

Impact of COVID-19 on TB Drug Development

Stephanie Seidel, TB Alliance
TBEC Webinar Series
October 7, 2020



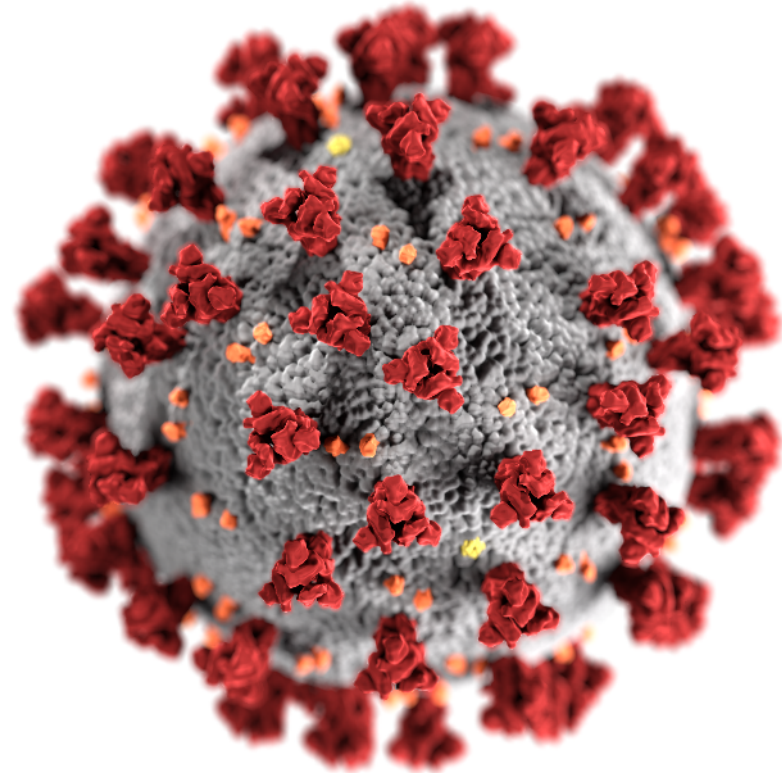
TB Alliance is a not-for-profit organization dedicated to the discovery, development and delivery of better, faster-acting and affordable tuberculosis drugs that are available to those in need.



Navigating COVID-19

A New Pandemic Threatens Progress - Hard-won Gains May Be Erased

- By disrupting the testing and treatment of TB and HIV, the COVID-19 pandemic could cause an additional 6.3 million TB cases and 1.4 million additional TB deaths through 2025
- Global TB incidence and deaths in 2021 could increase to levels last seen between 2013 and 2016 respectively – a setback of at least 5 to 8 years in the fight against TB



