TB Alliance
Stakeholders Association

Q&A

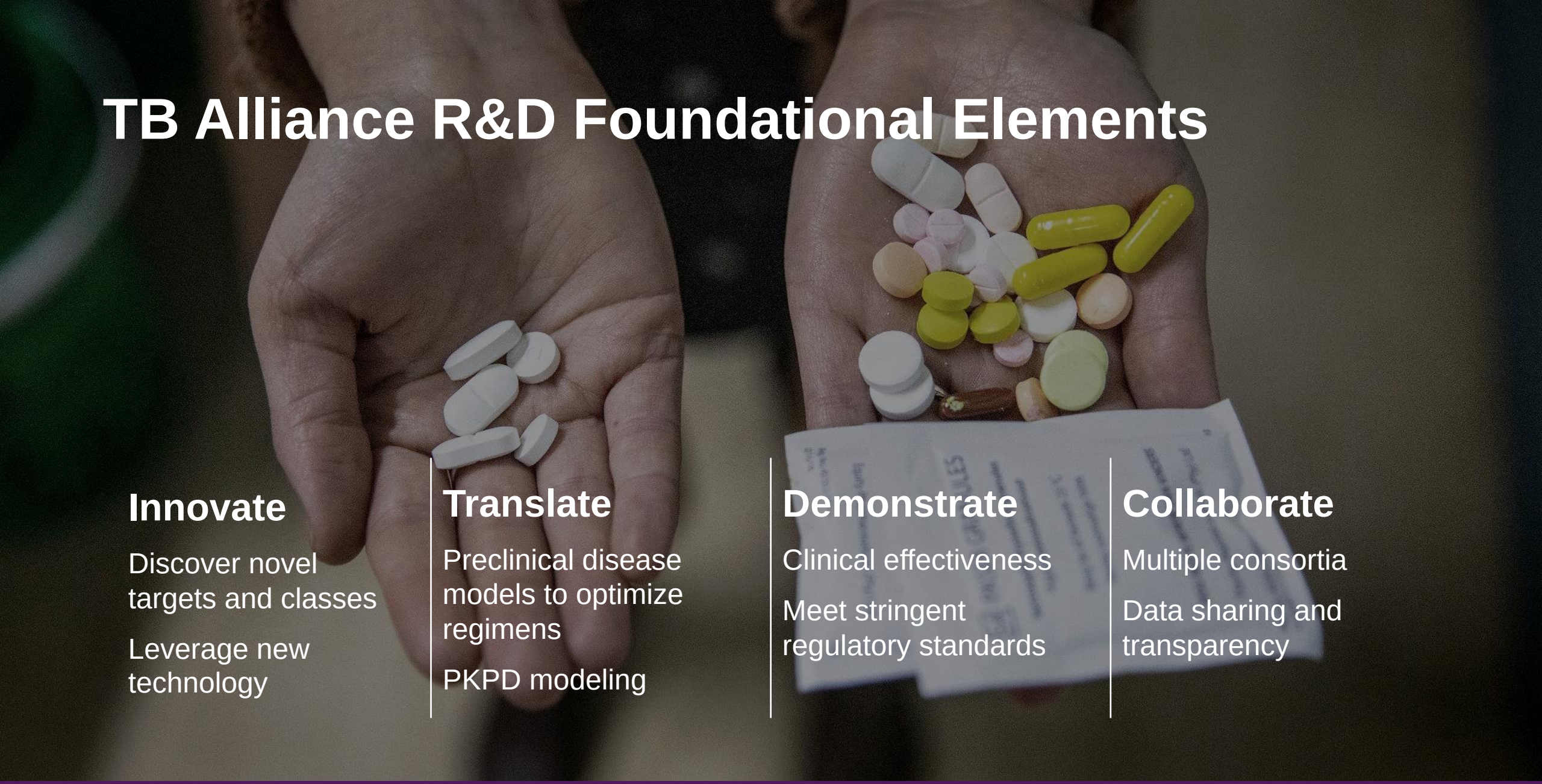
Research & Development Update

Eugene Sun, MD

Senior Vice President, R&D

TB Alliance

TB Alliance R&D Foundational Elements



Innovate

Discover novel targets and classes

Leverage new technology

Translate

Preclinical disease models to optimize regimens

PKPD modeling

Demonstrate

Clinical effectiveness

Meet stringent regulatory standards

Collaborate

Multiple consortia

Data sharing and transparency

The NEW ENGLAND JOURNAL of MEDICINE

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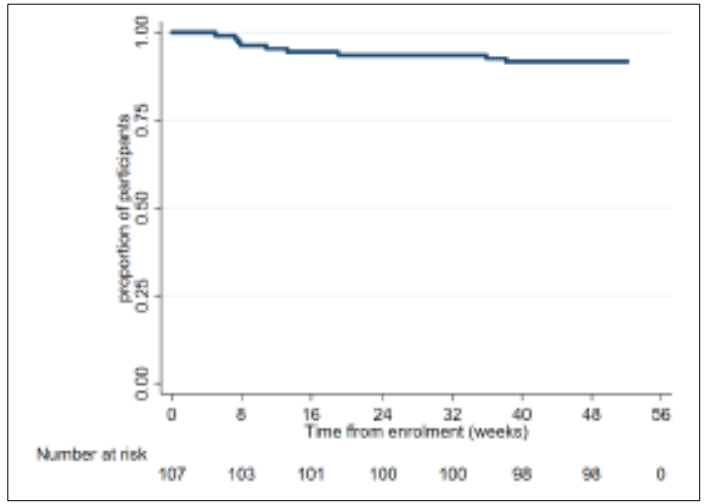
Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

Francesca Conradie, M.B., B.Ch., Andreas H. Diacon, M.D., Nosipho Ngubane, M.B., B.Ch., Pauline Howell, M.B., B.Ch., Daniel Everitt, M.D., Angela M. Crook, Ph.D., Carl M. Mendel, M.D., Erica