TB Alliance Late-Stage Clinical Programs: Update

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TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

TB ALLIANCE

Drug Development Pipeline As of October 2017

Discovery

Lead Identification

- Whole Cell Hit-to-Lead Programs
  - *Sanofi*
  - *GSK*
- RNA Polymerase Inhibitors
- Energy Metabolism Inhibitors *AUCK/UIC*
- Clp-C/PIP2 *Schrödinger*
- PEPCK *Roche/TAMU*
- POA Prodrugs *Yonsei*
- Hit-to-Lead Programs
  - *Shionogi*
  - *Daiichi Sankyo*
  - *Takeda*
- Hit ID Programs
  - *OP-BIO*
  - *Daiichi Sankyo Novare*
  - *HyphaGenesis*
  - *Chugai*

Lead Optimization

- Macrolides *Sanofi*
- MmpL3 Inhibitors *Abbvie*
- InhA Inhibitors
- Cyclopeptides *Sanofi*
- Squaramides *Sanofi*
- Pyrimidines *GSK*
- Arylsulfonamides *GSK*

Early Development

Preclinical Development

- TBI-223 / Oxazolidinone *IMM*
- TBAJ-587 / Diarylquinoline *Janssen/Merck*
- Preclinical TB Regimen Development *JHU*

Phase 1

- Optimization of Rifampicin in Children <5kg *Stellenbosch University*
- Sutezolid/ Oxazolidinone
- TBA-7371/ DprE1 Inhibitor *Eli Lilly/FNDR*

Phase 2A

- Linezolid Dose-Ranging Study

Late Development

Phase 2B

NC-005

- Bedaquiline / Pretomanid / Moxifloxacin / Pyrazinamide (BPaMZ)

Phase 3

STAND

- Pretomanid/ Moxifloxacin/ Pyrazinamide (PaMZ)

Nix-TB

- Bedaquiline/ Pretomanid/ Linezolid (BPaL)

Phase 4 / Marketed Products

Optimized Pediatric Formulations

- Rifampicin/ Isoniazid/ Pyrazinamide *Macleods*
- Rifampicin/ Isoniazid *Macleods*
- Isoniazid *Macleods*
- Ethambutol *Macleods*
- Pyrazinamide *Macleods*

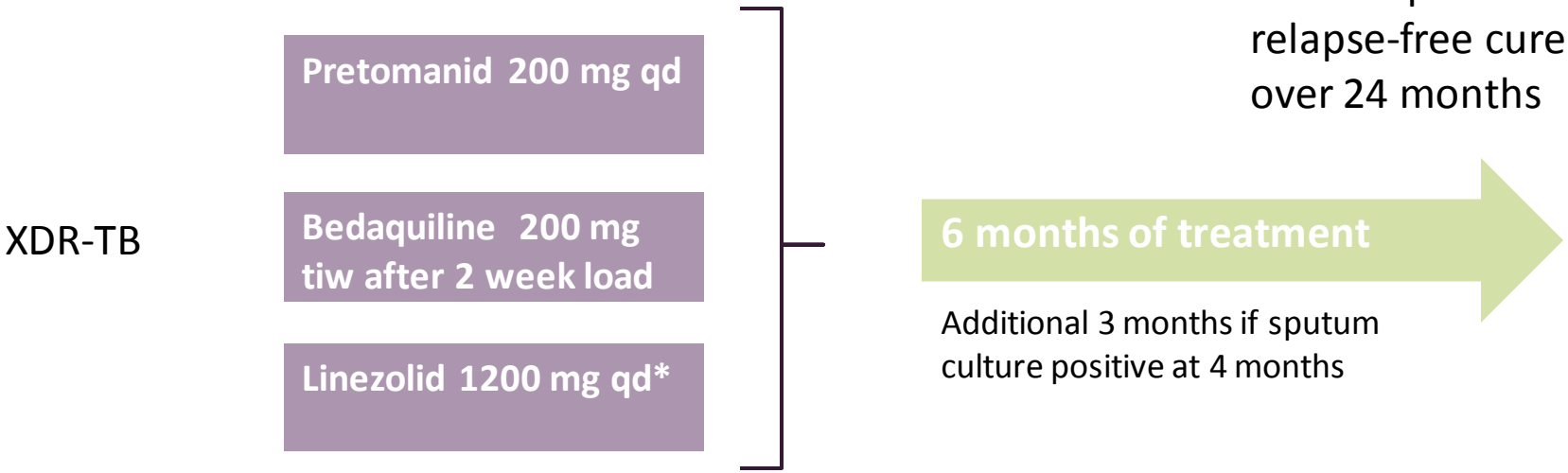
TB Alliance Portfolio Partners

Abbvie
Chugai
Daiichi Sankyo
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
Shionogi
Stellenbosch University
Takeda Pharmaceuticals
TB Drug Accelerator (TBDA)
University College London (UCL)
University of Auckland (AUCK)
University of Dundee (Dundee)
University of Illinois at Chicago (UIC)
Yonsei University