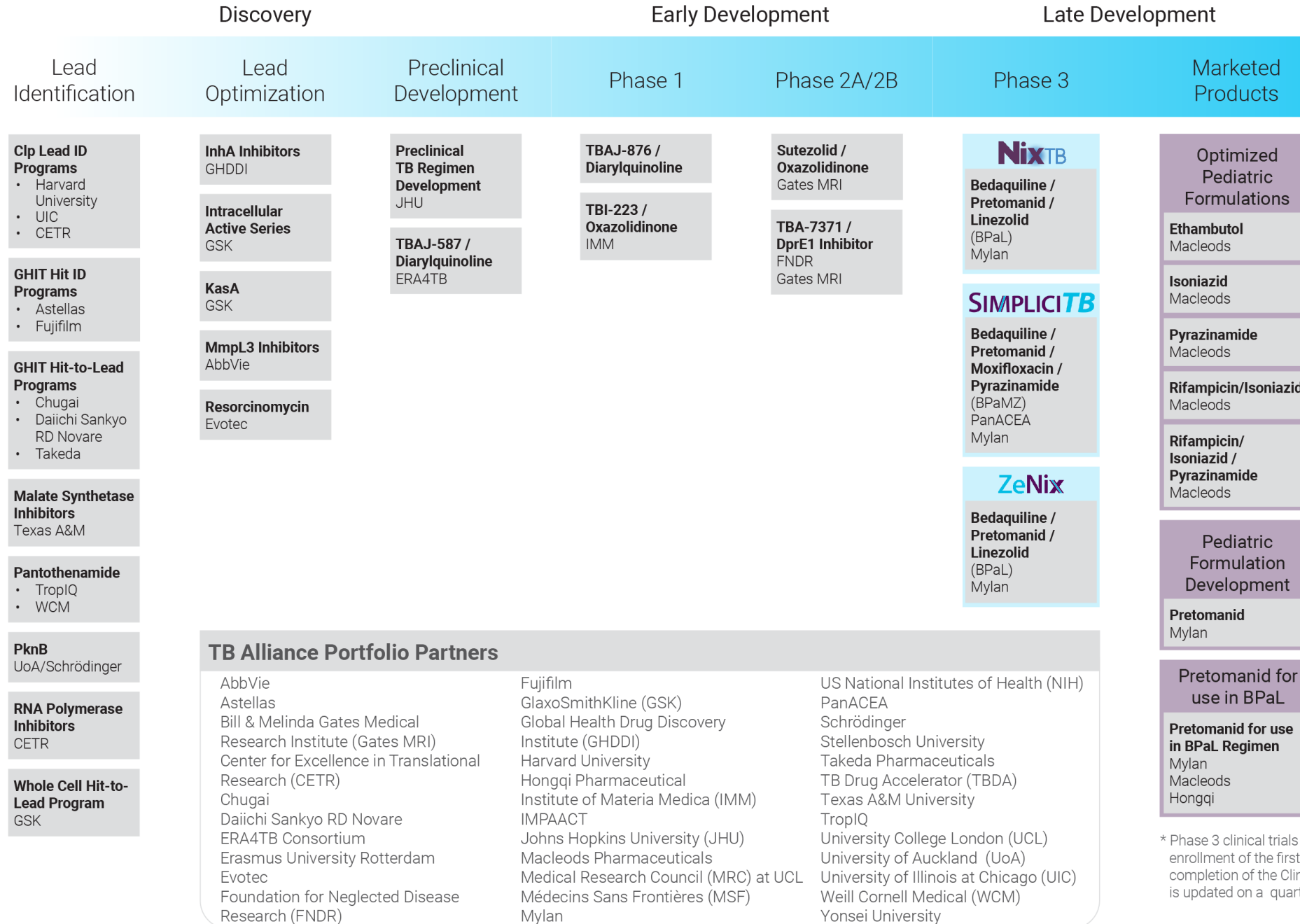
Putting science to work for better, faster TB cures

As an NIH-assigned Center of Excellence, we are a nonprofit R&D organization that has:

- Developed a **new treatment** for highly drug-resistant TB
- Launched **improved treatments** for children with TB
- **Transformed** how TB treatments are developed
- **Revived** the pipeline for new TB drugs
- **Mobilized** a global network of partners



AAA Mandate: Ensuring TB Alliance products are accessible to every person who needs them



* Phase 3 clinical trials are added to the pipeline after enrollment of the first patient and are removed after completion of the Clinical Study Report. This document is updated on a quarterly basis.