Egizi, M.P.H., Joanna Moreira, B.Sc., Juliano Timm, Ph.D., Timothy D. McHugh, Ph.D., Genevieve H. Wills, M.Sc., Anna Bateson, Ph.D., Robert Hunt, B.Sc., Christo Van Niekerk, M.D., Mengchun Li, M.D., Morounfolu Olugbosi, M.D., and Melvin Spigelman, M.D., for the Nix-TB Trial Team*

Nix-TB Efficacy: Time to Unfavorable Outcome



CONCLUSIONS

The combination of bedaquiline, pretomanid, and linezolid led to a favorable outcome at 6 months after the end of therapy in a high percentage of patients with highly drug-resistant forms of tuberculosis;

some associated toxic effects were observed.

- **81% peripheral neuropathy**
- **~2/3 interrupted, reduced, or discontinued linezolid**
- **All surviving patients completed 6 months of treatment**

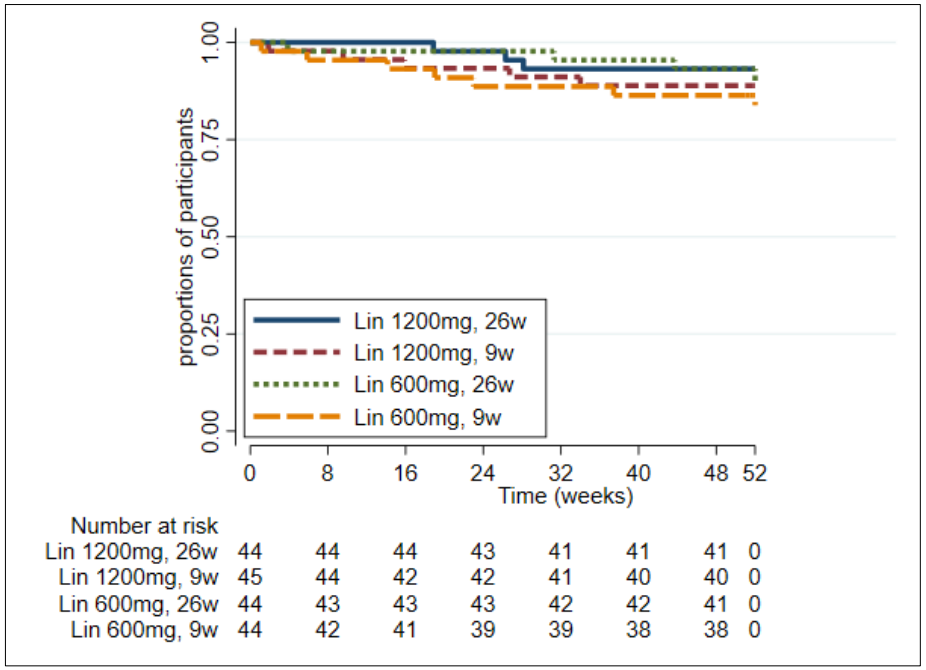
The NEW ENGLAND JOURNAL of MEDICINE
n engl j med 387;9 nejm.org September 1, 2022

