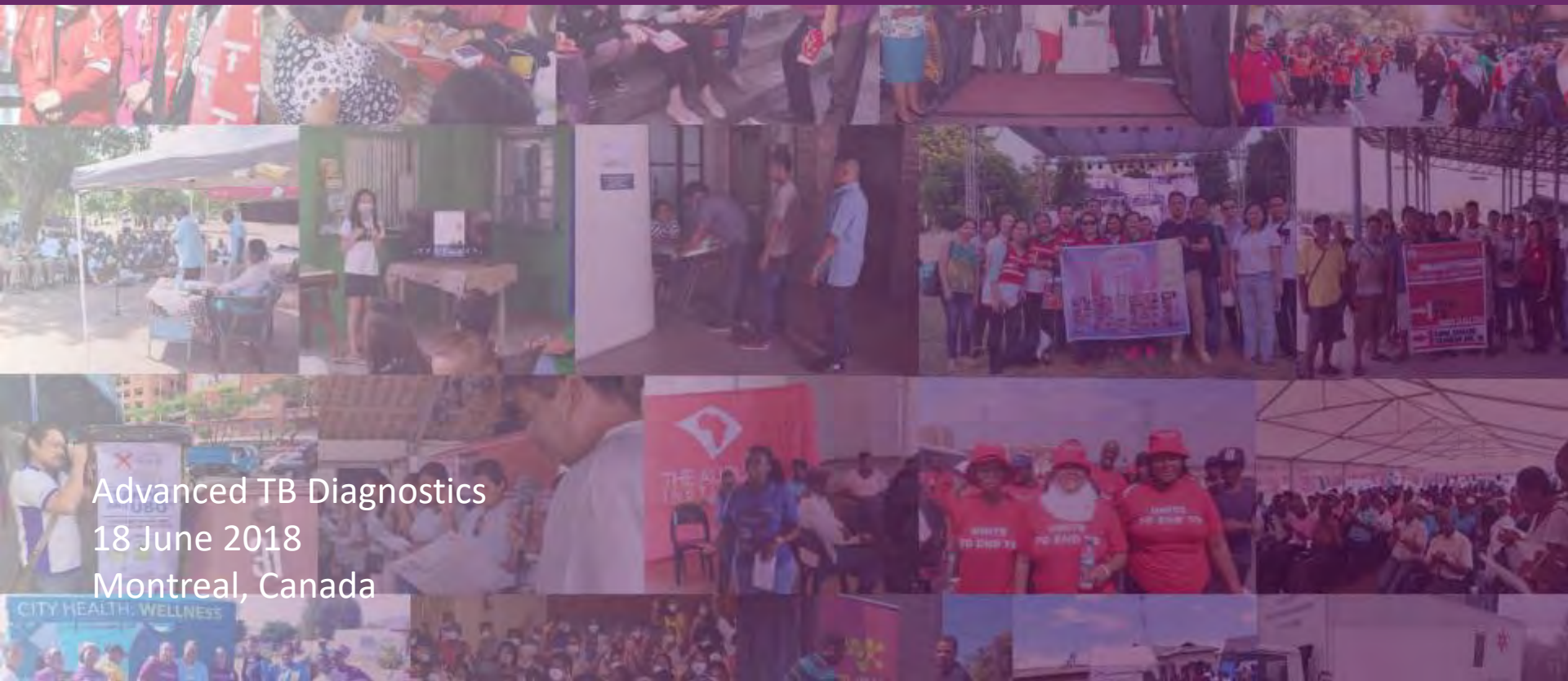
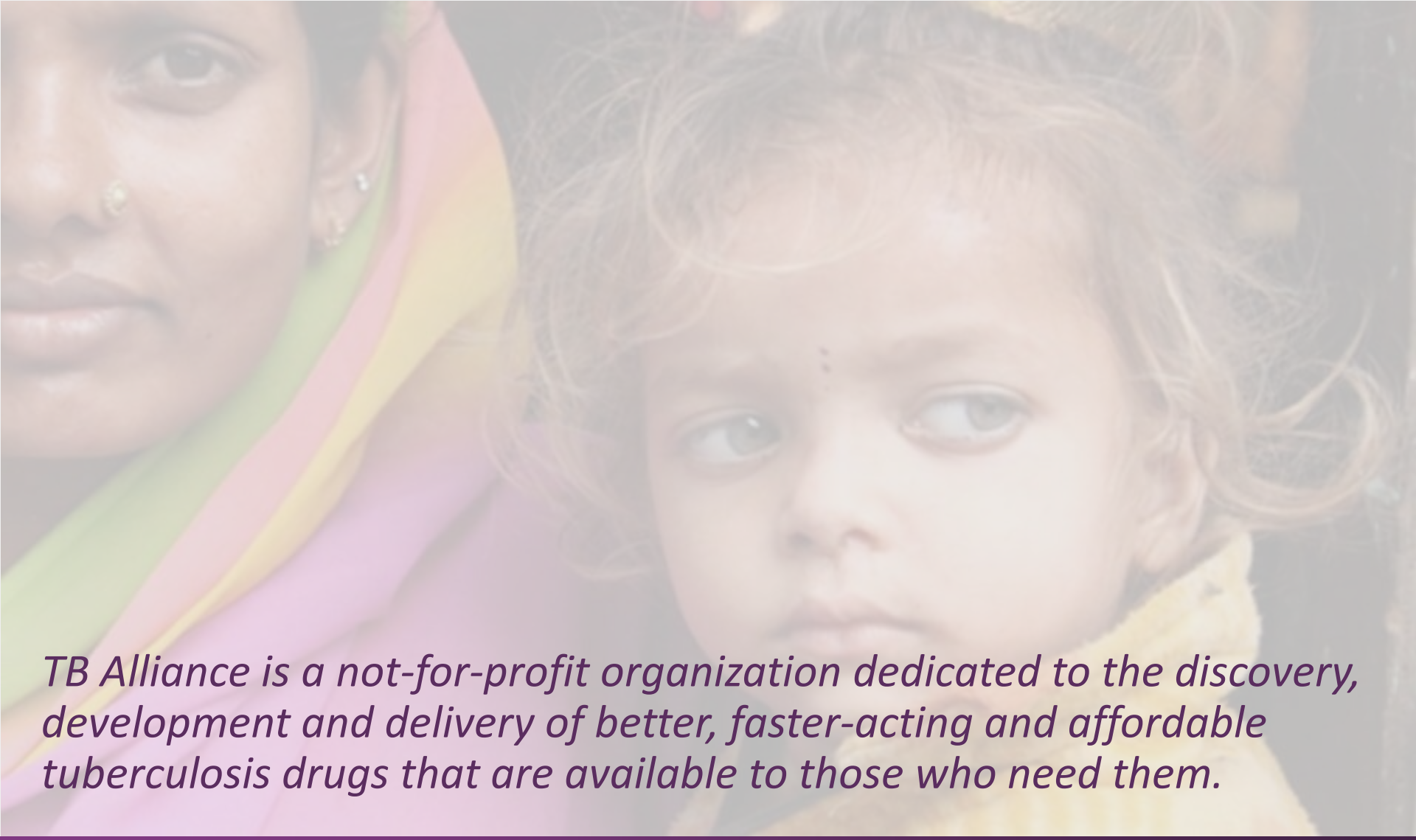
TB ALLIANCE