Nix-TB (BPaL) Trial

BPaL Regimen: NiX-TB Study

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



*Amended from 600 mg bid

Sites

Sizwe Hospital, Johannesburg, South Africa

Brooklyn Chest Hospital, Cape Town, South Africa

King Dinuzulu Hospital, Durban, South Africa

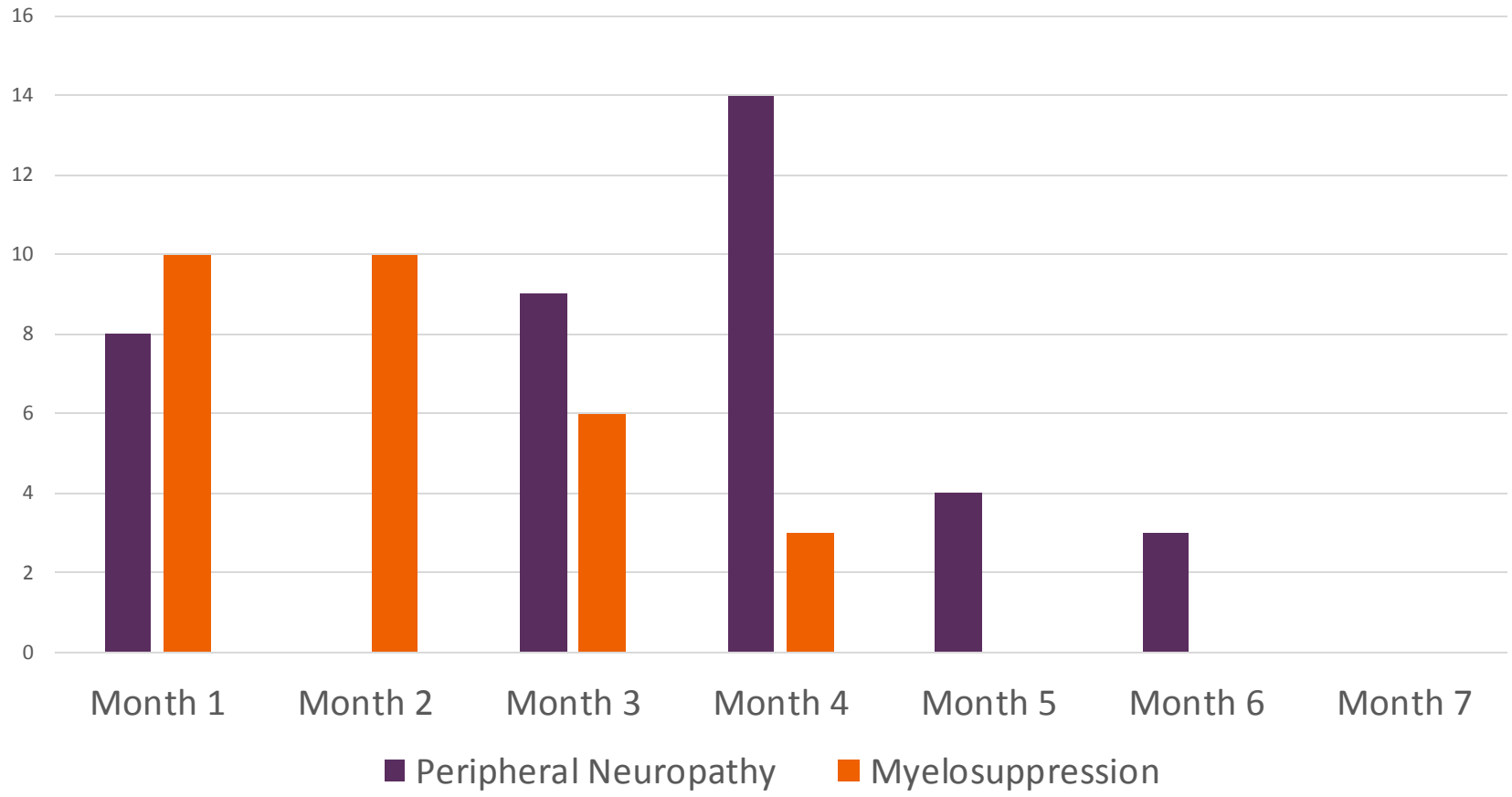
Status of Participants in Nix-TB

- 107 participants enrolled as of November 1, 2017
  - 72 have completed treatment
  - 45 have reached their primary endpoint (6 months after end of treatment; NDA cutoff)
  - 4 patients have completed the study (Month 30)
- No patients lost to follow up, no ambiguity of outcomes
  - Pure ITT analysis
- 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 85% failure rate)
- Enrollment ended November 15, 2017
  - Transition to ZeNix

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 generally in the first 2-3 months
- Neuropathy requiring interruption or reduction generally in months 4-6
  - 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

Characteristics of Anemia Course by Linezolid Interruption vs Reduction in First 50 Completing Therapy

Interruption for anemia
- N = 10

Reduction in dose for anemia and no interruption
- N = 8

Interruption Vs Reduction	N	Day 1 Hgb	Nadir	% Decrease	Wks for 80% incr of reduction
Interruption	10	Mean 12.1 (10-14.4)	Mean 8.7 (7.4-10)	Mean 27 (12-46)	Mean 3.1 (2-4)
Reduction	8	Mean 12.9 (11.8 – 14.4)	Mean 9.9 (6.8-11.8)	Mean 23 (5-45)	Mean 2.5 (1-5)