ORIGINAL ARTICLE

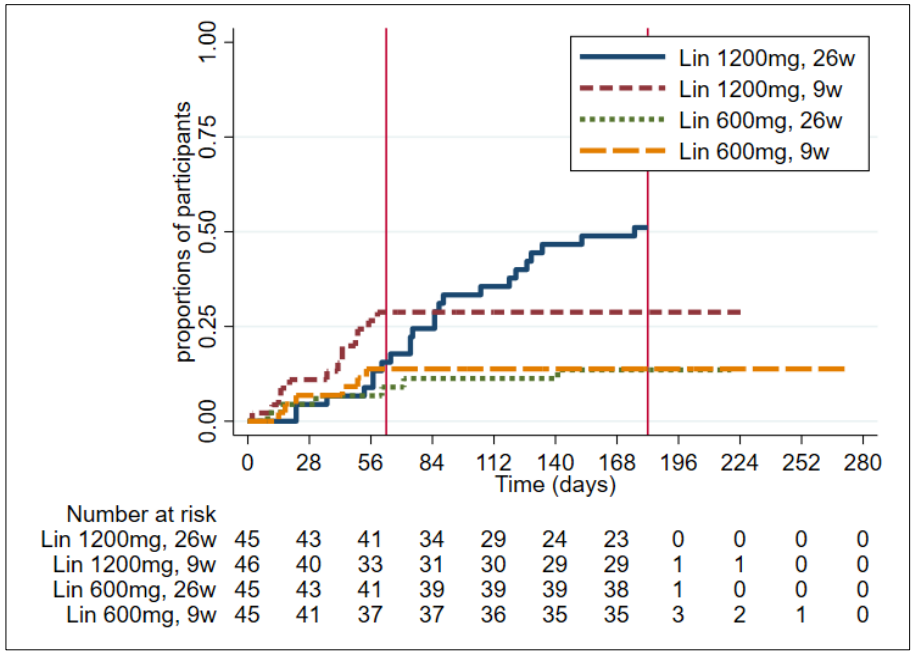
Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis

F. Conradie, T.R. Bagdasaryan, S. Borisov, P. Howell, L. Mikiashvili, N. Ngubane, A. Samoilova, S. Skornykova, E. Tudor, E. Variava, P. Yablonskiy, D. Everitt, G.H. Wills, E. Sun, M. Olugbosi, E. Egizi, M. Li, A. Holsta, J. Timm, A. Bateson, A.M. Crook, S.M. Fabiane, R. Hunt, T.D. McHugh, C.D. Tweed, S. Foraida, C.M. Mendel, and M. Spigelman, for the ZeNix Trial Team*

