IAS 2021

High rate of successful outcomes treating highly resistant TB in the ZeNix study of pretomanid, bedaquiline and alternative doses and durations of linezolid

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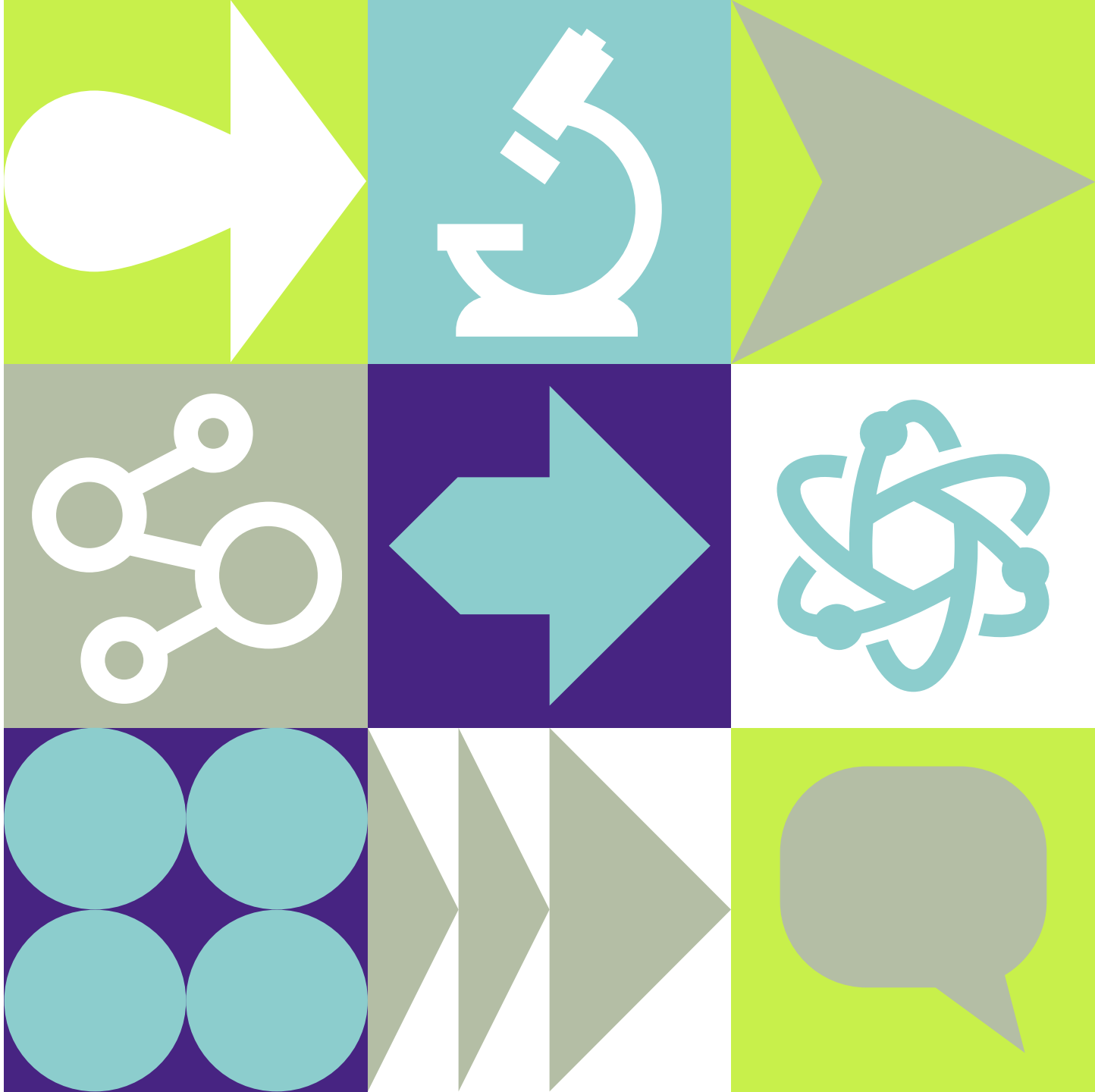
ZeNix

TB Alliance

WITS HEALTH CONSORTIUM



Background
Rationale for ZeNix

- Nix-TB results: 90%; (95% confidence interval, 83 to 95) had a favorable outcome in highly resistant TB with the BPaL(1200mg)

- Adverse events driven by linezolid often led to dose reductions or interruptions of linezolid
  - Peripheral neuropathy (occurring in 81% of patients)
  - Myelosuppression (48%)

