (%)	Linezolid 1200mg 9 weeks (N=46) n (%)	Linezolid 600mg 26 weeks (N=45) n (%)	Linezolid 600mg 9 weeks (N=45) n (%)	Total (N=181) n (%)
	Total Assessable (%)		44 (97.8%)	45 (97.8%)	44 (97.8%)	44 (97.8%)	177 (97.8%)
Favourable	Culture negative status at 6 months post treatment		41	40	40	37	158
	Sputum not produced at 6m post treat, but culture neg. earlier		0	0	0	0	0
	Total Favourable (% of assessable)		41 (93.2%)	40 (88.9%)	40 (90.9%)	37 (84.1%)	158 (89.3%)
Unfavourable	During treatment	Lost to follow-up	0	0	0	1[i]	1
		Withdrawn (AE)	1[j]	1[s]	0	2[a, l]	4
		Withdrawn (Investigator/Sponsor)	0	0	1[b]	0	1
		Withdrawn (patient decision)	0	2[n, v]	1[g]	1[t]	4
		Withdrawn (treatment failure)	**0**	**0**	**0**	**1[e]**	**1**
	Post treatment	**Confirmed relapse**	**0**	**2[c, q]**	**1[d]**	**1[f]**	**4**
		Re-treatment	2[o, u]	0	1[w]	1[r]	4
	Total Unfavourable (% of assessable)		3 (6.8%)	5 (11.1%)	4 (9.1%)	7 (15.9%)	**19 (10.7%)**

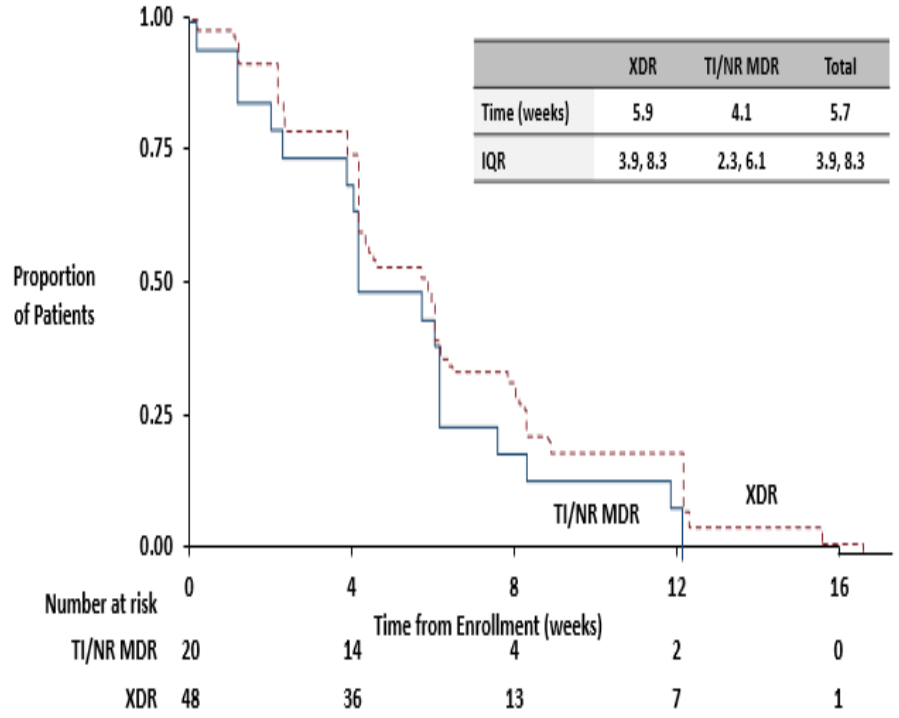
Time to culture negative status (MITT)

ZeNix



Number at risk								
Lin 1200mg, 26w	30	18	6	1	1	0	0	0
Lin 1200mg, 9w	32	19	9	3	2	0	0	0
Lin 600mg, 26w	32	19	6	2	2	1	1	1
Lin 600mg, 9w	35	23	16	7	4	1	0	0

Nix-TB



	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

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

Safety - Adverse Events

	Linezolid 1200mg 26 weeks (N=45) n (%)	Linezolid 1200mg 9 weeks (N=46) n (%)	Linezolid 600mg 26 weeks (N=45) n (%)	Linezolid 600mg 9 weeks (N=45) n (%)	Total (N=181) n (%)
Any grade ≥ 3 TEAE	14 (31.1%)	11 (23.9%)	9 (20.0%)	11 (24.4%)	45 (24.9%)
Any serious TEAE	3 (6.7%)	4 (8.7%)	1 (2.2%)	3 (6.7%)	11 (6.1%)

Incidence of Peripheral Neuropathy, Optic Neuropathy, and Anemia

	Linezolid 1200mg 26 weeks (N=45) n (%)	Linezolid 1200mg 9 weeks (N=46) n (%)	Linezolid 600mg 26 weeks (N=45) n (%)	Linezolid 600mg 9 weeks (N=45) n (%)	Total (N=181) n (%)
Number of participants with ≥ one TEAE of peripheral neuropathy	17 (37.8)	11 (23.9)	11 (24.4)	6 (13.3)	45 (24.9)
Number of participants with ≥ one TEAE of optic neuropathy	4 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.2)
Number of participants with worsening grade of anemia	10 (22.2)	8 (17.4)	1 (2.2)	3 (6.7)	22 (12.2)

Linezolid Dose Interruptions, Reductions and Discontinuations

	Linezolid 1200mg 26 weeks (N=45) (%)	Linezolid 1200mg 9 weeks (N=46) (%)	Linezolid 600mg 26 weeks (N=45) (%)	Linezolid 600mg 9 weeks (N=45) (%)
Linezolid dose modification (reduction, interruption, or discontinuation)	23 (51%)	13 (28%)	6 (13%)	6 (13%)

ZeNix – Early Conclusions

- Results support observed high efficacy of BPaL from Nix-TB. High efficacy across all 4 arms
- There appear to be lower adverse events of note with lower doses and/or shorter duration of linezolid
- 1200mg X 26 week group had more adverse events:
  - Neuropathy in particular
  - All 4 cases of optic neuropathy (all of which resolved)
- Reduced doses and/or shorter durations of linezolid than 1200mg for 6 months appear to have high efficacy and improved safety
- Additional analyses pending

PRACTECAL Trial for MDR-TB

Staged trial to evaluate BPaL-based regimens for all people with DR-TB (at least rifampicin-resistant), not just highly drug-resistant strains:

Stage 1

- Regimen 1 - BPaL + Moxifloxacin for 6 months
- Regimen 2 - BPaL + Clofazimine for 6 months
- Regimen 3 - BPaL for 6 months
- Local SOC: The local standard of care for MDR-TB is used as the internal control for both safety and efficacy.

Stage 2

- Regimen 1 - BPaL + Moxifloxacin for 6 months
- Local SOC

Sponsor: MSF

** Bedaquiline administered at 400mg dly for 2 weeks then 200mg 3X for 22 weeks. Linezolid administered at 600mg daily for 16 weeks then 300mg daily for the remaining 8 weeks or earlier when moderately tolerated*

Special Thanks

- Patients who enrolled in the trials
- Investigators and site staff
- Funders of the pretomanid trials
- DSMB Members
- And many partners and collaborators

Thank You!

Questions?
Please feel free to reach out
Email: Salah.Foraida@TBAlliance.org