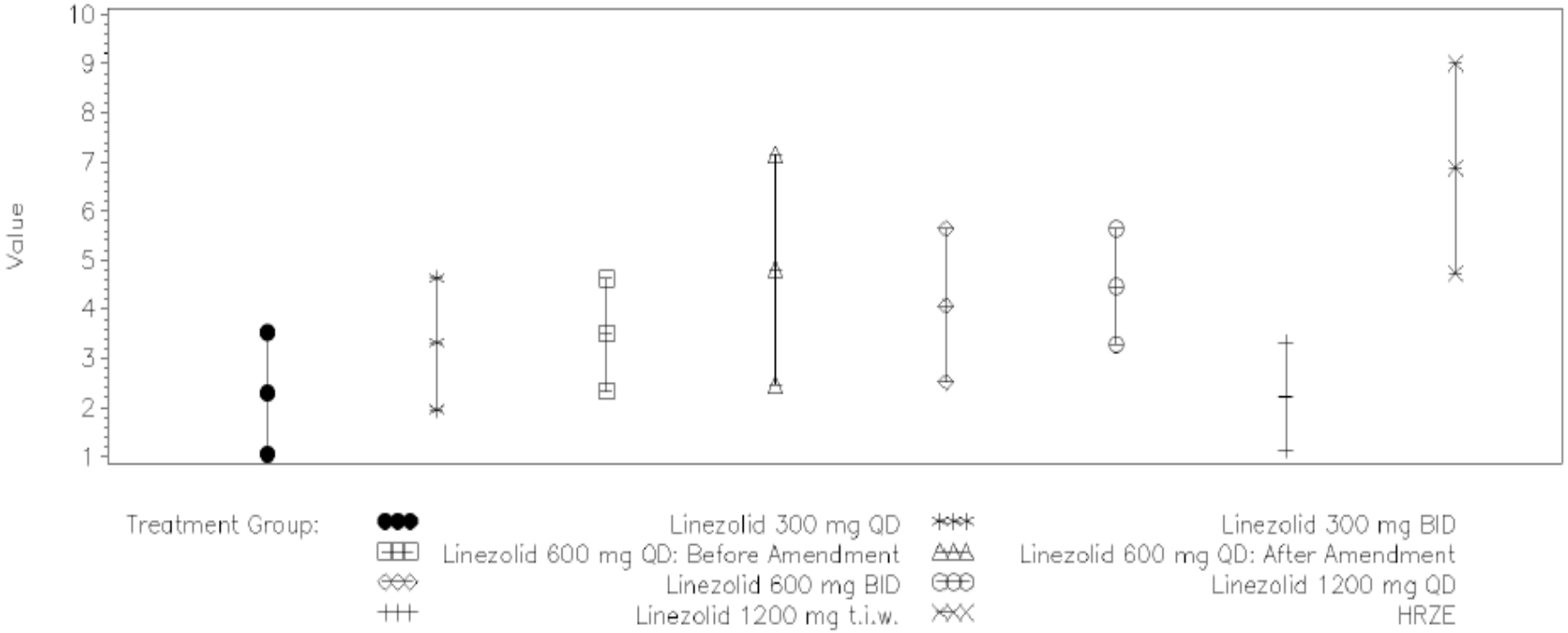
Linezolid Optimization Trial

Evaluate Linezolid dose

Evaluate Linezolid duration

LIN-CL001 Key EBA Findings

Posterior Estimates and 95% Bayesian Confidence Intervals of Mean Early Bactericidal Activity Time to Positivity, Days 0-14, Daily Percent Change



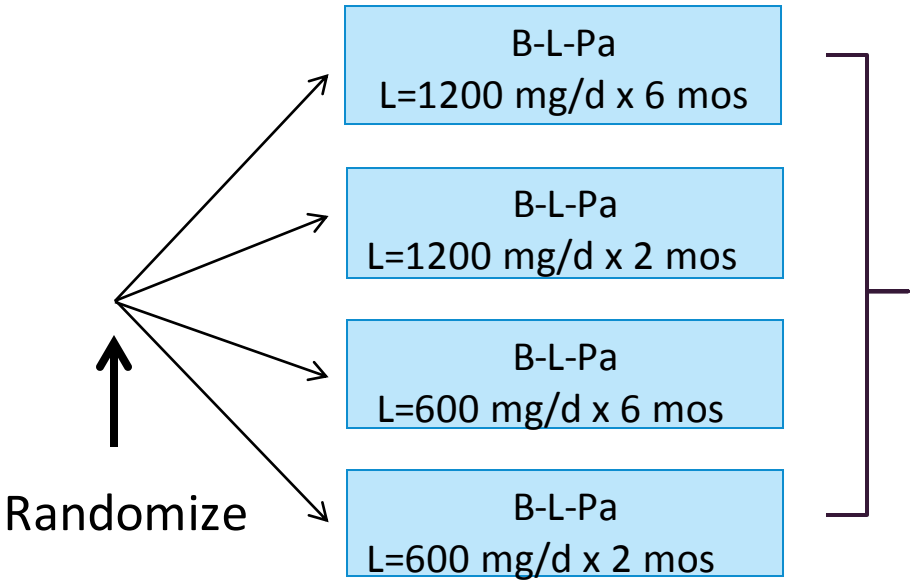
Linezolid (L) Sterilizing Activity on Background of Bedaquiline Plus Pretomanid (BPa) in BALB/c Mice—Data From Eric Nuermberger

	Proportion relapsing after treatment for:	
Regimen	**2 months**	**3 months**
2RHZ/RH		8/14 **(57%)**
BPa		3/14 **(21%)**
3BPaL	6/15 **(40%)**	0/15*† **(0%)**
2BPaL/1BPa		0/15*† **(0%)**
1BPaL/2BPa	9/15 **(60%)**	0/15*† **(0%)**