Nix-TB Results

New England Journal of Medicine, March 2020

PARTICIPANT STATS

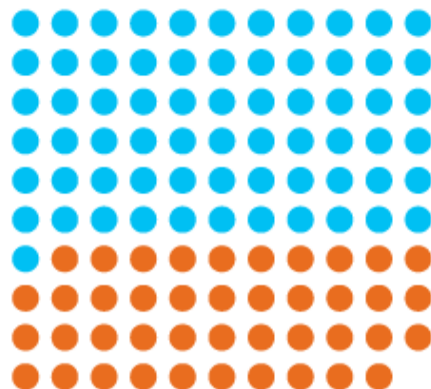
109 participants with confirmed TB

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



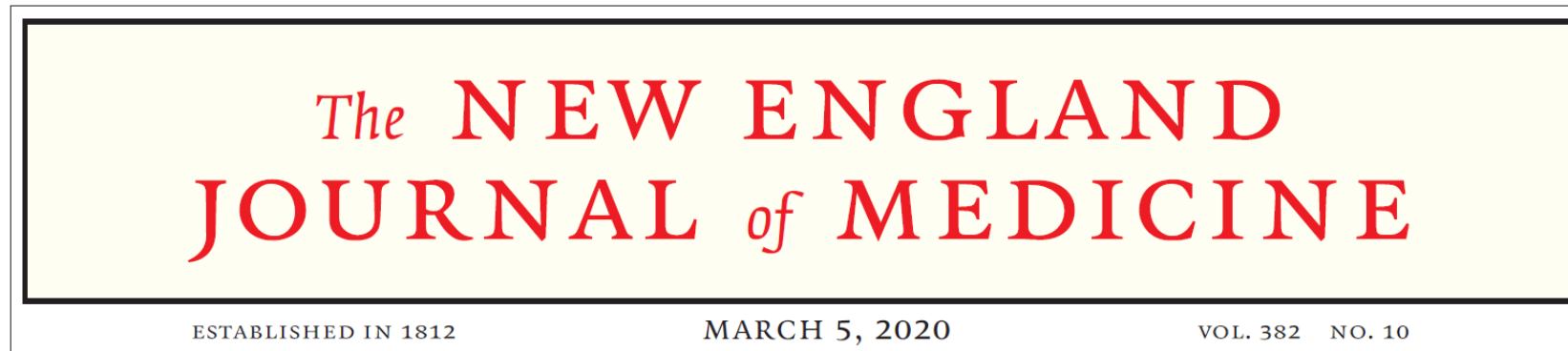
95% CI (83-95)



*Treatment intolerant or non-responsive MDR-TB

Pretomanid and the BPaL Regimen

- Full publication in the New England Journal of Medicine
<https://www.nejm.org/doi/full/10.1056/NEJMoa1901814>



Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

Francesca Conradie, M.B., B.Ch., Andreas H. Diacon, M.D., Nosipho Ngubane, M.B., B.Ch.,
Pauline Howell, M.B., B.Ch., Daniel Everitt, M.D., Angela M. Crook, Ph.D., Carl M. Mendel, M.D.,
Erica Egizi, M.P.H., Joanna Moreira, B.Sc., Juliano Timm, Ph.D., Timothy D. McHugh, Ph.D.,
Genevieve H. Wills, M.Sc., Anna Bateson, Ph.D., Robert Hunt, B.Sc., Christo Van Niekerk, M.D.,
Mengchun Li, M.D., Morounfolu Olugbosi, M.D., and Melvin Spigelman, M.D., for the Nix-TB Trial Team*

Spotlight on BPaL: Accelerating Product Access

One Year Since US Approval, Rapid Progress Toward Uptake

- Pretomanid was made available for **150 low and middle-income countries** through Stop TB Partnership's Global Drug Facility (GDF) at a price of **\$364** for a six-month treatment course.
- Commercialization agreements with additional manufacturing partners: **Macleods**, and **Hongqi Pharma**.
- Global commercialization partner **Mylan** established a Named Patient Access Program
- **The World Health Organization** recommended the BPaL regimen under operational research conditions.
- Enrollment was completed in TB Alliance's phase 3 **ZeNix** and **SimpliciTB**, with results expected in 2021. The 24-month follow-up on all patients in the pivotal **Nix-TB** trial was also completed.
- **DCGI** approval for conditional access under the National Tuberculosis Elimination Program.
- Conditional **European Commission** marketing authorization as part of BPaL regimen

Operations Research

- Recent TB Alliance groundwork in several countries & Mylan support in key countries has helped progress on ORs
 - 2 early movers – Ukraine & Tajikistan, funded by TB REACH [Stop-TB, TBA effort]
 - Nigeria, Kyrgyzstan, Indonesia: value proposition work by TB Alliance
 - South Africa: advocacy with DOH, local TBA & Mylan teams' support, Nix-TB trial site
 - India: local Mylan team, TB Alliance HQ missions, NTP on TB Alliance AAC
 - Philippines, Myanmar, Uzbekistan, Kazakhstan: direct engagement by us and through technical partners
- Mylan team and technical partners working in close coordination with us

Mylan Named Patient Access Program (NPAP)



- The NPAP is a means of providing access to pretomanid as part of the three-drug, all-oral BPaL regimen to patients in countries where the drug is not currently approved by a national regulatory authority.
- NPAP is designed specifically for patients who live in countries where regulatory approval for pretomanid is not yet available to help ensure that physicians can consider pretomanid as a viable treatment option for patients regardless of where they live.
- To learn more about this program and apply, please visit www.accesspretomanid.com.

