TB Alliance Clinical Programs Update

CPTR Annual Meeting, April, 2017

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GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

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Drug Development Pipeline 1Q 2017

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

TB Alliance Portfolio Partners

Chugai
Daiichi Sankyo
Daiichi Sankyo Novare
Eli Lilly
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)
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)
University of Pennsylvania School of Medicine (UPenn)
Yonsei University

TBAJ-587: a second generation BDQ

- Efficacy
  - More potent than BDQ *in vitro* against clinical TB isolates and BDQ-resistant *M.tb*
  - Superior bactericidal activity to BDQ, at similar exposures, in mouse models of TB
  - Superior treatment-shortening to BDQ with pretomanid and linezolid in BALB/c mice
  - Lower predicted clinical efficacious exposures than BDQ
- DMPK
  - 10 X Higher predicted clearance in humans than BDQ, suitable for daily dosing
    - Less potential for tissue accumulation
- Safety/Tox
  - Lower potential for QTc prolongation than BDQ
  - Higher safe exposure than BDQ in rats
  - Larger safety margins than BDQ, based on rat and dog toxicity study data
- CMC
  - Improved aqueous solubility (less lipophilic) than BDQ

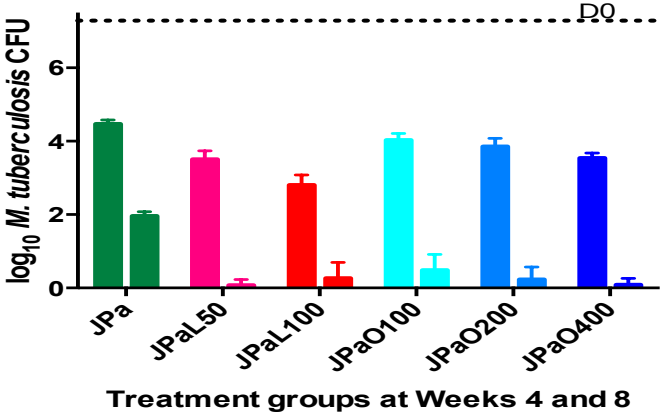
MIC range (µg/mL)	
TBAJ-587	**BDQ**
0.001-0.064	0.02 – 0.64

	Number of mice (%) with CFU after M months of treatment (+ 3 months no Rx)	
Regimen	**M1.5** (+3)	**M2** (+3)
$BDQ_{25}Pa_{100}L_{100}$	15/15 (100%)	15/15 (100%)
$S_{25}PaL$	10/14 (71%)*	4/13 (31%)**

Compound	**BDQ**	**TBAJ-587**
hERG IC_{50} (µM)	0.37*	28.6
Nav 1.5 IC_{50} (µM)	NA	>30

TBI-223: Safer Oxazolidinone

- Efficacy
  - Similar potency to LZD *in vitro* against clinical TB isolates
  - Similar activity to LZD, at similar exposures, in BALB/c and Kramnik mice
  - Similar treatment-shortening to LZD in combination with bedaquiline and pretomanid in BALB/c mice
- DMPK
  - Predicted clearance suitable for daily dosing
- Safety/Tox
  - Larger safety margins than LZD, comparing rat and dog safe/mouse efficacious or safe/predicted clinical efficacious exposure
  - No bone marrow toxicity observed at 4-10X (dog/rat) over mouse/predicted clinical efficacious exposures
- CMC
  - Similar to Linezolid