Putting science to work for better, faster TB cures

New TB Drugs and Regimens



Advanced TB Diagnostics
18 June 2018
Montreal, Canada



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 who need them.

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Current TB Therapy

OLD

Arsenal of drugs developed mostly in 1960s

LONG

TB treatment today takes 6-30+ months

COMPLEX

5-7 drug regimens for DR-TB, high pill burden, and daily injections

EXPENSIVE

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

INADEQUATE

Leads to resistance; incompatible with some HIV treatments; high failure rate for DR-TB

One day of treatment for drug-resistant TB

Our Vision: Better TB Medicines for All

Discover, develop and deliver better and faster TB regimens

Achieving maximum impact will require:

- **Simple**, **short**, and **effective** regimens
- **Combining novel drug with limited resistance** that are effective against all, or most, people with active TB
- Ensuring that new regimens are **Affordable, Adopted for use, and made widely Available** (AAA strategy)

SIMPLE

All-oral, highly effective regimens

SHORT

Three to six months of treatment

ACCESSIBLE

Adopted, available and affordable to people with TB

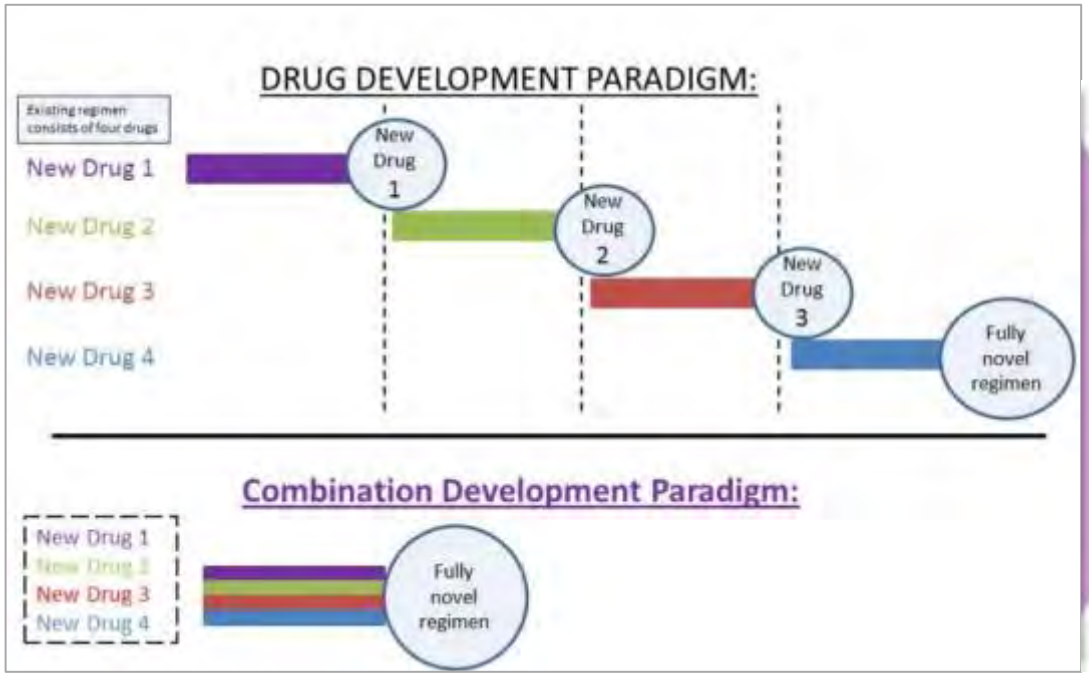
MILLIONS OF LIVES SAVED

Fight the TB epidemic and accelerate eradication

Innovative Paradigm: From Drugs to Regimens

TB Alliance is searching for the best combinations of novel drugs

- Multi-drug combinations prevent the development of resistance