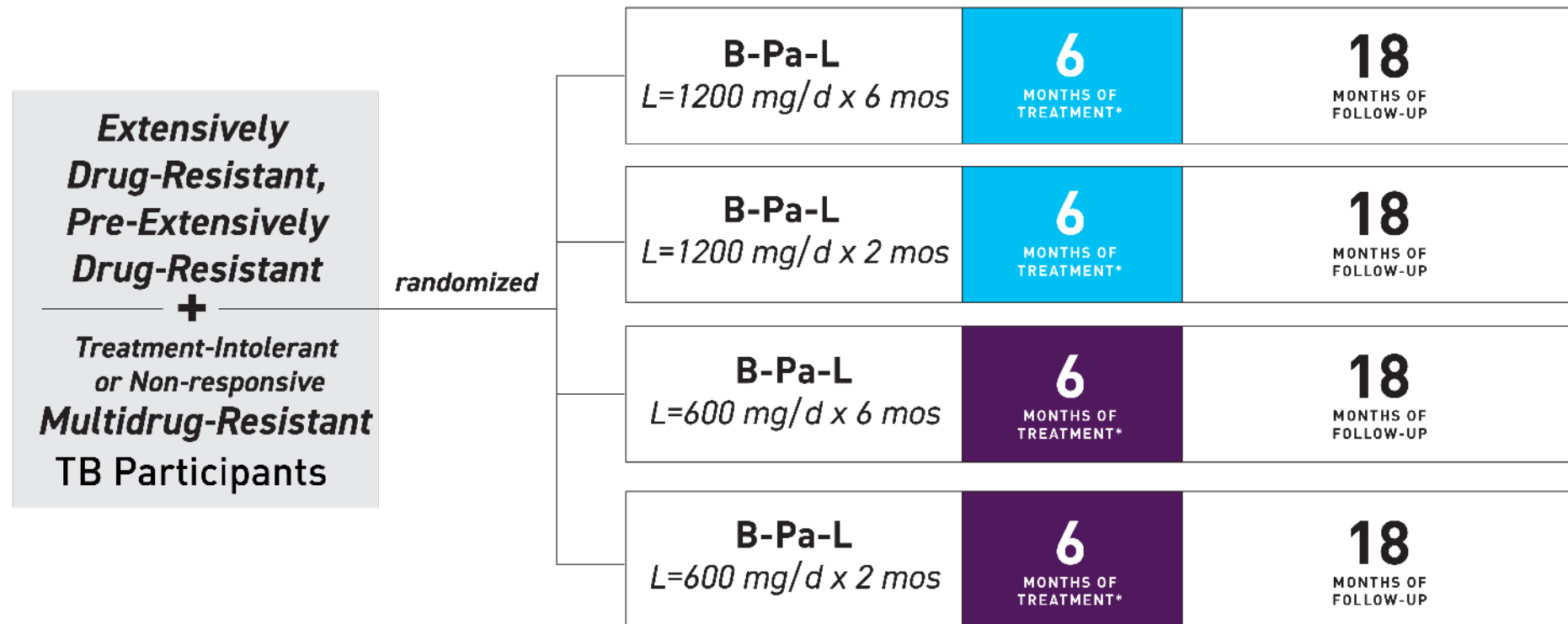
Trial Rationale

- Provide a 3-drug regimen where there is no expected resistance in the community for patients with limited treatment options
- Gather important efficacy and safety data on a regimen that could potentially treat all strains of TB
- Shorten treatment in patients who are susceptible to all drugs with Combination of B-Pa which is well tolerated
- **Nix-TB**- showed manageable toxicity and efficacy of an all oral 6-month regimen to patients with XDR. (Nix-TB all patients started with 1200 mg linezolid and Investigators could pause or adjust dose in response to toxicity.
- **ZeNix**-Blinded linezolid dose and duration differences to optimize dosing scheme for best efficacy to toxicity balance (risk/benefit) .