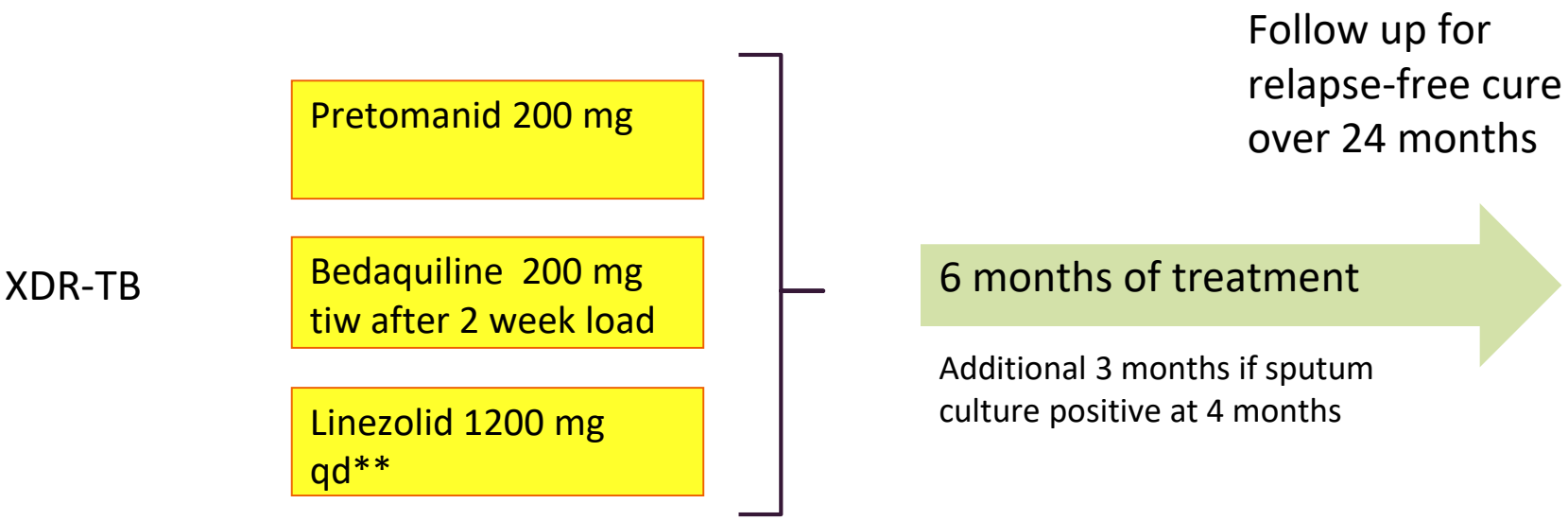
In Vivo Safety and Toxicity - MPS vs. Bone Marrow Toxicity and Hematological

Reduced activity against MPS led to reduced bone marrow toxicity

Compound	Linezolid	TBI-223
MPS (µM)	8.5	> 74
Mouse/human bone marrow progenitor cell suppression assay (µM)	24-60	>150
MED AUC (hr·µg/mL)	**131**	**179**
Bone Marrow Histopathology, platelet ↓, reticulocyte↓ (**Rat 28 day** study at mg/kg dose)	**150 mg/kg (AUC 425 µg·hr/mL) NOAEL at 20 mg/kg (IB)**	**> 300 mg/kg (AUC 1685 µg·hr/mL)**
Bone Marrow Histopathology, platelet↓, reticulocyte↓ (**Dog 14 day** study at mg/kg dose)	**NOAEL at 20 mg/kg (IB)**	**> 150 mg/kg (AUC 789 µg·hr/mL)**
Comments	**Death (day 11,12) at 300 mg/kg Death (day 21) at 150 mg/kg**	

Nix-TB Trial in XDR-TB

Patients with XDR-TB or Who Have Failed MDR-TB Treatment



**Just amended from 600 mg bid strategy

Sites: Sizwe and Brooklyn Chest, South Africa

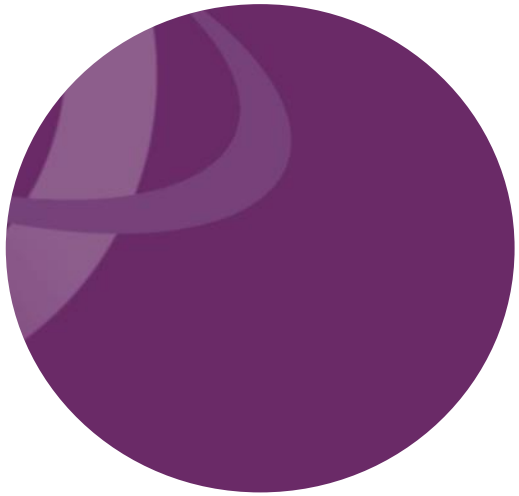
Status of Participants in Nix-TB Trial

75 Participants Enrolled 15 March 2017

Primary Endpoint

- 31 patients have reached 6 months since completion of treatment
  - One relapse/reinfection
  - XDR TB on LPA- Genome sequencing will determine whether relapse or new infection
- Four patients have died (all in the first 8 weeks)
  - 3 had multi-organ TB on autopsy
  - 1 had a GI bleed due to erosive esophagitis
- All surviving patients were culture negative at 4 months
- 26 (74%) negative at 8 weeks as of December 2016.