ZeNix Efficacy: Time to Unfavorable Outcome



ZeNix Safety: Time to First LIN Dose Modification



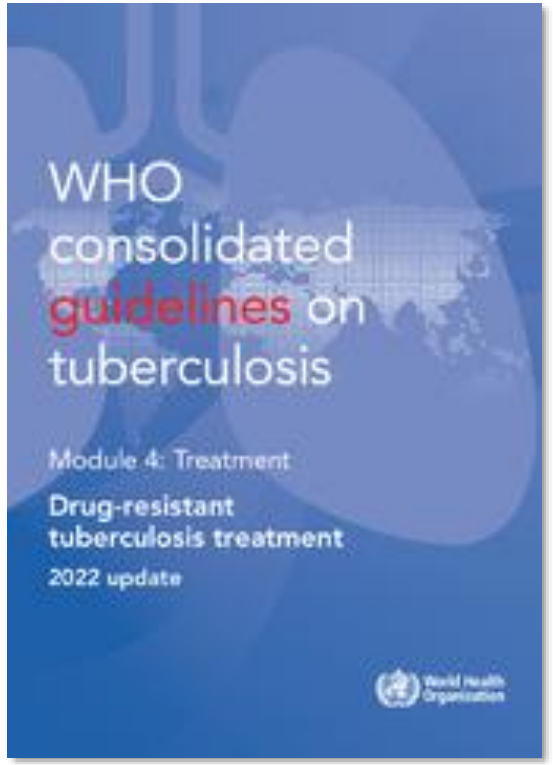
Primary Outcome, MITT

	SOC	BPaLM	BPaLC	BPaL
Number in mITT population	137	138	115	111
Number with no unfavourable outcome	81 (59.1%)	121 (88.3%)	88 (76.5%)	96 (86.5%)
Number with an unfavourable outcome	56 (40.9%)	16 (11.7%)	27 (23.5%)	15 (13.5%)
Number non-assessable	0	1	0	0
Unadjusted risk difference (two-sided 96.6% confidence interval)		-29.2% (-39.8% to -18.6%)	-	-
Unadjusted risk difference (two-sided 95% confidence interval)		-	-17.4% (-28.7% to -6.1%)	-27.4% (-37.8% to -17.0%)
Non-inferiority p-value (non-inferiority margin of +12%)		p<0.0001	p<0.0001	p<0.0001
Superiority p-value		p<0.0001	p=0.003	p<0.0001