*p = 0.11 vs. BPa; †p≤ 0.001 vs. RHZ

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

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

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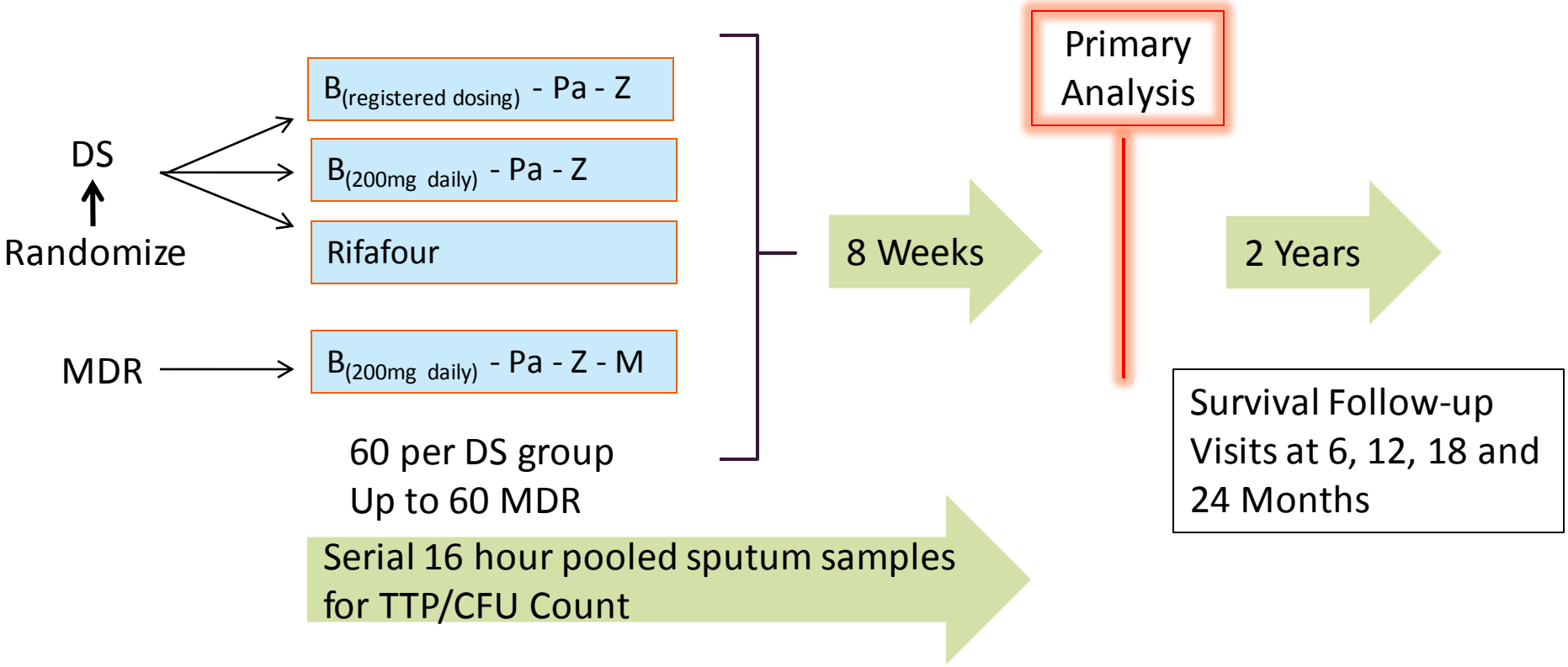
NC-005 – 8 week SSCC Study of B-Pa-Z-M

- 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 , $\mathbf{J}_{(registered\ dosing)}$ = bedaquiline 400mg for 14 days then 200mg three times a week, $\mathbf{J}_{(200mg\ daily)}$ = bedaquiline 200mg daily

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)