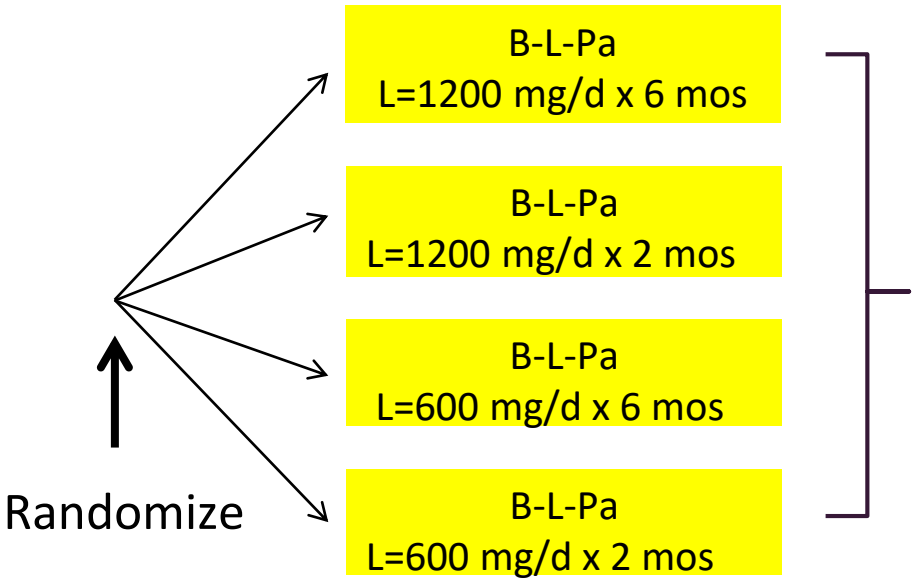
Plans for Next BPaL Trial



- Evaluate Linezolid dose
- Evaluate Linezolid duration

B-Pa-L Linezolid Optimization Trial: TB Alliance Study NC-007

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)

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 study for patients who relapse or who are sputum positive at end of 6 months of regimen dosing

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

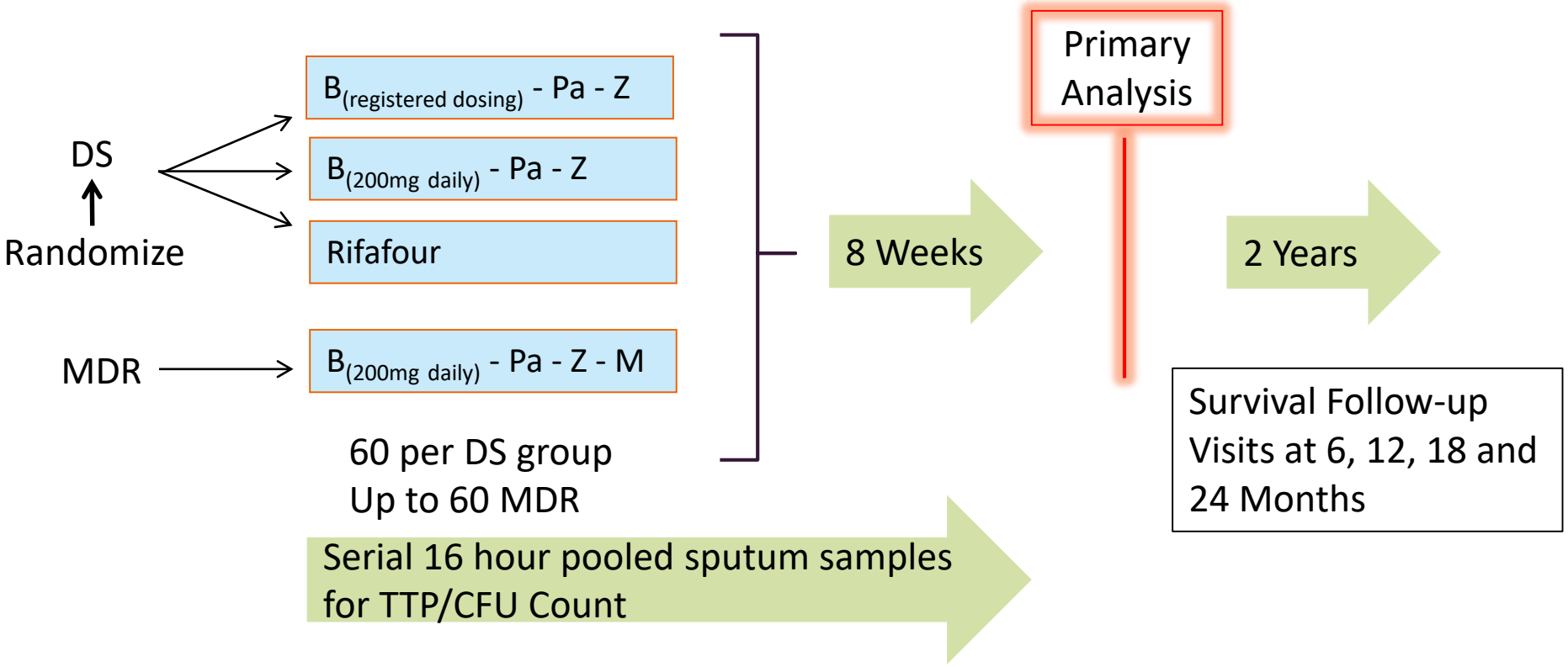
NC-005: Testing Combinations of Bedaquiline, Pretomanid, Pyrazinamide and Moxifloxacin (BPaZM)