- A critical mass of novel TB compounds are available to enable novel regimen development
- Potential to reduce R&D timelines from decades to years



Combination approach reduces time to market by 75%

Benefits of New Regimens

Positive impacts of new treatments are wide-reaching and multi-faceted

Novel regimens can simplify TB treatment, facilitate its scale-up and reduce its burden on health systems.

TB Drug Development Pipeline As of May 2018*

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

* 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.

TB Alliance Portfolio Partners

Abbvie
Chugai
Daiichi Sankyo Novare
Eli Lilly
Foundation for Neglected Disease Research (FNDR)
GlaxoSmithKline (GSK)
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)
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

Several Other Trials of New TB Drugs & Regimens

Trial	Regimen	Expected Results
Drug Resistant TB		
TB-PRACTECAL	BPaL, BPaLC, BPaLM x 6 mos	1Q 2021 (?)
STREAM	B plus 6 drugs x 9 months B, Knm plus 4 drugs x 6 mos	Pt 2 – 4Q 2021 (?)
END-TB	5 exp arms: B, D, L, 3 other drugs x 9 mos	4Q 2019 (?)
NExT	B, L, Lfx, Z, Eto or high dose H or Trz x 9 mos	4Q 2019 (?)
Delamanid Ph 3	D x 6 mos on SOC x 20 mos	4Q 2017
Drug Sensitive TB		
TBTC 31/ACTG 5349	H, P, Z, E or H, P, Z, M x 4 mos	4Q 2019

NiX-TB

Bedaquiline, Pretomanid, & Linezolid (BPaL)

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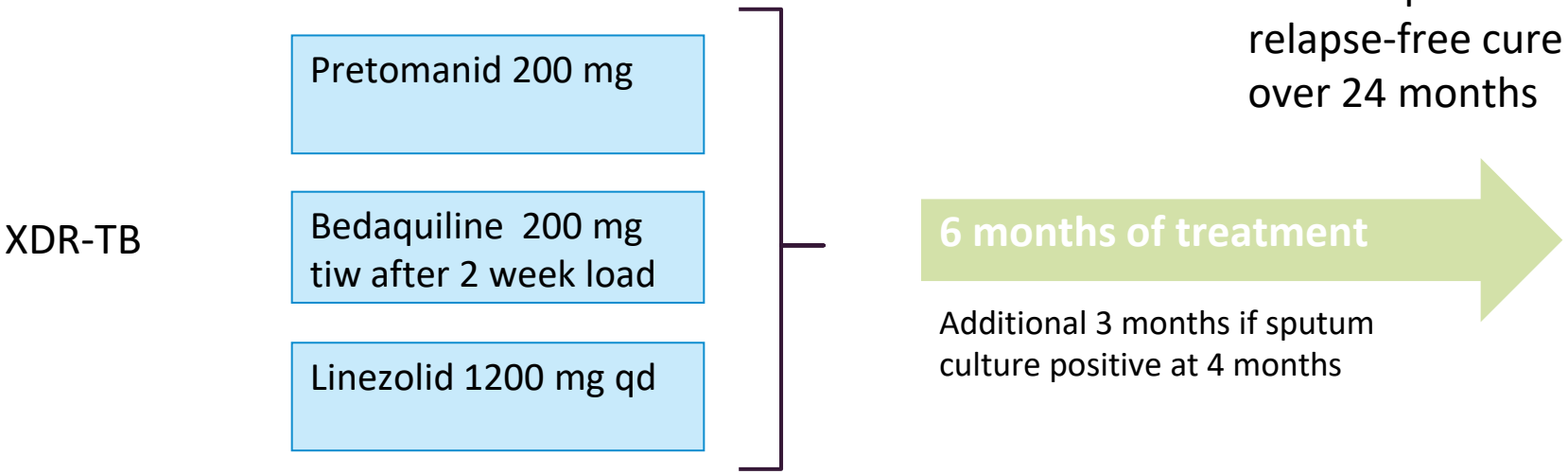
Nix-TB Trial in XDR-TB