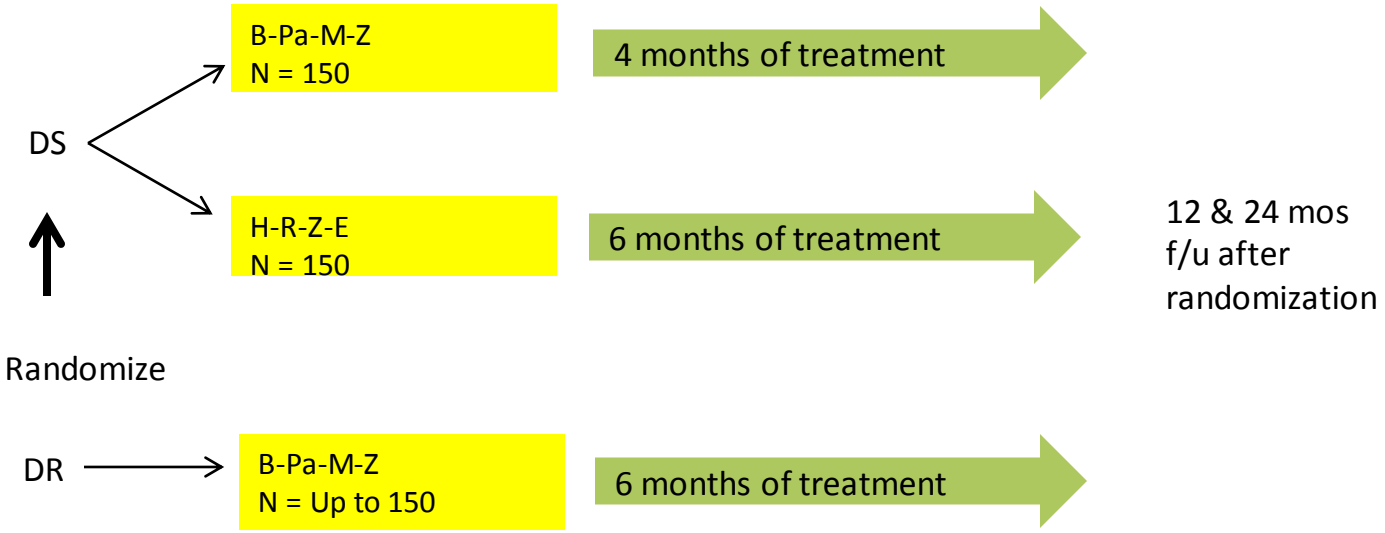
*Statistically significant vs HRZE

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

Participants with newly diagnosed DS- and MDR-TB

