Overview:
TB Alliance Drug Development Pipeline

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TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

TB ALLIANCE

TB Pandemic

- TB is the leading infectious disease killer, and a top 10 killer worldwide.
- TB kills 1 person nearly every 18 seconds; 1.7 million die each year.
- 10.4 million new cases annually.
- Leading killer of people with AIDS.
- Drug resistance is on the rise—over half a million annual cases.
- 1 million children become ill with TB each year and 210,000 die.

Current TB Therapy

OLD

Arsenal of drugs developed mostly in 1960s.

LONG

TB treatment today takes 6-30+ months.

COMPLEX

Many pills must be taken daily; Drug-resistant treatment includes daily injections.

EXPENSIVE

Drug-resistant TB drugs can cost > $10,000 per treatment.

INADEQUATE

Breeds resistance & default; incompatible with some HIV treatments; DR-TB treatment often fails.

One day of treatment for drug-resistant TB

About TB Alliance: A Product Development Partnership

Catalyzing and advancing new TB cures

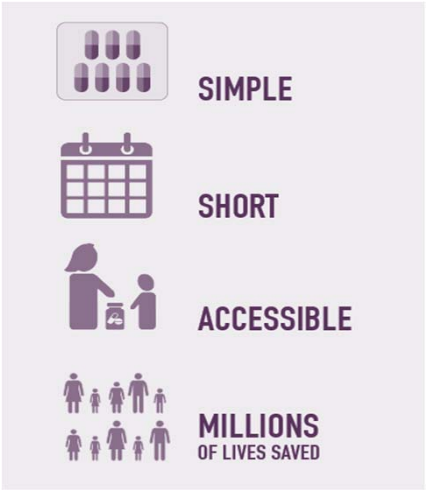
- Established in 2000
- Largest TB drug pipeline in history
- Redefining the way TB drugs are developed
  - Virtual business model promotes innovation and efficient progress
  - Leverage global pipeline of drugs to find the most promising TB regimens
  - Transform treatment with new regimens that treat drug-sensitive and drug-resistant TB
- "AAA Mandate": All new regimens will be adopted, available, and affordable

Our Vision: Better TB Medicines for All

Discover, develop and deliver better and faster TB regimens

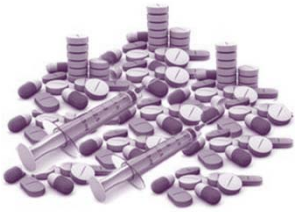
Achieving maximum impact will require:

- A sustainable pipeline of novel drugs to form the basis for universal regimens effective in all people with active TB
- An ultra short and effective therapy for latent infection
- All TB treatments appropriately formulated for children.



Product Development Strategy

Success will require novel drug combinations

Current Treatment	New Treatments in Development	Aspirational Goal
		
6-30 Months	3-6 Months	7-10 Days

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Drug Development Pipeline As of January 2018

Discovery			Early Development		Late Development		
Lead Identification	Lead Optimization	Preclinical Development	Phase 1	Phase 2A	Phase 2B	Phase 3	Phase 4 / Marketed Products
Clp-C/PIP2 *Schrödinger*	Arylsulfonamides *GSK*	Preclinical TB Regimen Development *JHU*	Optimization of Rifampicin in Children <5kg *Stellenbosch University*	Linezolid Dose-Ranging Study	NC-005	Nix-TB	Optimized Pediatric Formulations
Energy Metabolism Inhibitors *AUCK/UIC*	Cyclopeptides *Sanofi*	TBAJ-587 / Diarylquinoline *Janssen/Merck*	Sutezolid/ Oxazolidinone		Bedaquiline / Pretomanid / Moxifloxacin / Pyrazinamide (BPaMZ)	Bedaquiline/ Pretomanid/ Linezolid (BPaL)	Ethambutol *Macleods*
GHIT Hit ID Programs • *OP-BIO* • *Daiichi Sankyo Novare* • *HyphaGenesis* • *Chugai*	InhA Inhibitors	TBI-223 / Oxazolidinone *IMM*	TBA-7371/ DprE1 Inhibitor *Eli Lilly/FNDR*			ZeNix	Isoniazid *Macleods*
GHIT Hit-to-Lead Program *Takeda*	Intracellular Phenotypic Hits *GSK*					Bedaquiline/ Pretomanid/ Linezolid (BPaL)	Pyrazinamide *Macleods*
Natural Product Hit-to-Lead Program *Sanofi*	KasA *GSK*						Rifampicin/ Isoniazid *Macleods*
PEPCK *Roche/TAMU*	Macrolides *Sanofi*						Rifampicin/ Isoniazid/ Pyrazinamide *Macleods*
PknB *Schrödinger*	MmpL3 Inhibitors *Abbvie*						
POA Prodrugs *Yonsei*	Squaramides *Sanofi*						
RNA Polymerase Inhibitors							
Whole Cell Hit-to-Lead Program *GSK*							