- Pilot Phase 3 for patients with XDR-TB or who have failed MDR-TB treatment



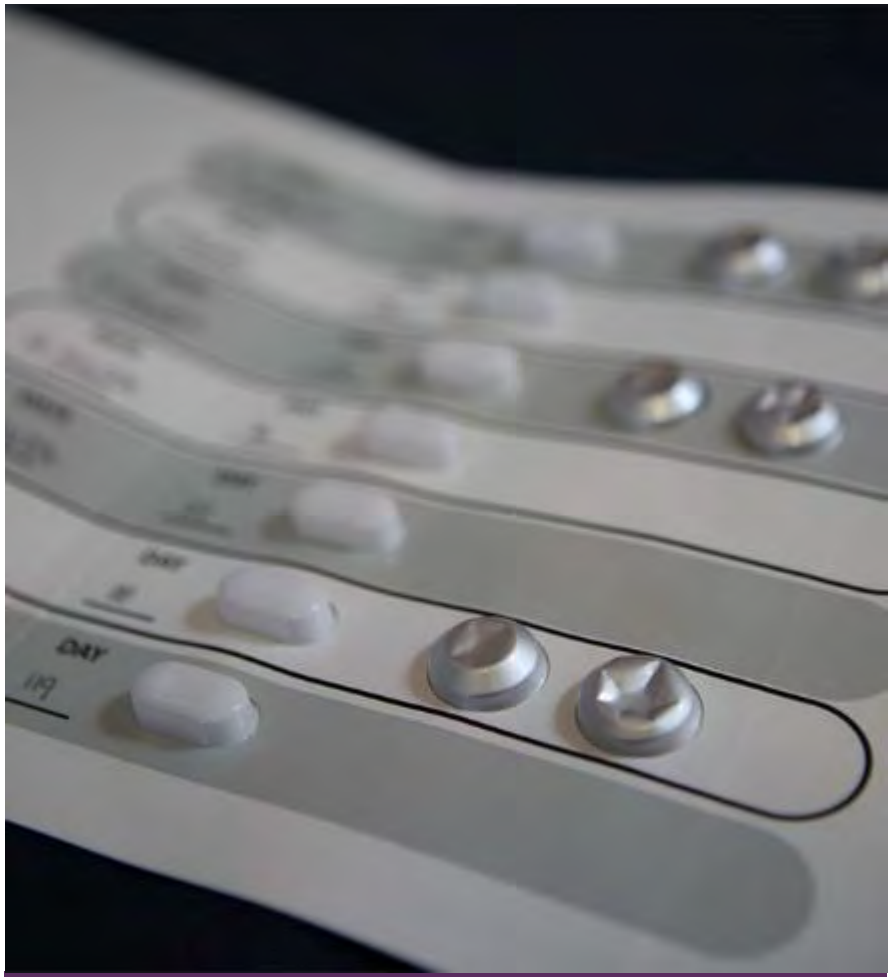
Sites: Sizwe, Brooklyn Chest, and King Dinuzulu Hospital, South Africa

Status of Nix-TB

- Enrollment ended November 15, 2017; transitioned to ZeNix
  - 109 enrolled
- Formal analysis performed after each cohort of 15 subjects followed for 6 months post completion of therapy (primary endpoint)
- Overall relapse-free cure of TB disease consistent with earlier results (dramatic improvement vs. historical 15 - 30%)
- Plans for filing based on results from NiX; submission planned for Q4 2018
- Working with WHO to plan for parallel review of file to support timely guidance.