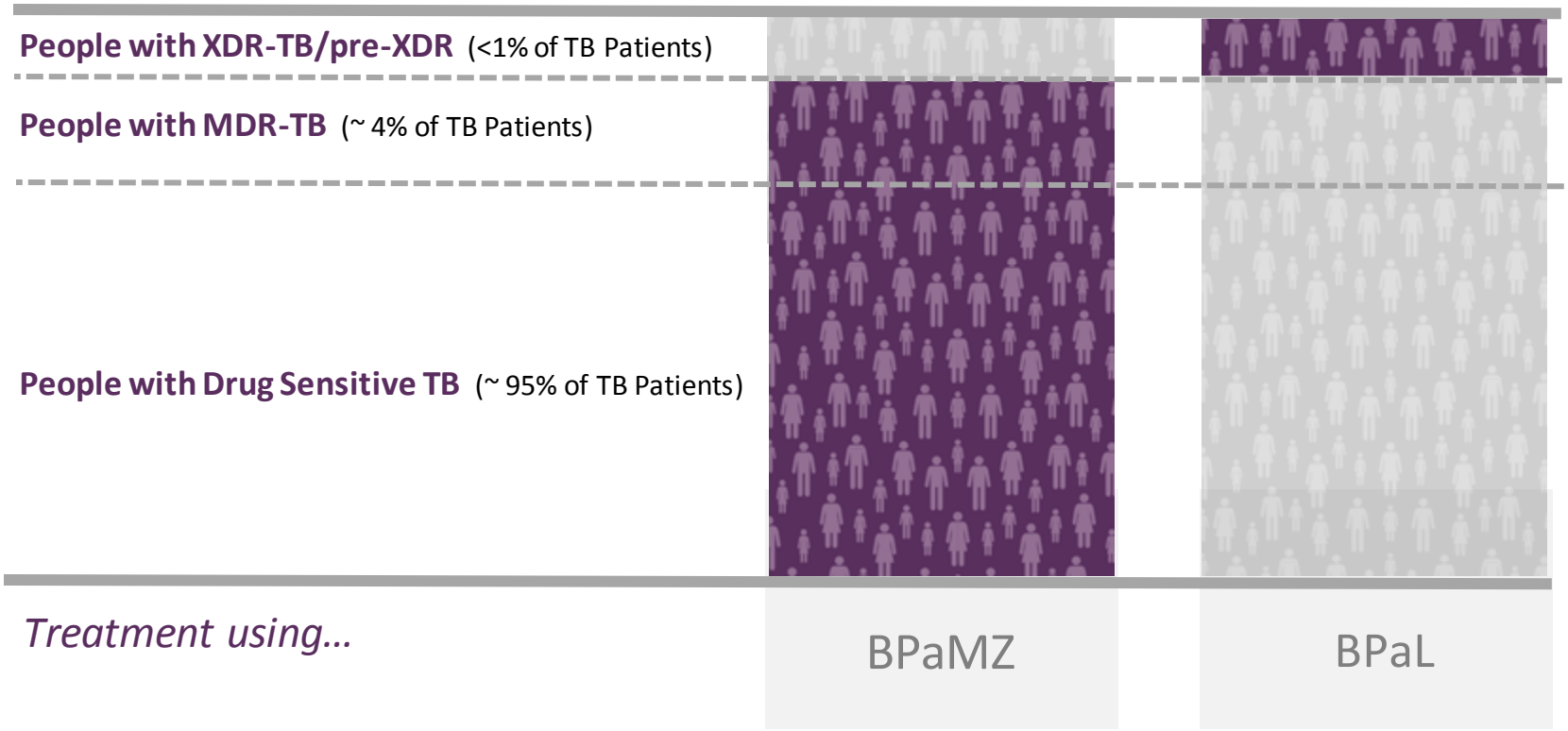


B = bedaquiline 200 mg x 8 wks, then 100mg Pa = pretomanid 200 mg

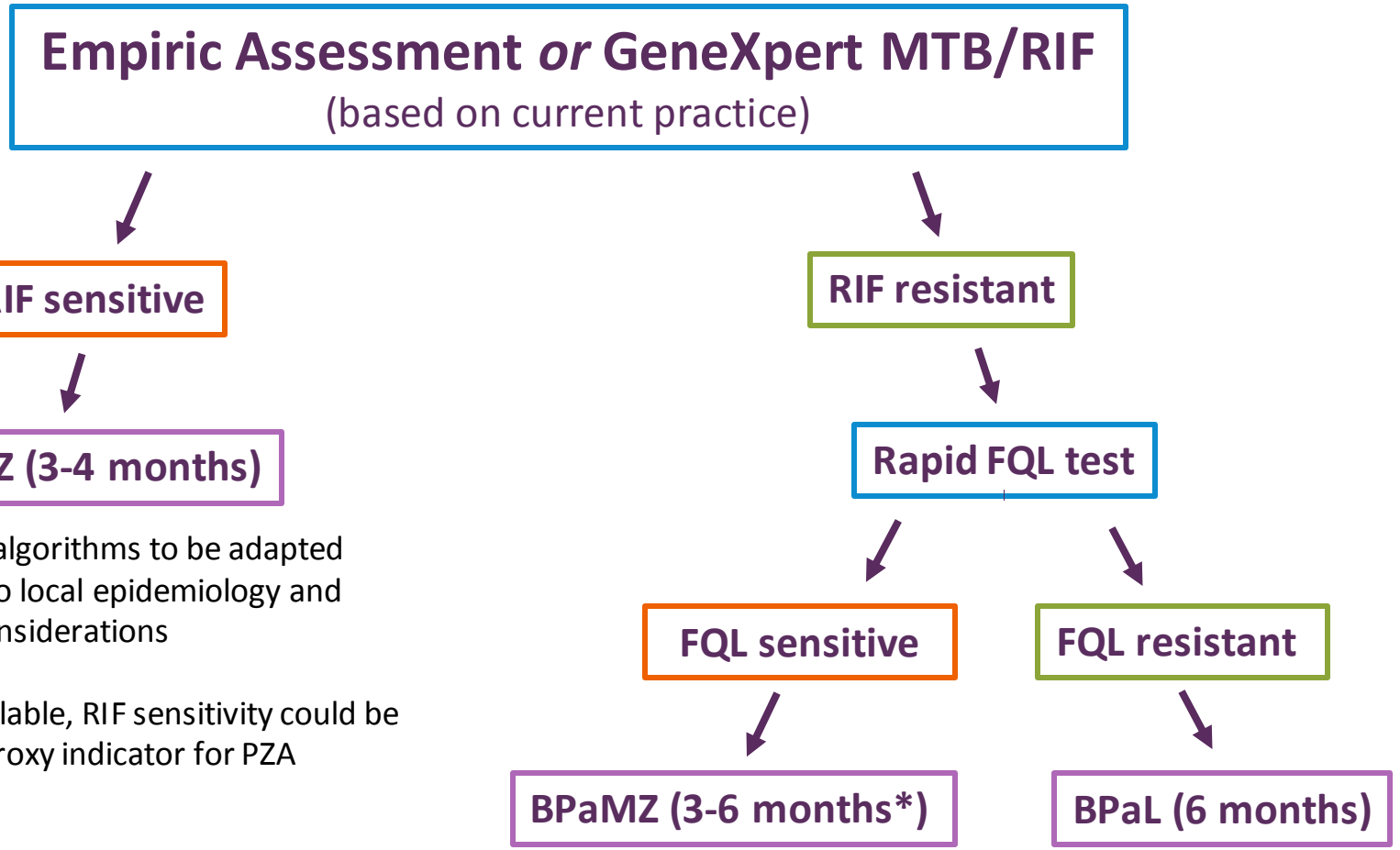
M = moxifloxacin 400 mg Z = pyrazinamide 1500mg

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

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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

UNITAID

United States Agency for International Development