TB Alliance Portfolio Partners

Abbvie
Chugai
Daiichi Sankyo Novare
Eli Lilly
Foundation for Neglected Disease Research (FNDR)
GlaxoSmithKline (GSK)
HyphaGenesis
Institute of Materia Medica (IMM)
IMPAACT
Janssen [Johnson & Johnson]
Johns Hopkins University (JHU)
Macleods Pharmaceuticals
Medical Research Council (MRC) at UCL
Médecins Sans Frontières (MSF)
Merck
US National Institutes of Health (NIH)
OP-BIO
Roche Pharmaceuticals
Sanofi
Schrödinger
Stellenbosch University
Takeda Pharmaceuticals
TB Drug Accelerator (TBDA)
Texas A&M University (TAMU)
University College London (UCL)
University of Auckland (AUCK)
University of Dundee (Dundee)
University of Illinois at Chicago (UIC)
Yonsei University

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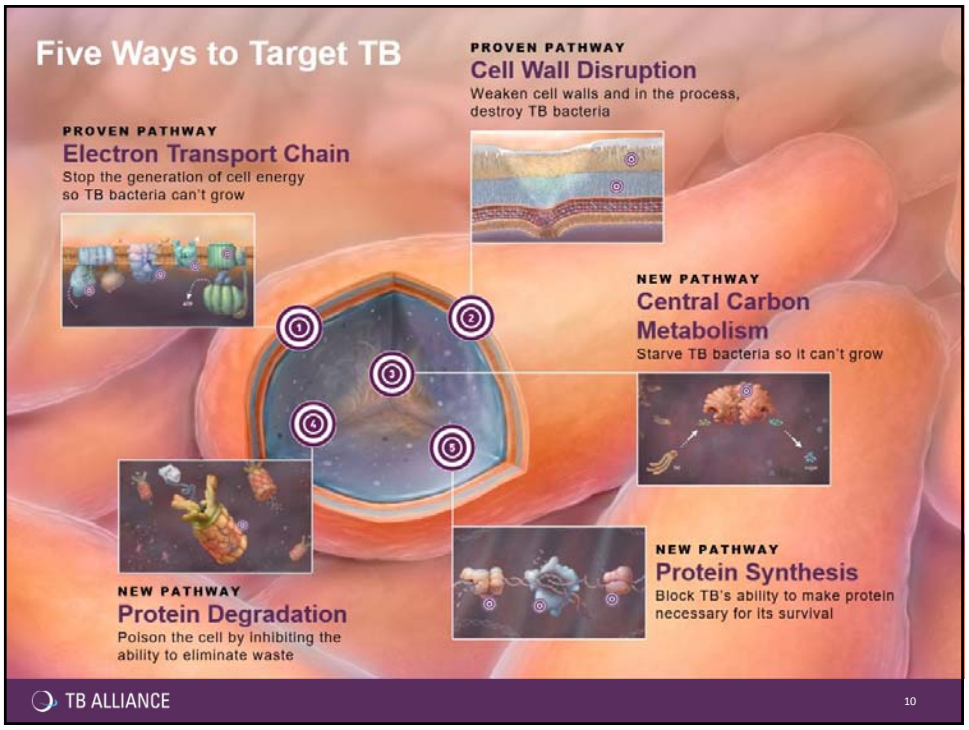
Early-Stage Research: Filling the Pipeline

A three-pronged approach

TB Alliance leverages industry and other partners to support the continued growth of the global TB drug pipeline.

