Late-Stage Clinical Programs

Carl Mendel, TB Alliance

INTERTB, St. George's, University of London

October 22, 2018

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

TB Drug Development Pipeline As of August 2018*

TB ALLIANCE

Discovery			Early Development		Late Development	
Lead Identification	Lead Optimization	Preclinical Development	Phase 1	Phase 2A/2B	Phase 3	Phase 4 / Marketed Products
Clp-C/PIP2 Eli Lilly Harvard University	Arylsulfonamides GSK	Preclinical TB Regimen Development JHU	Optimization of Rifampicin in Children <5kg Stellenbosch University		NixTB Bedaquiline/ Pretomanid/ Linezolid (BPaL)	Optimized Pediatric Formulations
Energy Metabolism Inhibitors AUCK/UIC	InhA Inhibitors GHDDI	TBAJ-587 / Diarylquinoline Merck	TBA-7371/ DprE1 Inhibitor Eli Lilly/FNDR		SIMPLICITB Bedaquiline / Pretomanid / Moxifloxacin / Pyrazinamide (BPaMZ)	Ethambutol Macleods
GHIT Hit ID Programs • Astellas • Chugai • Daiichi Sankyo RD Novare • Fujifilm • HyphaGenesis	Intracellular Phenotypic Hits GSK	TBI-223 / Oxazolidinone IMM			ZeNix Bedaquiline/ Pretomanid/ Linezolid (BPaL)	Isoniazid Macleods
GHIT Hit-to-Lead Program Takeda	KasA GSK	TBAJ-876 / Diarylquinoline				Pyrazinamide Macleods
Natural Product Hit-to-Lead Program Evotec	Macrolides Evotec					Rifampicin/ Isoniazid Macleods
PEPCK Roche/TAMU	MmpL3 Inhibitors AbbVie					Rifampicin/ Isoniazid/ Pyrazinamide Macleods
PknB UoA/Schrödinger	Squaramides Evotec					
RNA Polymerase Inhibitors						
Whole Cell Hit-to-Lead Program GSK						

TB Alliance Portfolio Partners

AbbVie
Astellas
Chugai
Daiichi Sankyo RD Novare
Eli Lilly
Evotec
Fujifilm
Foundation for Neglected Disease Research (FNDR)
GlaxoSmithKline (GSK)
Global Health Drug Discovery Institute (GHDDI)
Harvard University
HyphaGenesis
Institute of Materia Medica (IMM)
IMPAACT
Johns Hopkins University (JHU)
Macleods Pharmaceuticals
Medical Research Council (MRC) at UCL
Médecins Sans Frontières (MSF)
Merck
US National Institutes of Health (NIH)
Roche Pharmaceuticals
Schrödinger
Stellenbosch University
Takeda Pharmaceuticals
TB Drug Accelerator (TBDA)
Texas A&M University (TAMU)
University College London (UCL)
University of Auckland (UoA)
University of Illinois at Chicago (UIC)
Yonsei University

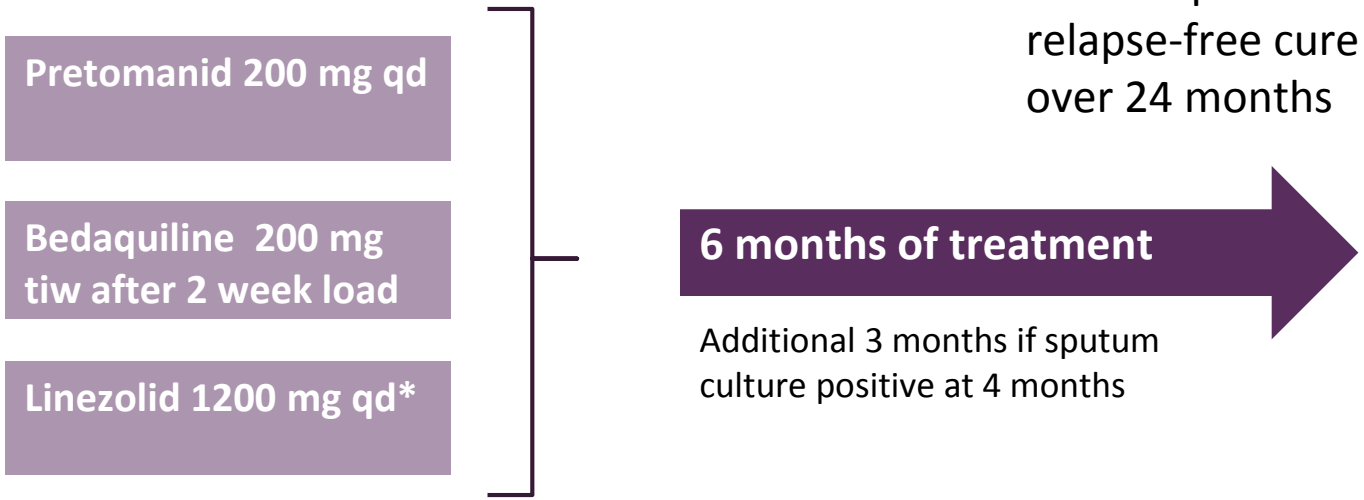
* Clinical trials are added to the pipeline after enrollment of the first patient and are removed after completion of the Clinical Study Report. This document is updated on a quarterly basis.