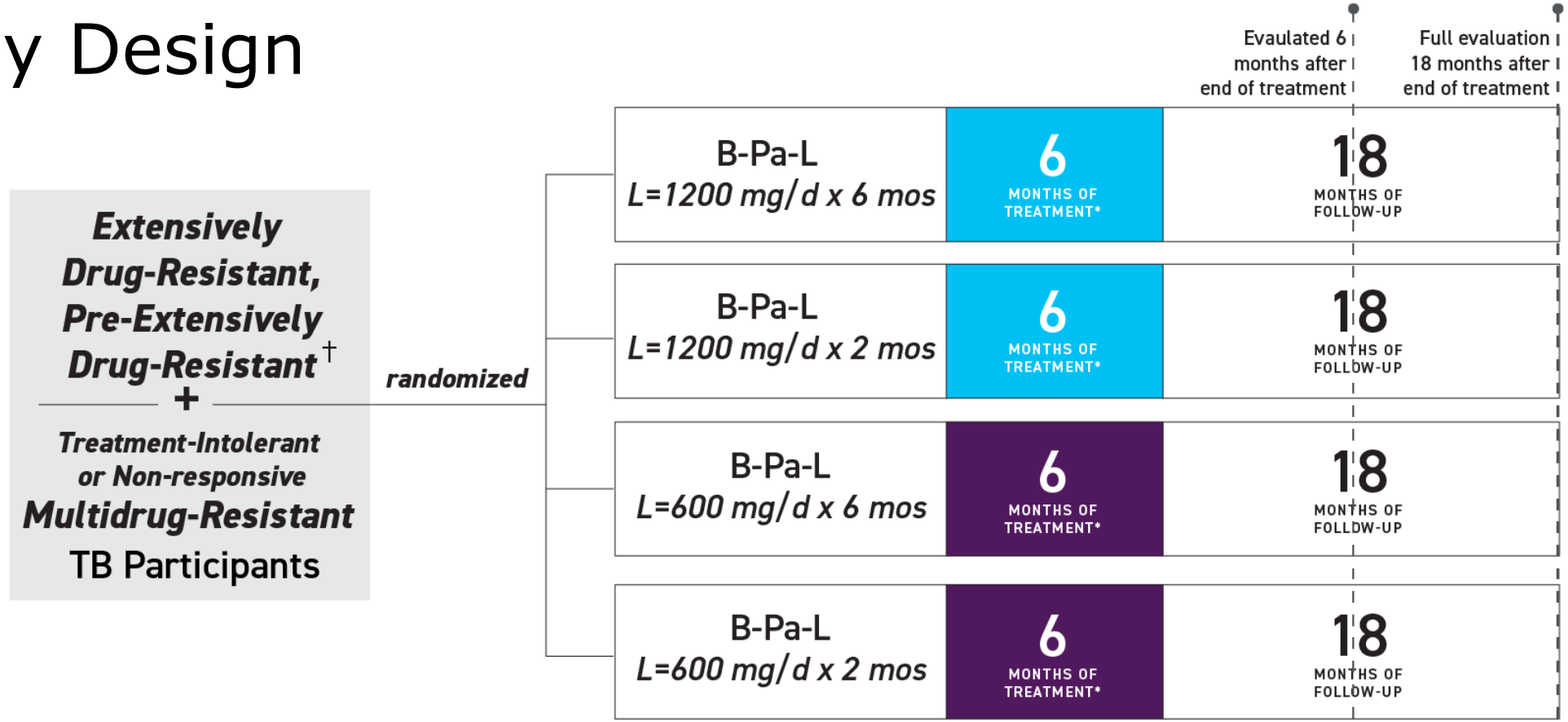
- Led to the initial approval of BPaL by the U.S. FDA

Source: Conradie et al. Bedaquiline, pretomanid and linezolid for treatment of extensively drug resistant, intolerant or non-responsive multidrug resistant pulmonary tuberculosis. *N Eng J Med* 2020;382:893-902.

Study Design

- A Phase 3, multi-center, partially-blinded, randomized clinical trial in four parallel treatment groups
  - Bedaquiline and pretomanid treatment not blinded
  - Linezolid treatment dose and duration double-blinded

Study Design



*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

Primary Endpoint

- Incidence of bacteriologic failure, relapse or clinical failure through follow up until 6 months after the end of treatment

Selected Inclusion Criteria

For full inclusion criteria see: ClinicalTrials.gov NCT03086486

- Male or female, aged 14 years or older. (Male or female, aged 18 years or older in Moldova or Russia.)