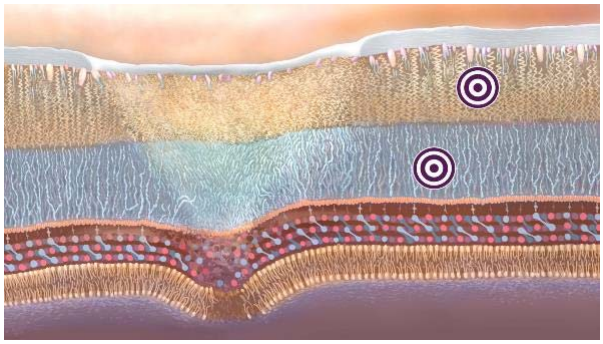
Optimize known compound classes	• Fully capitalize on the success of compounds already in development
Develop novel classes based on known targets	• Leverage validated drug targets, discover novel classes to address resistance
Develop novel classes based on novel targets	• Discover new drug classes with novel modes of action



TBA-7371

New Phase 1 Compound

- Last sample from Phase 1 study expected June 2018
- A novel mechanism of action
- Target: DprE1



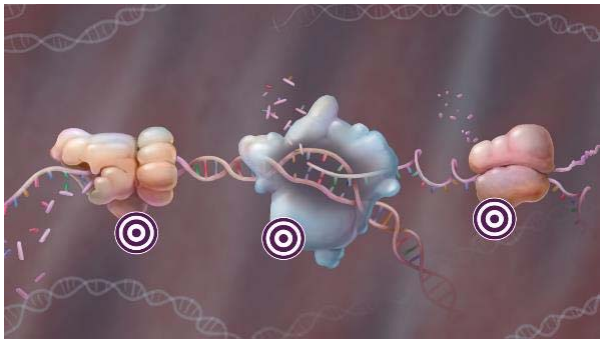
Mechanism of Action

Cell Wall Disruption

Sutezolid

New Phase 1 Study

- Oxazolidinone - similar class as linezolid
- Phase 1 began in September 2017
- Investigating relative advantages to linezolid



Mechanism of Action

Protein Synthesis

Recent Discovery Progress

Advancing the pipeline

- Expanded partnership with GHIT
- Two IND filings expected late 2018:
  - TBAJ-587 (diarylquinoline) in partnership with Merck
  - TBA-223 (oxazolidinone)
- Progression of Sanofi and GSK partnered projects

Late-stage Clinical program update

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Nix-TB (BPaL) Trial

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BPaL Regimen: NiX-TB Study

NixTB

- Pilot Phase 3 for patients with XDR-TB or who have failed or are intolerant to MDR-TB Treatment

XDR-TB

- Pretomanid 200 mg qd
- Bedaquiline 200 mg tiw after 2 week load
- Linezolid 1200 mg qd*

→ **6 months of treatment**

Additional 3 months if sputum culture positive at 4 months

Follow up for relapse-free cure over 24 months

*Amended from 600 mg bid

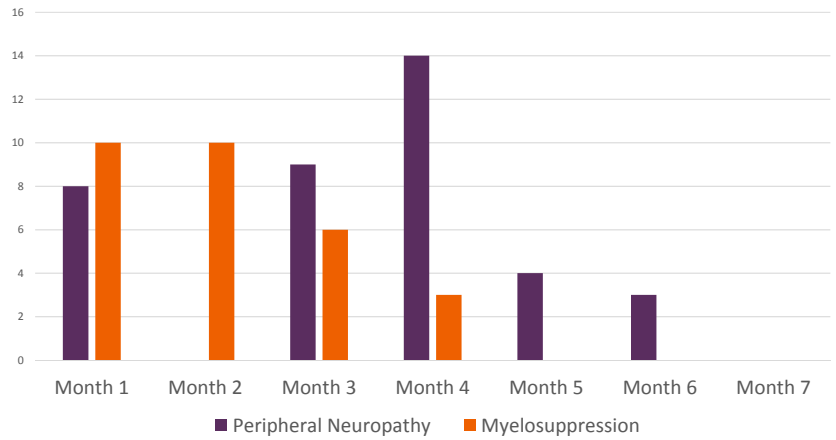
Sites

Sizwe Hospital, Johannesburg, South Africa
Brooklyn Chest Hospital, Cape Town, South Africa
King Dinuzulu Hospital, Durban, South Africa

Status of Participants in Nix-TB

- 109 participants enrolled as of end enrollment November 15, 2017
- Status as of February 2018:
  - 85 have completed treatment
  - 63 have reached their primary endpoint (6 months after end of treatment)
  - 11 patients have completed the study (Month 30)
- Overall relapse-free cure of TB disease among the first 30 followed to primary endpoint 6 months after end of therapy:
  - 26 / 30 = 87% (vs. historical up to 85% failure rate)
  - Transitioned to Zenix

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

Linezolid Optimization

- Safety management in clinical trial Vs in the field
- Efficacy Vs Safety
- Duration Vs dosage
  - Linezolid dose ranging study result
  - Mouse data