Late-Stage Clinical Programs

- Nix-TB (BPaL)
- ZeNix (BPaL)
- SimpliciTB (BPaMZ)
- Pediatric program

Nix-TB Phase 3 Trial in XDR-TB

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



*Amended from 600 mg bid strategy

Sites

Sizwe Hospital, Johannesburg, South Africa

Brooklyn Chest Hospital, Cape Town, South Africa

King Dinuzulu Hospital, Durban, South Africa

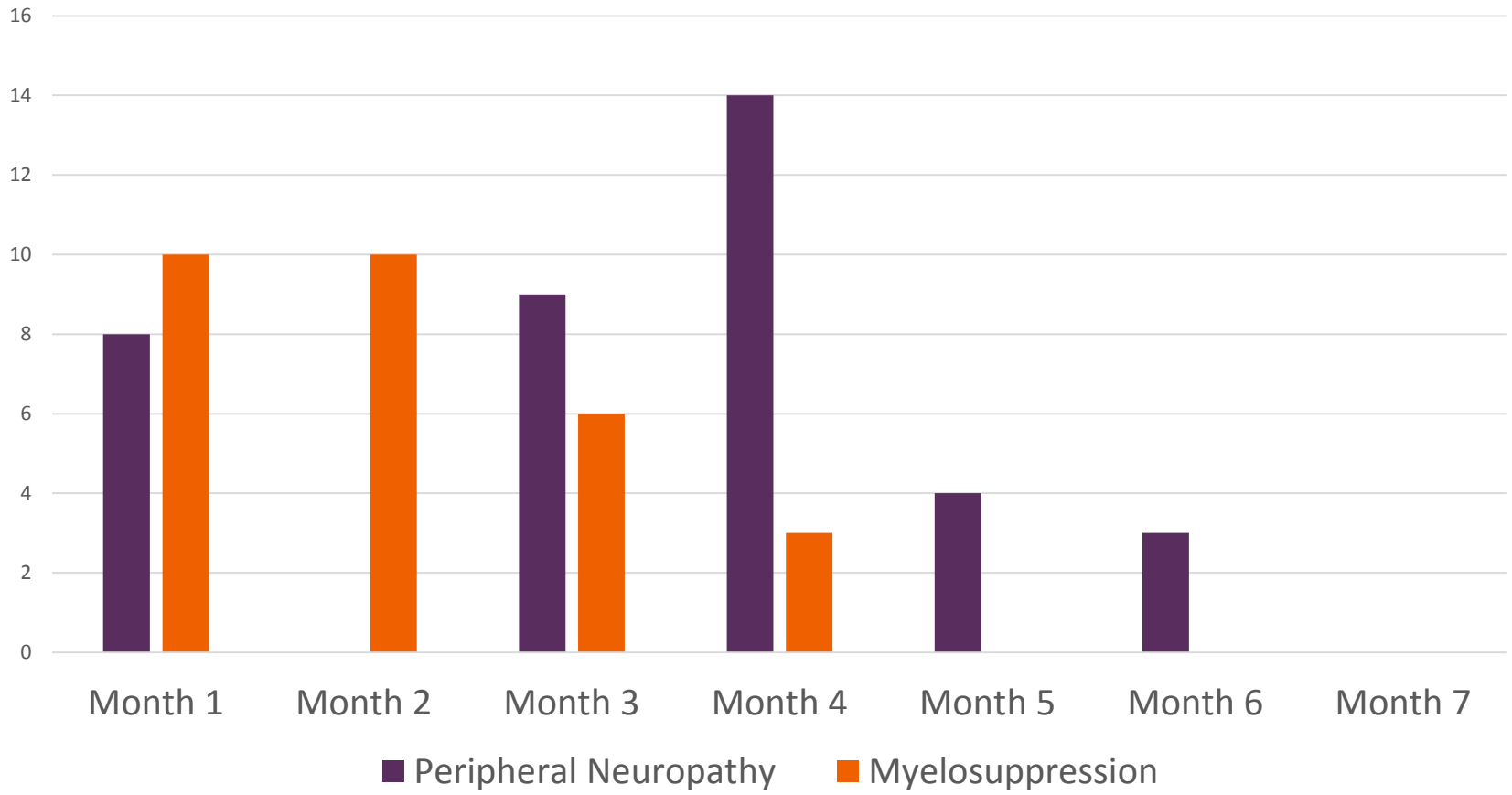
Status of Participants in Nix-TB

- Enrollment ended November 15, 2017; transitioned to ZeNix
  - 109 enrolled
  - All have completed 6 months of treatment
  - 95 have reached their primary endpoint (6 months after end of treatment)
  - 35 patients have completed the study (month 30)
