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

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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

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%)

Study Design

Extensively Drug-Resistant, Pre-Extensively Drug-Resistant + Treatment-Intolerant or Non-responsive Multidrug-Resistant TB Participants

Randomized

- **B-Pa-L**
  - L=1200 mg/d x 6 mos
  - 6 MONTHS OF TREATMENT
  - 18 MONTHS OF FOLLOW-UP

- **B-Pa-L**
  - L=1200 mg/d x 2 mos
  - 6 MONTHS OF TREATMENT
  - 18 MONTHS OF FOLLOW-UP

- **B-Pa-L**
  - L=600 mg/d x 6 mos
  - 6 MONTHS OF TREATMENT
  - 18 MONTHS OF FOLLOW-UP

- **B-Pa-L**
  - L=600 mg/d x 2 mos
  - 6 MONTHS OF TREATMENT
  - 18 MONTHS OF FOLLOW-UP

*Additional 3 months if sputum culture positive between week 16 and week 26 treatment visits

- Pa: pretomanid dose = 200 mg daily
- 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.
Other B-Pa Containing Regimens and Next Steps

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”