Key Results

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

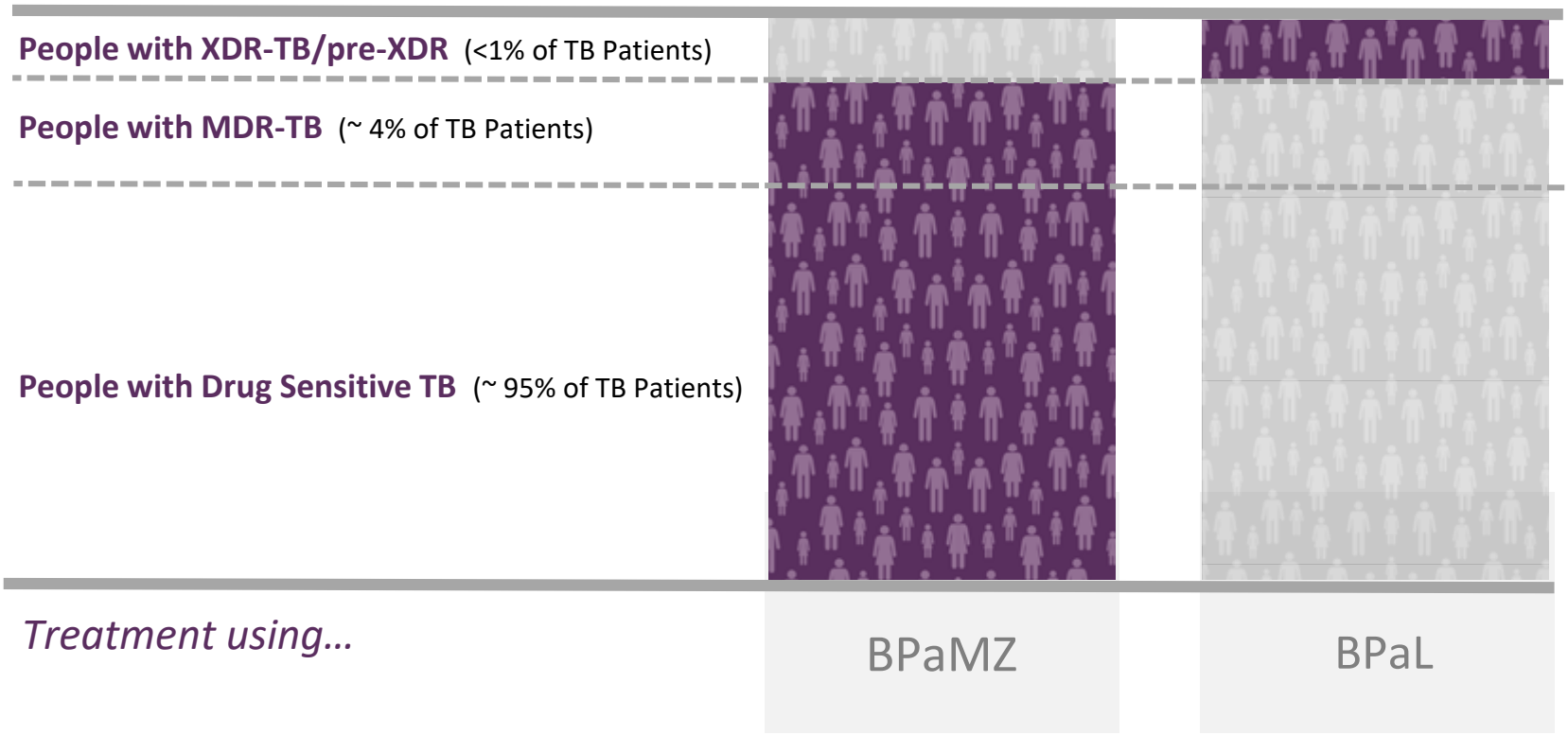
Percent of Patients Culture Negative at 2 Months