- Overall relapse-free cure rate of TB disease among the first 75 followed to primary endpoint (6 months after end of treatment):
  - To be presented at IUATLD meeting Thursday afternoon

Experience with Linezolid Toxicity

- 67% of Participants had at least one interruption of linezolid
  - Maximum mean duration of dose interruption = 23 days
  - 4 months was the minimum total amount of exposure time to linezolid
- 55% had at least one reduction of linezolid dose
- Myelosuppression requiring interruption or reduction occurred generally in the first 2-3 months
- Neuropathy requiring interruption or reduction generally occurred in months 3-4
  - Data on resolution of neuropathies is evolving

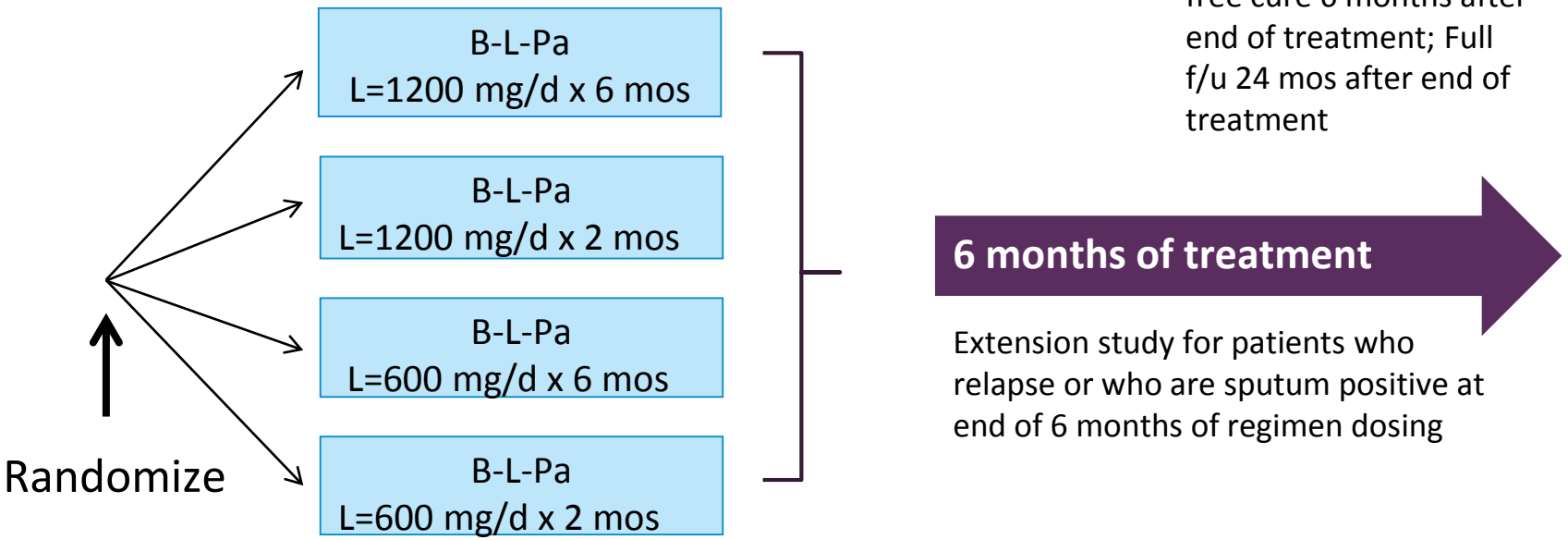
Number and Type of Linezolid Adverse Events by Month