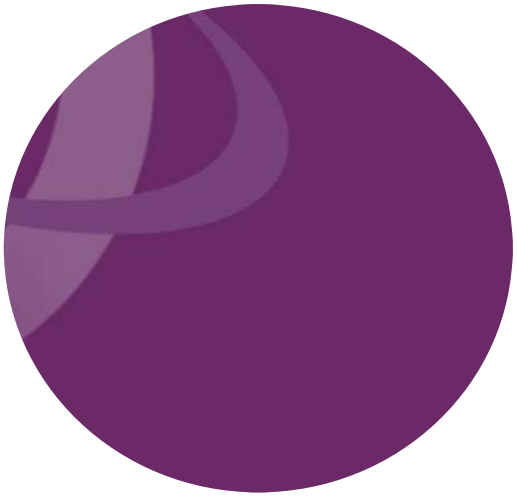
Shorter, Simpler Treatment for XDR-TB

One day of XDR treatment today
Treatment duration: 2+ years



One week of BPaL regimen in Nix-TB trial
Treatment duration: 6 months

ZeNix: Linezolid Optimization Trial



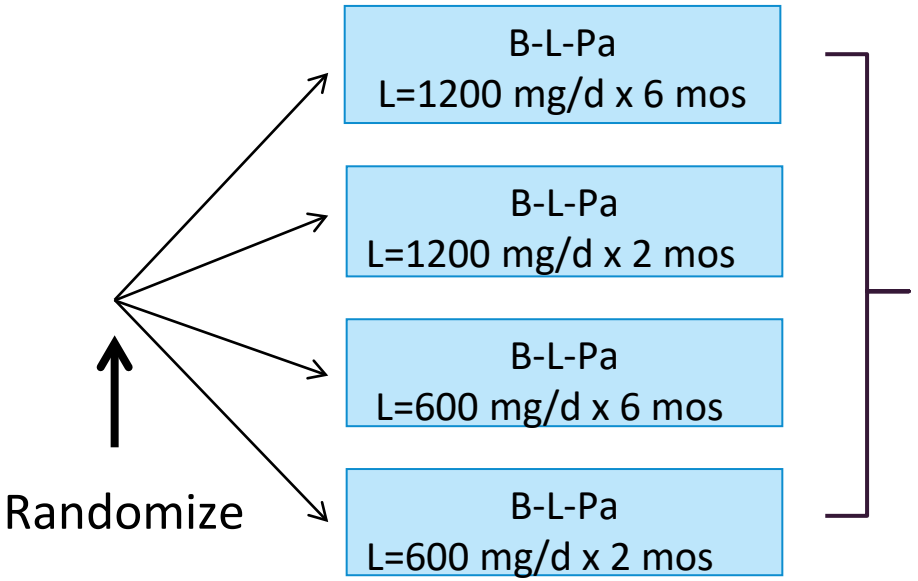
Evaluate Linezolid dose

Evaluate Linezolid duration

Simplify dosing/administration

BPaL Regimen: ZeNix Study

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



1º follow up for relapse-free cure 6 months after end of treatment; Full f/u 24 mos after end of treatment