Disease Characteristics:

- Participants with one of the following pulmonary TB conditions:

  a. XDR-TB
  b. Pre-XDR-TB
  c. MDR-TB non-response
  d. MDR-TB intolerance

Exclusion Criteria

For full exclusion criteria see: ClinicalTrials.gov NCT03086486

- TB infection with historic DST or MIC results with values suggesting likely resistance to pretomanid, delamanid, linezolid or bedaquiline
- Previous and Concomitant Therapy with more than 2 weeks of bedaquiline, linezolid or delamanid
- Diagnostic and Laboratory Abnormalities

Results

181 patients enrolled in four countries

- South Africa **66**
- Georgia **34**
- Russia **71**
- Moldova **10**

Demographic and Baseline Characteristics

	Total (N=181) n (%)
Age (mean, years)	37.1
Sex (male)	122 (67.4%)
Race: White	115 (63.5%)
Race: Black	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%)

Demographics and Baseline Characteristics

	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 (%)
Age (years)					
Mean	37.4	35.1	39.2	36.8	37.1
Sex					
Male	30 (66.7%)	30 (65.2%)	31 (68.9%)	31 (68.9%)	122 (67.4%)
Race					
White	34 (75.6%)	28 (60.9%)	24 (53.3%)	29 (64.4%)	115 (63.5%)
Black	11 (24.4%)	18 (39.1%)	21 (46.7%)	16 (35.6%)	66 (36.5%)
HIV Status					
Positive	9 (20.0%)	9 (19.6%)	9 (20.0%)	9 (20.0%)	36 (19.9%)
Current TB Type					
MDR-TB (NR)	2 (4.4%)	5 (10.9%)	2 (4.4%)	3 (6.7%)	12 (6.6%)
MDR-TB (TI)	3 (6.7%)	1 (2.2%)	2 (4.4%)	3 (6.7%)	9 (5.0%)
Pre-XDR	19 (42.2%)	22 (47.8%)	22 (48.9%)	22 (48.9%)	85 (47.0%)
XDR	21 (46.7%)	18 (39.1%)	19 (42.2%)	17 (37.8%)	75 (41.4%)

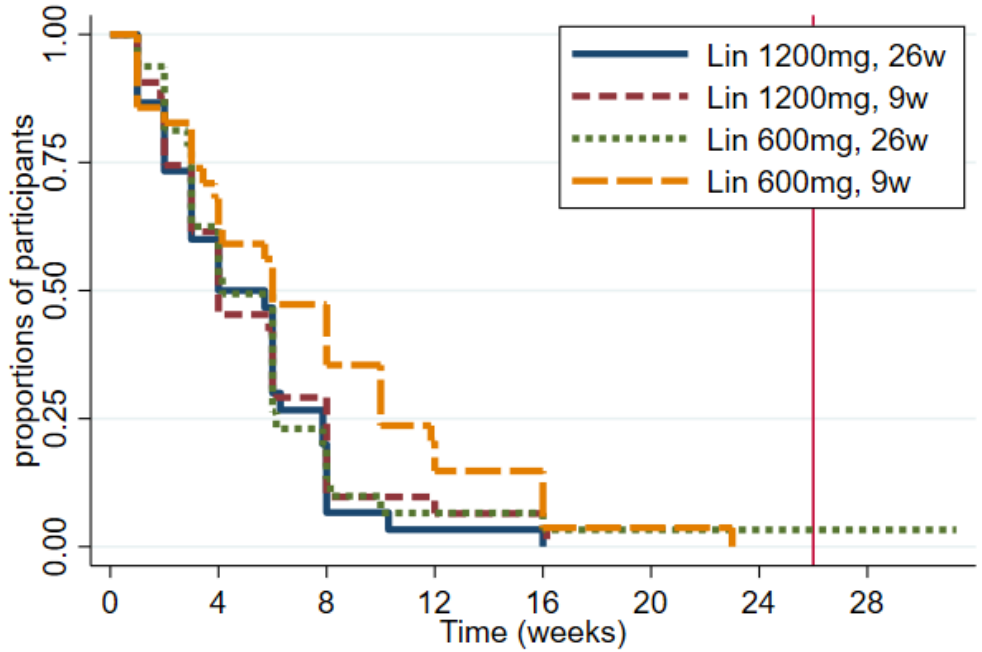
Primary Efficacy Analysis (MITT)

89.3%	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 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 month 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	1
		Withdrawn (AE)	1	1	0	2	4
		Withdrawn (Investigator/Sponsor)	0	0	1	0	1
		Withdrawn (patient decision)	0	2	1	1	4
		Withdrawn (treatment failure)	0	0	0	1	1
	Post treatment	Confirmed relapse	0	2	1	1	4
		Re-treatment	2	0	1	1	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)



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

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%)

Conclusions

- Results support observed high efficacy of BPaL from Nix-TB
- 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
  - 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