Based on the first 50 participants enrolled in Nix-TB who completed the full 6 months of therapy

B-Pa-L Linezolid Optimization Trial: ZeNix

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



N=45 per group; total 180 (30/group XDR)

Pa dose = 200 mg daily; B Dose = 200 mg daily X 8 wks, then 100 mg daily

Status of ZeNix

- 61 patients enrolled across 1 site in Georgia, 3 sites in South Africa, and 4 sites in Russia
- Additional sites to be added
  - South Africa
  - Moldova

Registration / Access Plans Around Nix-TB

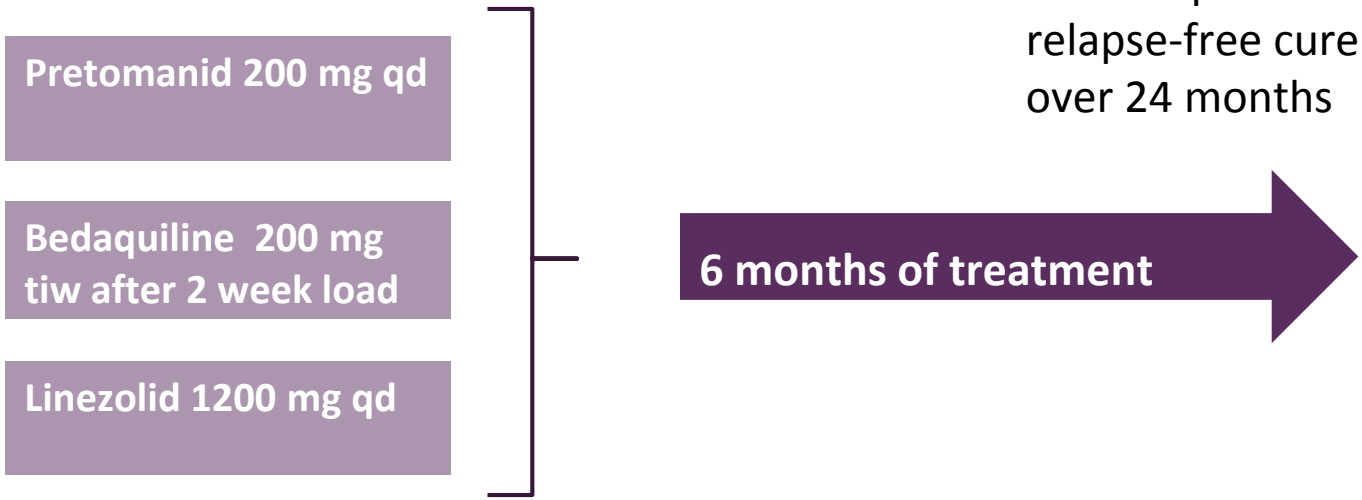
- NDA submission (FDA) END2018
  - Approval expected 3Q2019
- MAA submission (EMA) 1Q2019
  - Approval expected 1Q2020
- Inclusion in WHO guidelines expected 4Q2019
  - Availability through GDF expected 4Q2019
- (ZeNix results 2Q2020)
- Other markets

Size of Clinical Trial Database in Pretomanid NDA

- Nix-TB trial: N = 109 on pretomanid
  - 101 at primary endpoint (6 mos after end of treatment)
  - 37 at secondary endpoint (24 mos after end of treatment)
- All phase 1/2/3 studies: N = 1168 on pretomanid