6 months of treatment

Extension possible for patients who are culture positive at 4 months

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

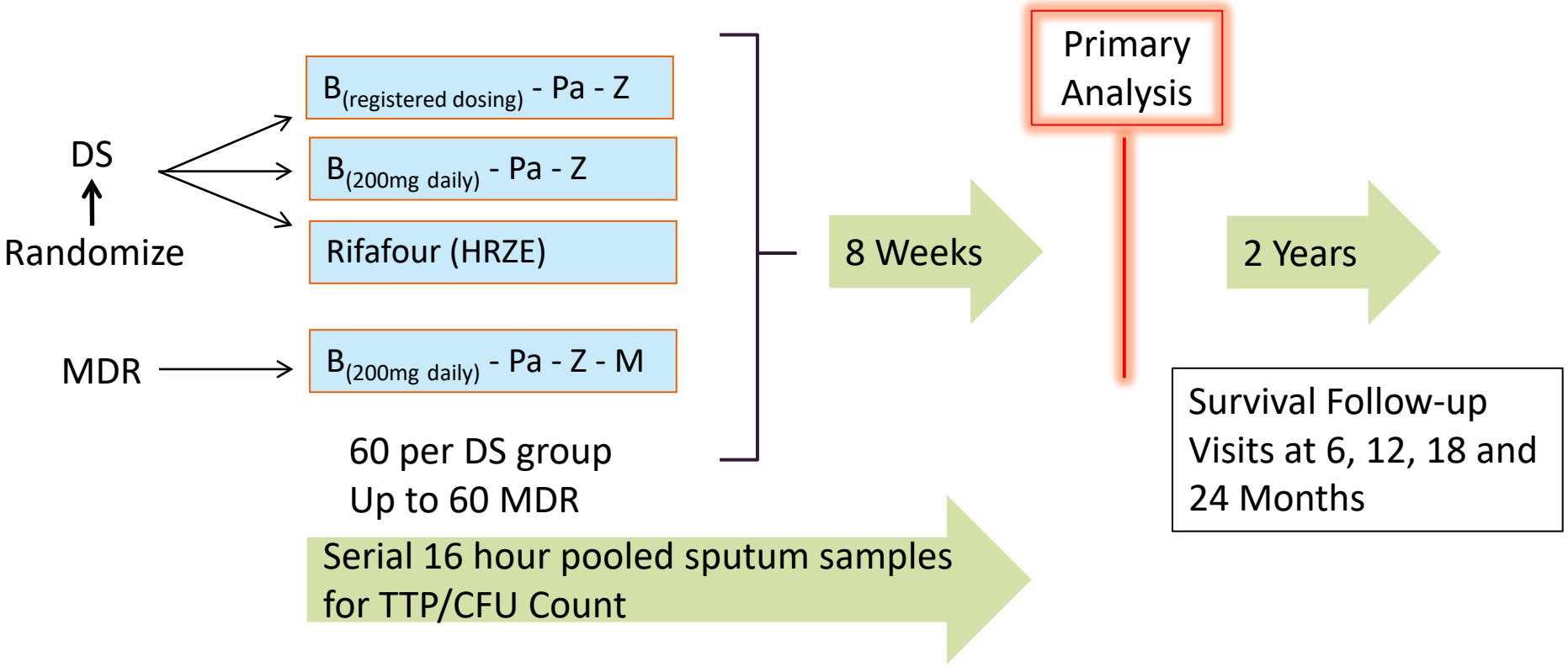
Status of Zenix

- 29 patients randomized
- Regulatory approvals in Georgia (1 site), South Africa (3 sites) and Russia (4 sites)
- Sites under consideration
  - Belarus
  - South Africa – 2 additional sites
  - Moldova
  - India

Bedaquiline, Pretomanid, Moxifloxacin, and Pyrazinamide (BPaMZ)

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

- Participants with newly diagnosed smear positive DS- and MDR-TB



Z=pyrazinamide (1500mg daily), **M** = moxifloxacin 400mg daily, **Pa** = PA-824 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

	Liquid Culture	Solid Culture
B(loading)PaZ	1.7* (1.1 – 2.8)	1.3 (0.9 – 1.8)
B(200mg)PaZ	2.0* (1.3 – 3.2)	1.1 (0.8 – 1.6)
BPaMZ (MDR) Z-Sensitive	**3.3* (2.1 – 5.2)**	**2.3* (1.5 – 3.4)**
HRZE Control	--	--

*Statistically significant vs HRZE

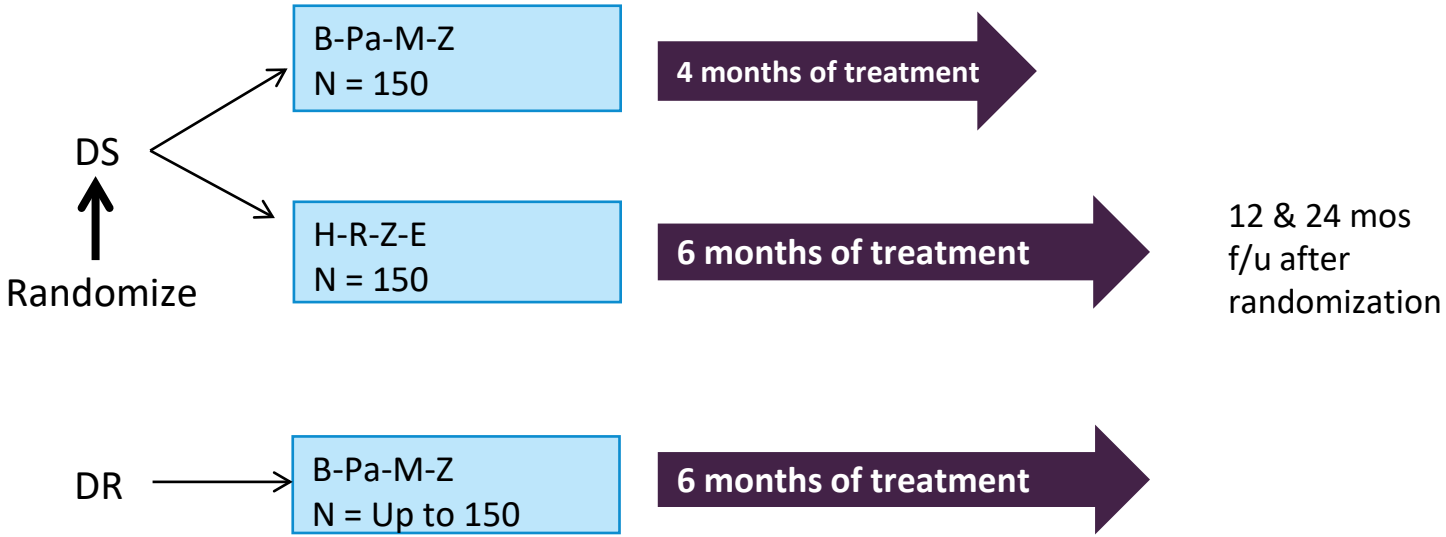
NC-005: BPaMZ Results

Promising Results

- Clinical trial participants receiving BPaMZ cleared TB bacteria from their sputum **3 times as quickly** as those on the standard treatment regimen at the end of two months.
- Almost all participants receiving BPaMZ had culture converted after the two months of treatment.
- Bedaquiline (200mg daily) appears at least as active and safe as the labeled dose.