Kaplan-Meyer Analysis

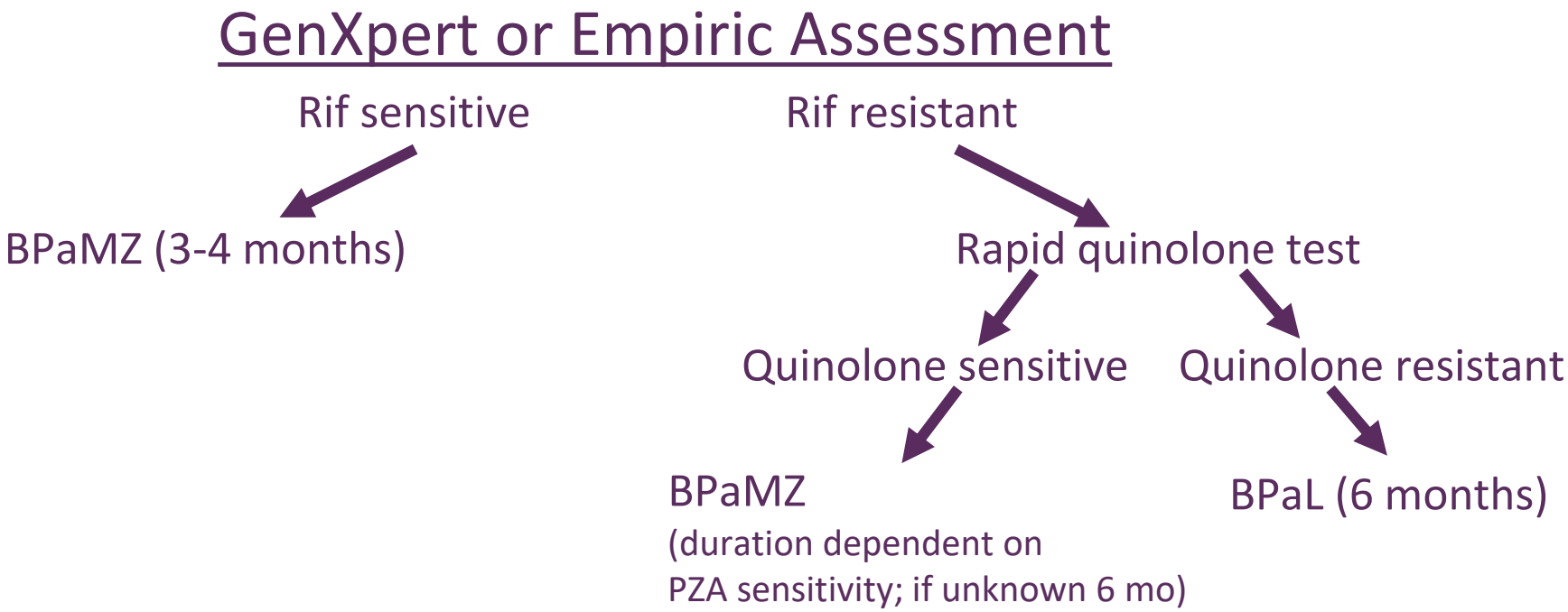
	Liquid Culture		Solid Culture	
	Overnight	**Spot**	**Overnight**	**Spot**
B(loading)PaZ	66%	84%*	89%	88%*
B(200mg)PaZ	75%*	79%	84%	92%*
BPaZM (MDR) Z-sensitive	96%*	89%*	100%*	97%*
BPaZM (MDR) Z-resistant	78%*		95%*	
HRZE control	51%	63%	86%	79%

*Statistically significant vs HRZE

Paradigm Shift: Treatment For All



Proposed Treatment Algorithm



- Common backbone of BPa for all
  - Common therapy for virtually all DS and MDR
- All treatments conducive to FDCs
- Marked simplification and rationalization of present state

Thank You to the Trial Participants, Investigators, TB Alliance Staff, Partners & Funders who have Made our Studies Possible

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