BPaL: Regimen Development

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

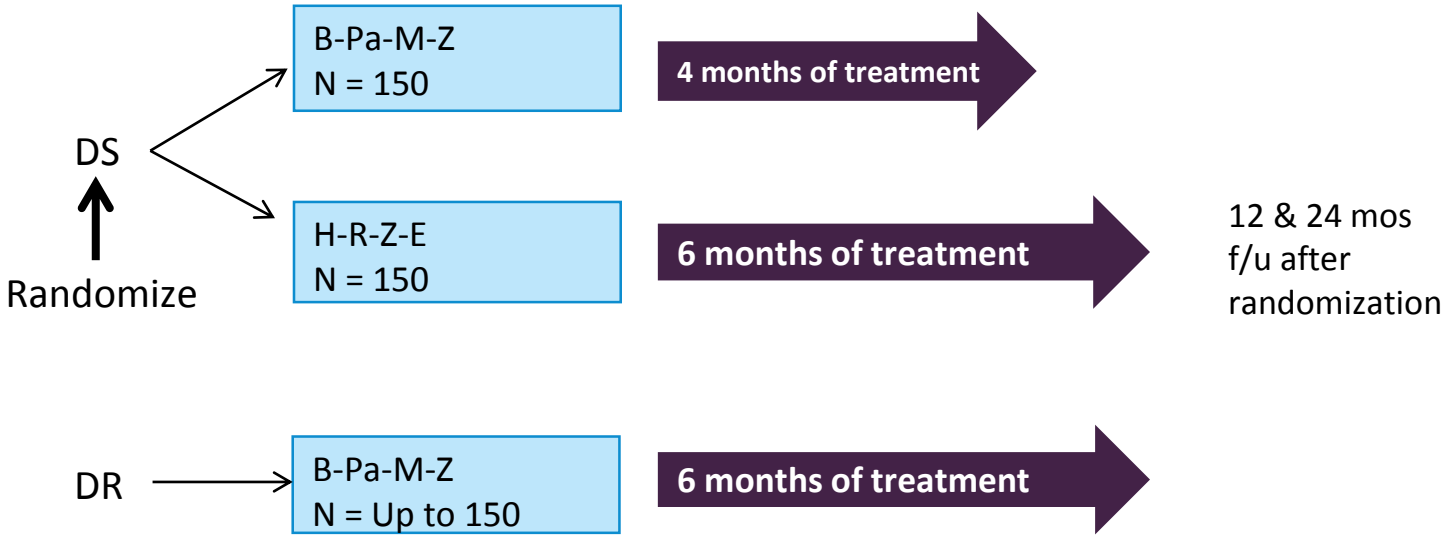


First Example of Regimen Development (NCE) in TB:

- Advantaged regimen available at launch of NCE
- How to use it, including treatment duration and evidence of durable effect, available at launch

SimpliciTB Trial: BPaMZ

Participants with newly diagnosed DS- and MDR-TB



B = bedaquiline 200 mg x 8 wks, then 100mg Pa = pretomanid 200 mg

M = moxifloxacin 400 mg Z = pyrazinamide 1500mg

Status of SimpliciTB

- Targeted countries (26 sites, 10 countries, 4 continents):
  - Africa: Ethiopia x1, South Africa x8, Tanzania x4, Uganda x1
  - Asia: Malaysia x1, Philippines x3, Thailand x1
  - Eastern Europe: Georgia x1, Russia x4
  - South America: Brazil x2
- Regulatory filings complete; all approvals expected this year
- FPI 30 July in Georgia
  - Actively recruiting in Georgia and South Africa
  - Tanzania and Malaysia to begin recruiting this month
- 15 randomized participants

Key Timings Upcoming

- BPaL FDA approval — Mid2019
  - Breakthrough rx for XDR-TB
- ZeNix results — Mid2020
  - Potential expansion of BPaL into first line MDR-TB
- BPaMZ results — End2020
  - Expansion of pretomanid into DS-TB and first line MDR-TB
- BPaOx development program — End2024
  - Universal regimen
- DPaOx — End2025
  - Universal regimen, ultra-short treatment duration

Timing Estimates for Pediatric Implementation Plan

- Semen analysis study in adult TB patients—no longer on critical path
  - Required before *multiple* dosing in pediatric study
  - 1Q 2019 – 4Q 2020
- Juvenile tox study
  - Review by FDA needed before any pediatric dosing
  - Initial results 1Q 2019 / full report 3Q 2019
- CMC GMP manufacture of pediatric formulation
  - Needed for start of clinical work
  - 4Q 2018 – Dec 2019
- Phase 1 BA study in adults of pediatric formulation
  - Feb 2020 – Jul 2020
- SD PK study in children "Pediatric 1": all age groups simultaneously
  - Jan 2021 – Oct 2022
- Long term PK, efficacy, and safety study in children "Pediatric 2":
  - Apr 2023 – Apr 2025 (all age groups simultaneously), then CSR and file

TB Alliance Donors

Australian Aid

Bill & Melinda Gates Foundation

Dutch Ministry of Foreign Affairs

German Federal Ministry of Education and Research

United States Food and Drug Administration

Global Health Innovative Technology Fund [Japan]

Indonesia Health Fund

Irish Aid

Medical Research Council

National Institute of Allergy and Infectious Disease

UK aid

UK Department of Health

United States Agency for International Development