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

NC-008 (B-Pa-Z-M) *[Phase 2c/3]*

SIMPLICITB

Global Study

South Africa
Tanzania
Uganda
Philippines
Thailand
Georgia
Russian Federation
Ethiopia
Brazil
Malaysia
India

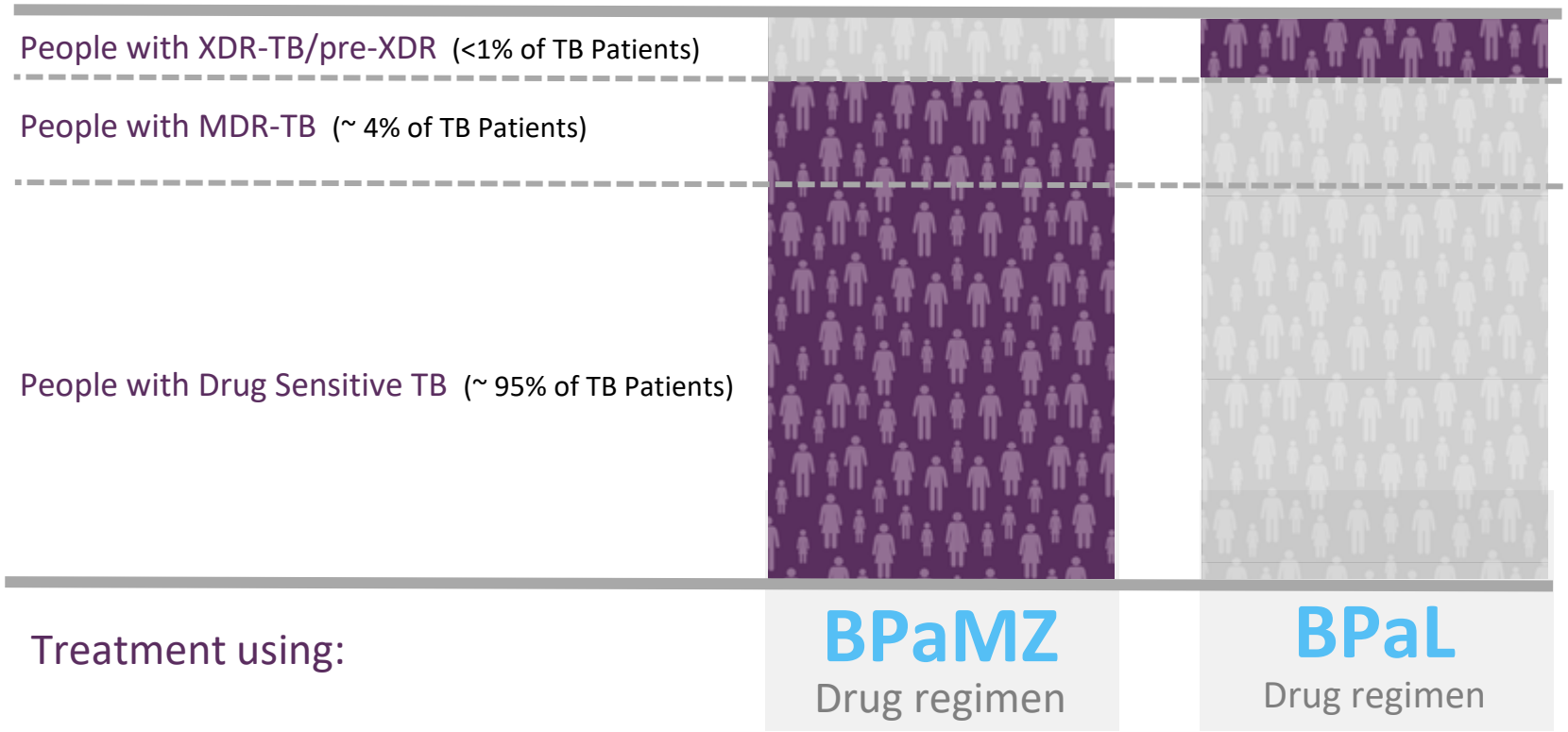
- Trial starting August this year
- Regulatory filing anticipated 2021