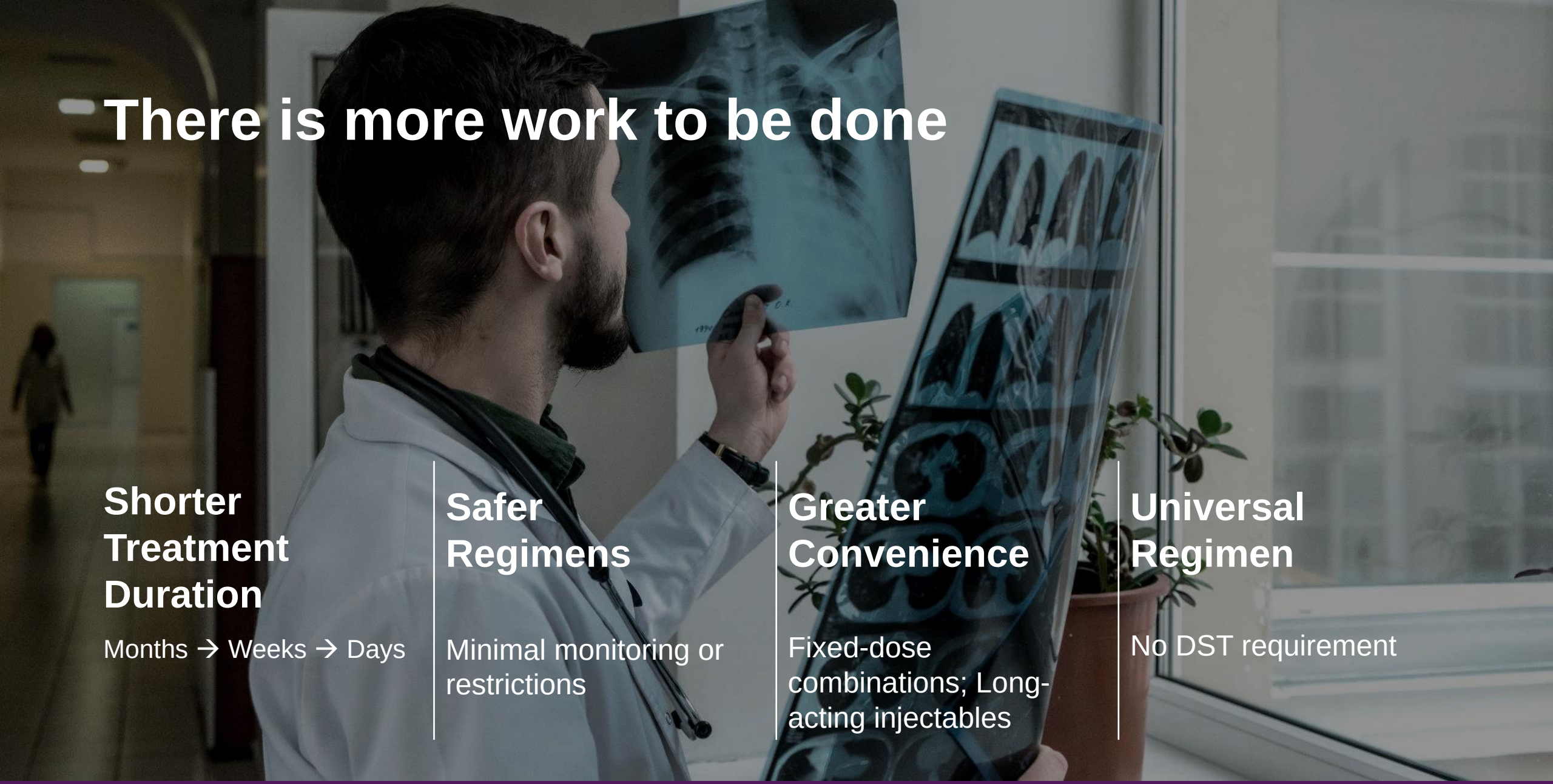
Updated WHO Guidelines December 2022

Scientific outcomes lead to global impact

- BPaLM, BPaL
- Nearly all DR-TB patients
- Programmatic implementation recommended
- 14 years and older
- LZD dose: 600 mg throughout the treatment with dose reduction as needed
- BDQ dosing alternatives (per label, or QD)
- Reproductive safety: “New data have largely alleviated previous concerns on reproductive toxicities observed in animal studies, suggesting that adverse effects on human male fertility are unlikely”