ZeNix: Linezolid Optimization Trial



Patients with XDR-TB, Pre-XDR-TB or who have failed or are intolerant to MDR-TB treatment



*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

ZeNix Trial Population

Expanded, just XDR and MDR intolerant and non-responsive in Nix-TB.

ZeNix trial included patients with:

- XDR-TB
- Pre-XDR-TB or
- MDR-TB who have failed or are intolerant to treatment

ZeNix Timelines

- First Patient Randomized **November 2017**
- Last Patient completed treatment **June 2020**
- Last Patient to complete 6-month follow-up (Primary Endpoint) **December 2020**
- Primary Endpoint Analysis Complete/Available **September 2021**
- Last Patient to complete trial **December 2021**

COVID-19 Issues and Actions

- Working with sites to ensure participants supported in Follow up:
 - Encourage documentation of missed visits, assessments and out of window visits due to COVID-19
 - Instruct sites to perform telephone visits where on-site visits not possible, on-site visit to be scheduled as soon as possible to ensure sputum sample collection
 - On-site monitoring visits were suspended and have started again
 - TB Alliance emailing monthly reminders of upcoming visits for primary and secondary endpoints (Follow-up week 26 and 78)

All ZeNix patients in follow-up

**Important for patients to return for follow up visits to provide sputum
6 months after treatment completion (primary endpoint) and at the end
of the trial, 18 months after treatment completion.**

BPaMZ Regimen

SimpliciTB Clinical Trial

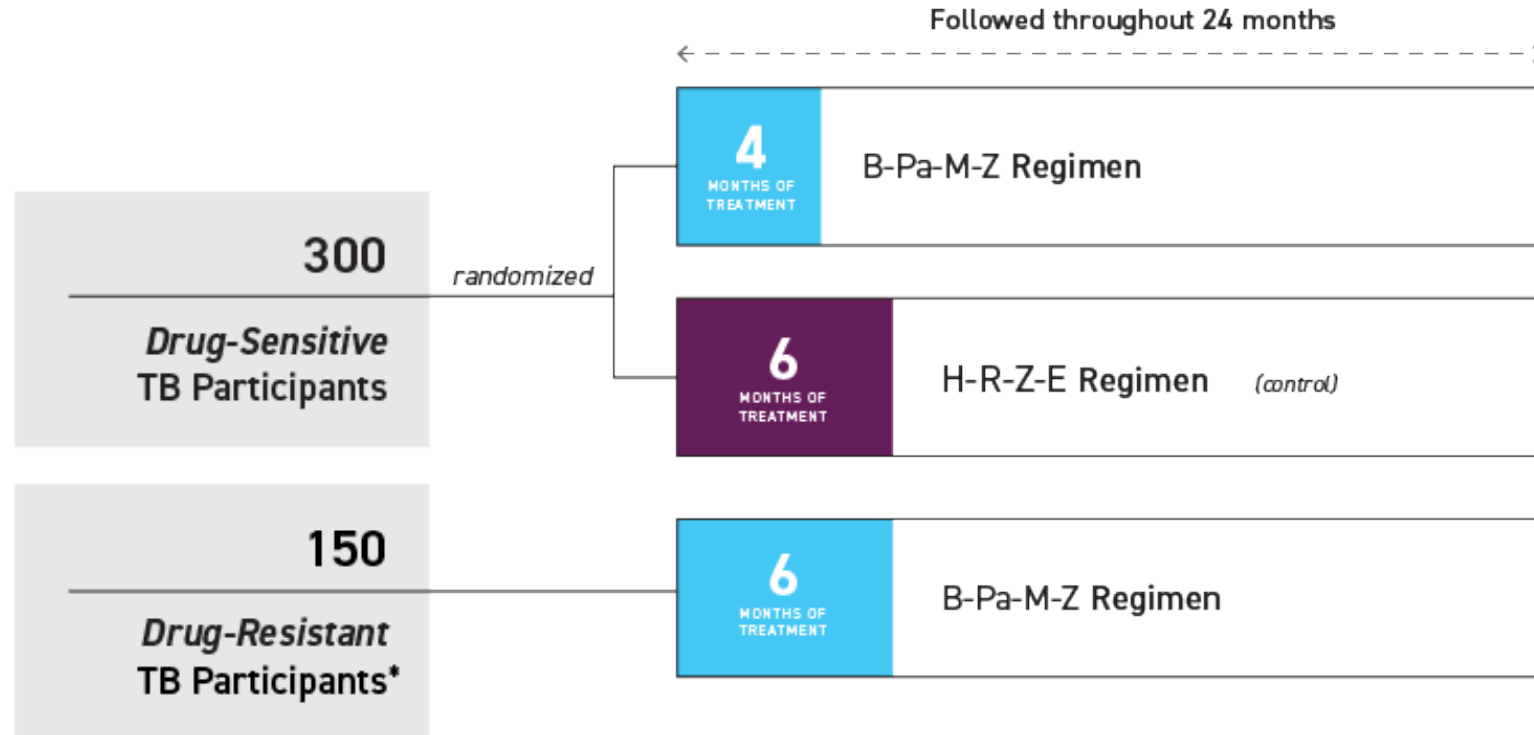
- The SimpliciTB clinical trial seeks to test a novel regimen consisting of bedaquiline (B), pretomanid (Pa), moxifloxacin (M) and pyrazinamide (Z) (BPaMZ)
- This trial evaluates
 - The effectiveness of a 4-month regimen of BPaMZ in people with DS-TB versus six months of HRZE (control/standard of care)
 - The safety, tolerability and efficacy of a 6-month BPaMZ regimen for patients with DR-TB
- Enrollment commenced on 30 July 2018
 - Enrollment completed on 2 March 2020
 - Patients enrolled in 27 sites in 8 countries on 4 continents