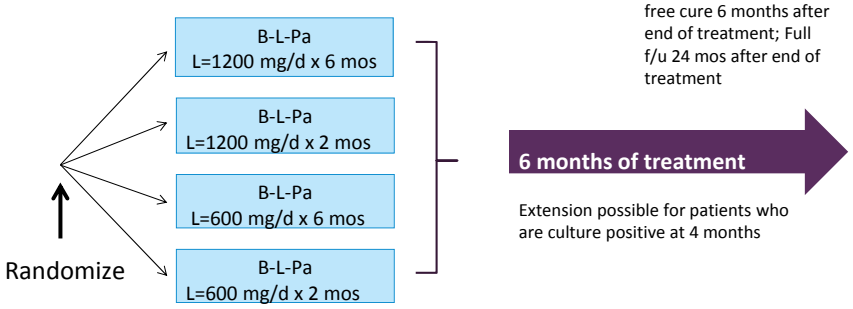
Linezolid Optimization Trial

- Evaluate Linezolid dose
- Evaluate Linezolid duration

BPaL Regimen: ZeNix Study

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 weeks, then 100 mg daily

Testing Combinations of Bedaquiline, Pretomanid, Pyrazinamide and Moxifloxacin (BPaZM)

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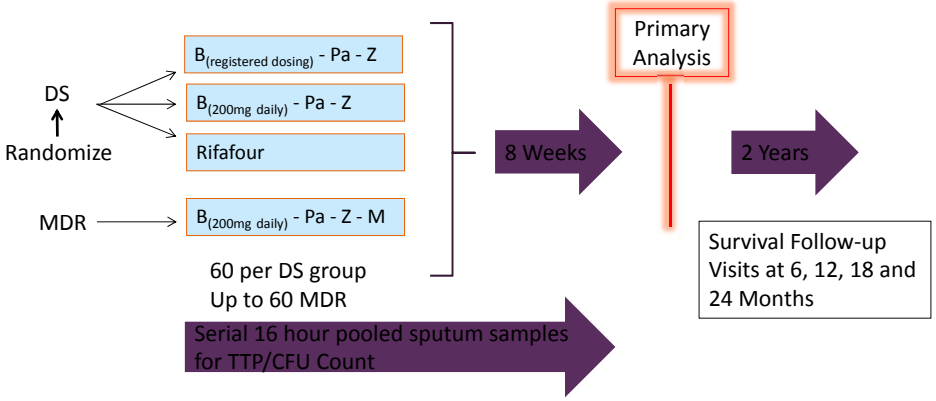
NC-005 – 8 week SSCC Study of B-Pa-Z-M

- B, Pa, Z and M containing regimens
- Participants with newly diagnosed smear positive DS- and MDR-TB



Z=pyrazinamide (1500mg daily), **M** = moxifloxacin 400mg daily, **Pa** = PA-824 200mg daily , $J_{(registered\ dosing)}$ = bedaquiline 400mg for 14 days then 200mg three times a week, $J_{(200mg\ daily)}$ = bedaquiline 200mg daily

Percent of Patients Culture Negative at 2 Months

Kaplan-Meyer Analysis

	Liquid Culture		Solid Culture	
	Overnight	**Spot**	**Overnight**	**Spot**
B(loading)PaZ	67%	84%*	89%	88%*
B(200mg)PaZ	76%*	79%	84%	92%*
BPaZM (MDR) Z-sensitive	96%*	89%*	100%*	97%*
BPaZM (MDR) Z-resistant	80%*		95%*	
HRZE control	51%	63%	86%	79%

*Statistically significant vs HRZE

NC-005: Time to Culture Negativity

Hazard Ratio vs HRZE (95% CI)

	Liquid Culture	Solid Culture
B(loading)PaZ	1.8* (1.1 – 2.9)	1.3 (0.9 – 1.8)
B(200mg)PaZ	2.0* (1.3 – 3.2)	1.1 (0.8 – 1.6)
BPaZM (MDR) Z-sensitive	3.3* (2.1 – 5.2)	2.2* (1.5 – 3.2)
BPaZM (MDR) Z-resistant	2.2* (1.3 – 3.9)	2.6* (1.4 – 4.5)
HRZE Control	--	--

NC-002	Liquid Culture	Solid Culture
PaMZ	1.7* (1.1 – 2.7)	1.6* (1.1 – 2.2)