There is more work to be done



Shorter Treatment Duration

Months → Weeks → Days

Safer Regimens

Minimal monitoring or restrictions

Greater Convenience

Fixed-dose combinations; Long-acting injectables

Universal Regimen

No DST requirement

TB Alliance Drug Development Pipeline As of October 2023*

Discovery | Early Development | Late Development

Lead Identification	Lead Optimization	Preclinical Development	Phase 1	Phase 2	Phase 3	Marketed Products
GHIT Hit ID Programs • Daiichi Sankyo RD Novare • Texas A&M • UIC	**Anti-TB Natural Products** • Evotec	**Preclinical TB Regimen Development** • JHU	**TBAJ-587 / Diarylquinoline** • ERA4TB	**BPaMZ /SEM** • UoSA	**NixTB** **BPaL** (bedaquiline + pretomanid + linezolid) • Viatris	**Optimized Pediatric Formulations** (with Macleods) Ethambutol Isoniazid Pyrazinamide Rifampicin / Isoniazid Rifampicin / Isoniazid / Pyrazinamide
GHIT Hit-to-Lead Programs • Astellas • Chugai • Daiichi Sankyo RD Novare • Takeda • UIC	**ClpC1** • CETR • Harvard • UIC	**PAN-TB Collaboration** • Gates MRI		**Sutezolid / Oxazolidinone** • PAN-HM | Aurum • PAN-TB | Gates MRI, Janssen, Otsuka • RAD-TB | ACTG	**ZeNix** **BPaL** (bedaquiline + pretomanid + linezolid) • Viatris	**Pediatric Formulation Development** Pretomanid • Viatris
Intracellular Active Series • Evotec	**ClpP1P2 Programs** • CETR • Harvard • Texas A&M • UIC			**TBA-7371 / DprE1 Inhibitor** • FNDR • Gates MRI	**SIMPLICITB** **BPaMZ** (bedaquiline + pretomanid + moxiflaxacin + pyrazinamide) • PanACEA • Radboud • Viatris	**Pretomanid for use in BPaL** Pretomanid for use in BPaL and BPaLM Regimens • Hongqi • ITRC • KNCV • Lupin • Macleods • Viatris
Malate Synthetase Inhibitors • Texas A&M	**InhA Inhibitors** • GHDDI			**TBAJ-876 / Diarylquinoline**	**TB Practecal** Innovating MDR-TB Treatment **BPaL/M** (bedaquiline + pretomanid + linezolid + moxiflaxacin) • MSF Amsterdam	
Pantothenamide • TropIQ • WCM	**Intracellular Active Series** • GSK			**TBI-223 / Oxazolidinone** • IMI • RAD-TB | ACTG		
PknB • Schrödinger • UoA	**KasA** • GSK			**Q-203** • Qurient		
PptT • Evotec • Texas A&M • UNC • WCM	**MmpL3 Inhibitors** • AbbVie • ERA4TB					
Rho • GSK	**RNA Polymerase Inhibitors** • CETR					
Whole Cell Hit-to-Lead Program • GSK						