SimpliciTB Trial: BPaMZ



Participants with newly diagnosed DS- and MDR-TB



*Specifically MDR-TB and mono-resistance to isoniazid or rifampicin.

B bedaquiline 200 mg x 8 weeks, then 100 mg | Pa pretomanid 200 mg | M moxifloxacin 400 mg | Z pyrazinamide 1500 mg

H isoniazid | R rifampin | Z pyrazinamide | E ethambutol

- Immediate Intervention from TB Alliance
 - Weekly, then bi-weekly, internal TC's and tracking
 - No changes since August 2020
 - Direct communication with all sites and vendors
 - Weekly monitoring of safety and IMP supplies, proactive ordering etc
 - Participant visits – telephonic, remote and EDC completion instructions
 - Support for COVID-19 testing and reimbursement
 - Regular newsletters to sites

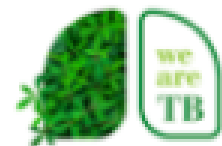
COVID-19 Impact on Community Engagement

- All site programs have transitioned to using virtual platforms and tools to communicate with Community Advisory Boards and affected communities
- Site-level CE programs are now including COVID-19 prevention and safety in their educational programs, in addition to TB disease and research education
- CE teams have reported general difficulty with supporting patients in for their treatments and follow ups.
- Ongoing survey of TB Alliance site-level CE and research teams, CABs and communities to understand overall impact of COVID-19.
- Early responses are consistent with published reports on impact at the community-level.



The impact of COVID-19 on the TB epidemic: A community perspective

https://drive.google.com/file/d/1rxREVzu_K-5EYNqLahMmTnKHJSaff0-Q/view



Upcoming Event

Stakeholders Association Annual Meeting

**November
2020**

20
**YEARS OF
IMPACT**

TB Alliance Donors

20 YEARS OF
IMPACT



Indonesia
Health Fund



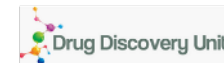
TB Alliance Stakeholders



Community Representative,
Maurine Murenga



Community Representative,
Sarah Mulera



Louder Than TB: Coalition of Partners

More than 50 organizations have joined the campaign



Thank you!