*Statistically significant vs HRZE

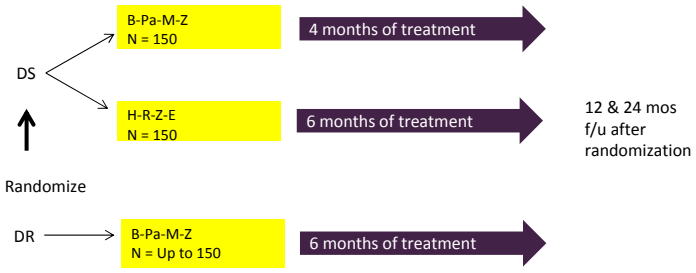
Conclusions

- BPaZ and BPaZM active and well tolerated
  - BPaMZ > BPaZ > PaMZ > HRZE in both clinical and preclinical data
- BPaZM appears to be markedly superior to HRZE in terms of time to culture negativity and potentially time to cure
  - Additional advantages over both PaMZ and BPaZ in MDR
    - Patients with Z resistance can be treated
    - Rapid DST for Z not needed, DST for Z not needed
- B(200mg) appears at least as active and safe as B(labeled dose)

BPaMZ: SimpliciTB Trial

SIMPLICITB

Participants with newly diagnosed DS- and MDR-TB

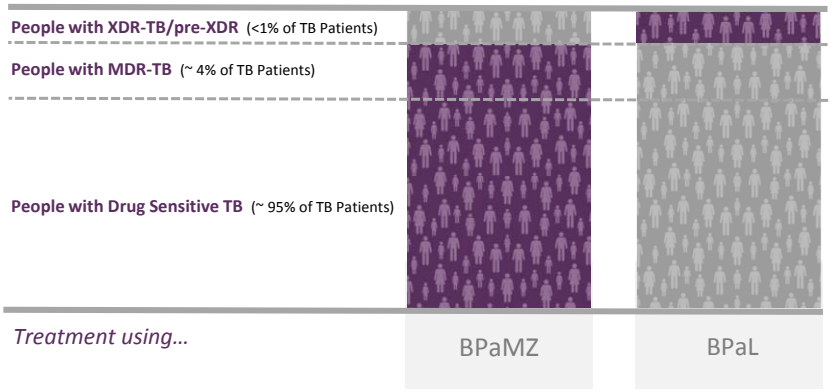


B = bedaquiline 200 mg x 8 wks, then 100mg Pa = pretomanid 200 mg

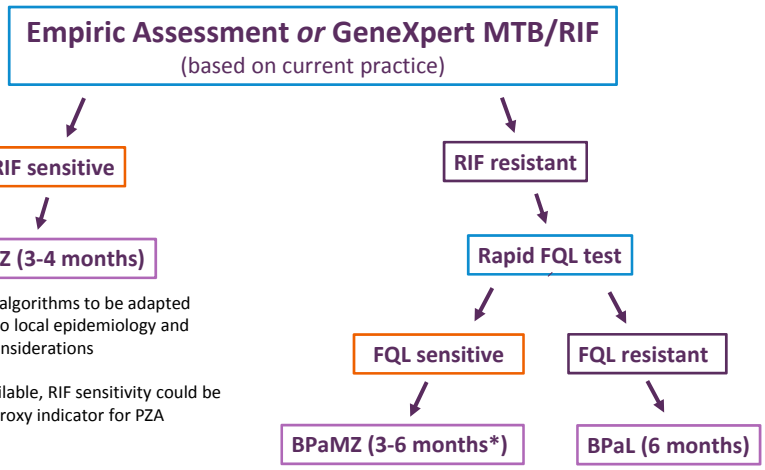
M = moxifloxacin 400 mg Z = pyrazinamide 1500mg

Current Perspectives Based on Emerging Data

Treatment For All With Universal Backbone of B-Pa



Potential Therapeutic Algorithm



- Diagnostic algorithms to be adapted according to local epidemiology and capacity considerations
- Where available, RIF sensitivity could be used as a proxy indicator for PZA sensitivity
- RIF resistant patients can go on to rapid FQL testing to determine appropriate regimen

*BPaMZ duration dependent on PZA sensitivity; if unknown, 6 months

TB Alliance Donors

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German Federal Ministry of Education and Research

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Global Health Innovative Technology Fund

Indonesia Health Fund

Irish Aid

National Institute of Allergy and Infectious Disease

UK aid

UK Department of Health

United States Agency for International Development

Thank You