BPaL and BPaMZ address key hurdles to scale up

Strong value proposition compared with treatment alternatives

Value proposition	WHO SoC (MDR-TB, XDR-TB)	9 mo. regimen	HRZE	BPaMZ	BPaL
Duration	18-32 mo.	9-12 mo.	6 mo.	**4-6 mo.**	**6 mo.**
# Drugs in regimen	5-7	7	4	**4**	**3**
FDC compatible	No	No	Yes	**Yes**	**Yes** ***(dose optimized)***
Daily pill burden	10-11 pills & 6-8 mo daily injections	9-14 pills & 4-6 mo. injections	3-5 pills/day	**3 pills/day**	**3-7 pills/day**
Level of health care	Tertiary	Tertiary	De-centralized	**De-centralized**	**Tertiary & potentially secondary level**

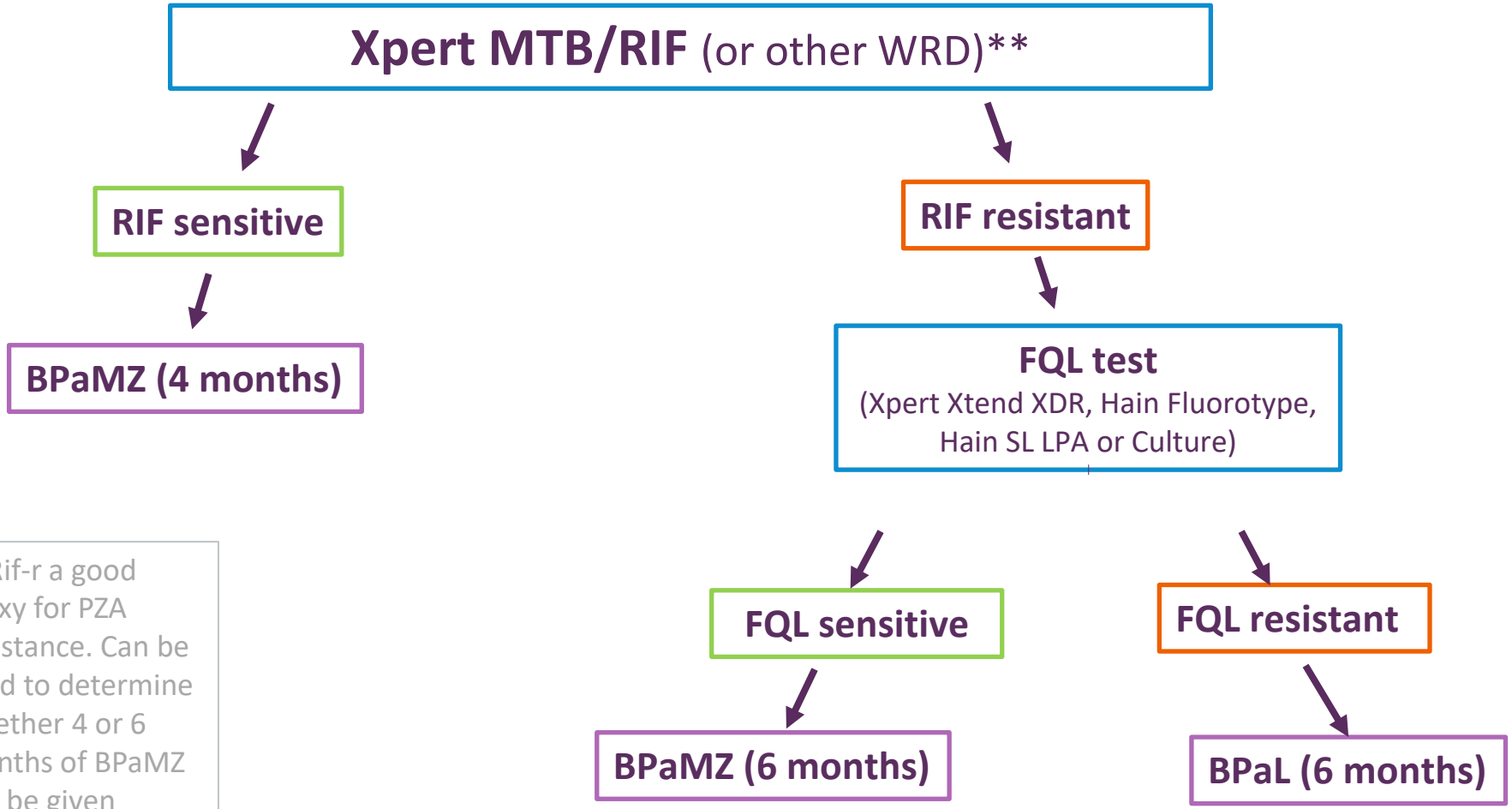
Regimens on the Horizon: Potential Treatment for All



B = Bedaquiline | **Pa** = Pretomanid | **L** = Linezolid | **M** = Moxifloxacin | **Z** = Pyrazinamide

Potential Algorithm for BPaL & BPaMZ

WHO recommended diagnostic algorithm could be streamlined



**Rif-r a good proxy for PZA resistance. Can be used to determine whether 4 or 6 months of BPaMZ will be given

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

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

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