TB Alliance

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

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
- WHO Rapid Communication May 2022

Nix-TB Results

New England Journal of Medicine, March 2020

PARTICIPANT STATS

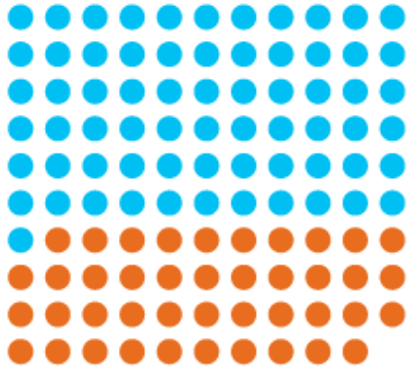
109 participants with **confirmed TB**

71 with **XDR-TB**

65%

38 with **MDR-TB***

34%



THE RESULTS

Favourable outcomes

with **XDR-TB**

89%

79-95 (95% CI)

with **MDR-TB***

92%

79-98 (95% CI)

90% of all participants had **favourable outcomes**

95% CI (83-95)

Clinical resolution
6 months after therapy

*Treatment intolerant or non-responsive MDR-TB

Background

IAS 2021 18 –21 July

ZeNix

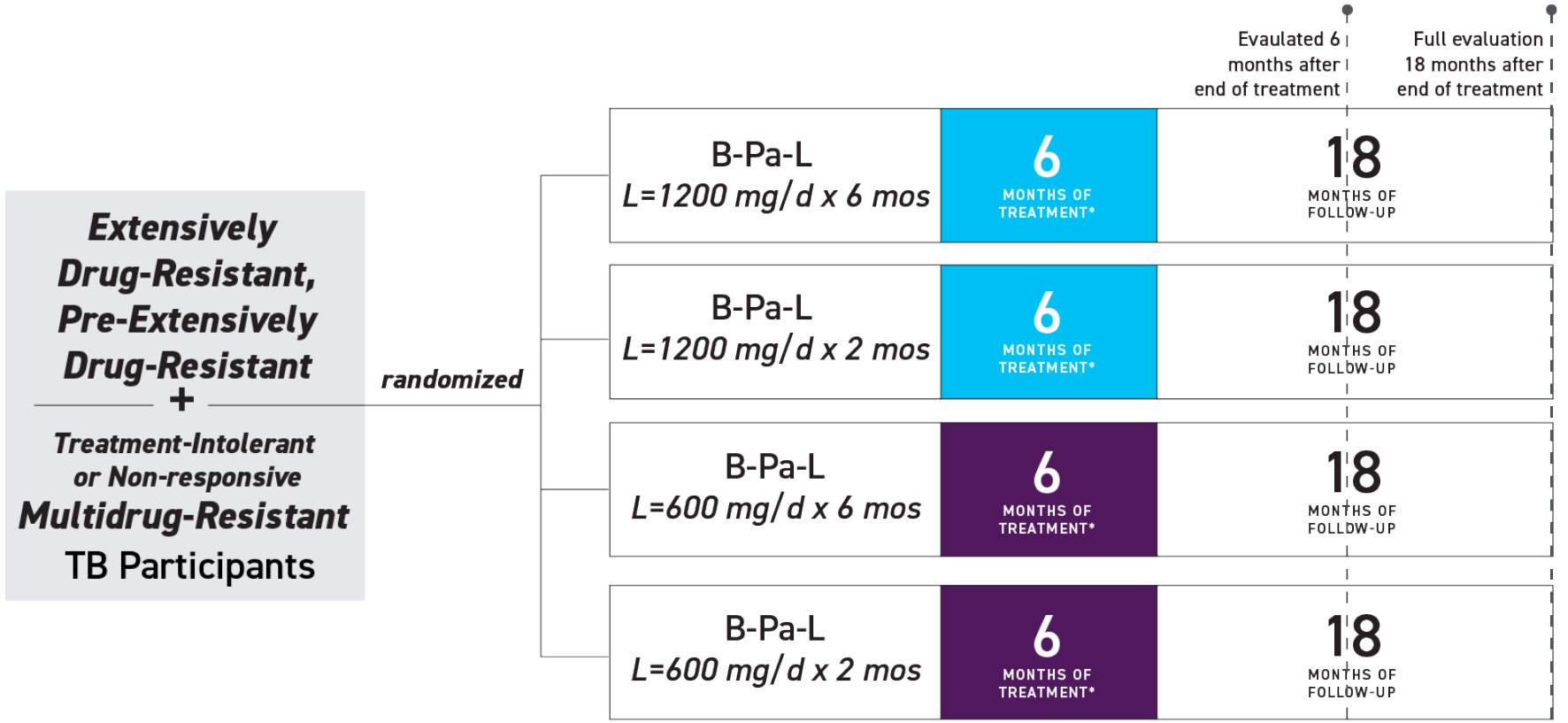
Rationale for ZeNix

- 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, interruptions or discontinuation of linezolid
  - Peripheral neuropathy (occurring in 81% of patients)
  - Myelosuppression (48%)

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



*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

Conclusions

- There appear to be lower adverse events of note with lower doses and/or shorter duration of linezolid
- A high success rate at primary endpoint was observed across all 4-arms, suggesting that a 6-month 600 mg regimen appears to have the most favorable risk-benefit profile.

TB-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*

WHO Rapid Communication May 2022

GDG meetings and updated WHO guidance

- BPaLM, BPaL
- All DR-TB patients
- Under Programmatic Conditions
- LZD dose: "*Evidence suggested that the optimal dosing of linezolid is 600 mg daily*"
- Reproductive safety: *"Evidence has largely alleviated previous concerns on reproductive toxicities observed in animal studies"*