TB Alliance Portfolio Partners

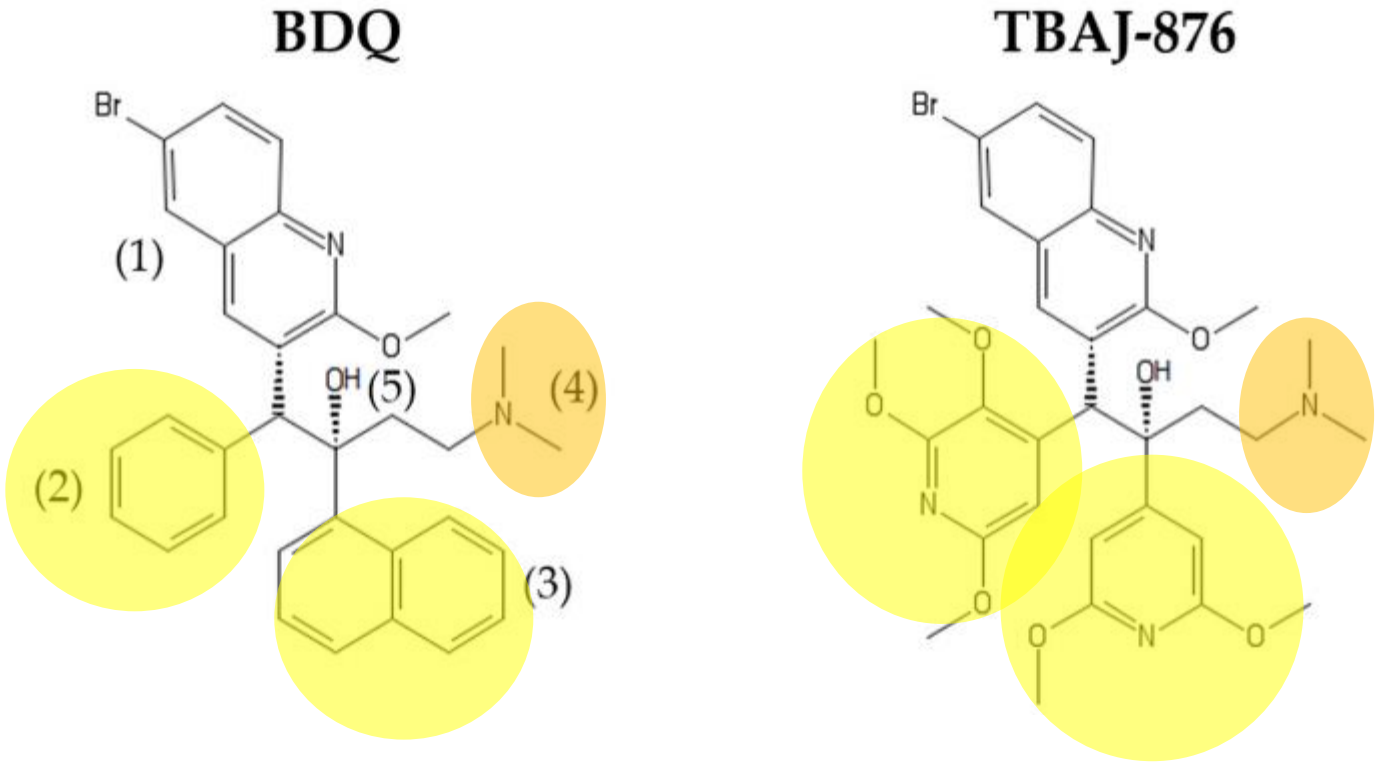
AbbVie
AIDS Clinical Trial Group (ACTG)
Astellas
Aurum Institute
Bill & Melinda Gates Medical Research Institute (Gates MRI)
Center for Excellence in Translational Research (CETR)
Chugai
Daiichi Sankyo RD Novare
ERA4TB Consortium
EU-Pearl Consortium
Evotec
Foundation for Neglected Disease Research (FNDR)
GlaxoSmithKline (GSK)
Global Health Drug Discovery Institute (GHDDI)
Harvard University
Hongqi Pharmaceutical
Institute of Materia Medica (IMM)
IMPAACT
International Tuberculosis Research Center (ITRC)
Janssen Pharmaceuticals
Johns Hopkins University (JHU)
KNCV Tuberculosefonds
Lupin Pharmaceuticals
Macleods Pharmaceuticals
Medical Research Council (MRC) at UCL
Médecins Sans Frontières (MSF)
Médecins Sans Frontières (MSF) Amsterdam Office
National Institutes of Health (NIH)
Otsuka
PanACEA
PAN-TB Consortium
Qurient
Schrödinger
Stellenbosch University
Takeda Pharmaceuticals
TB Drug Accelerator (TBDA)
Texas A&M University
TropIQ
UNITE4TB Consortium
University College London (UCL)
University of Auckland (UoA)
University of Illinois at Chicago (UIC)
University of North Carolina (UNC)
University of St. Andrews (UoSA)
Viatris
Weill Cornell Medical (WCM)
Yonsei University

TB Alliance

This document is updated on a quarterly basis.

TBAJ-876: next generation Diarylquinoline

- Increased potency and improved efficacy vs. bedaquiline
  - TBAJ-876 has higher anti-MTB potency than BDQ
  - Potential to reduce treatment duration demonstrated in mouse models
  - Better potency against most common BDQ-R strains (Rv0678 mutants)
- Improved safety profile
- Excellent candidate for long-acting injectable



Oral Presentation OA13-298-16, Thur 08:30-10:00, 243: “Antimycobacterial activity of a novel diarylquinoline TBAJ-876” (T. Black)
Oral Presentation OA13-300-16, Thur 08:30-10:00, 243: “Toxicological assessment of TBAJ-876 in rats and dogs” (R. Bruning-Barry)

Treatment-shortening of 876-PaL vs BPaL in BALB/c Relapsing Mouse Model

	Months of Treatment Required for Complete Sterilization of Mouse Lungs								
Regimen	M0.75	M1	M1.5	M2	M2.5	M3	M3.5	M4	M4.5
BDQ (25 mpk) +PaL									
876 (1.56 mpk) + PaL									
876 (3.125 mpk) + PaL		3/3							
876 (6.25 mpk) + PaL		2/6							
876 (12.5 mpk) + PaL		0/6							

876 dose-dependent sterilizing activity in combination with PaL

3.125 mpk dose of 876 sterilized faster than BDQ 25 mpk dose

= Mouse lungs sterile at 3 months after end of treatment

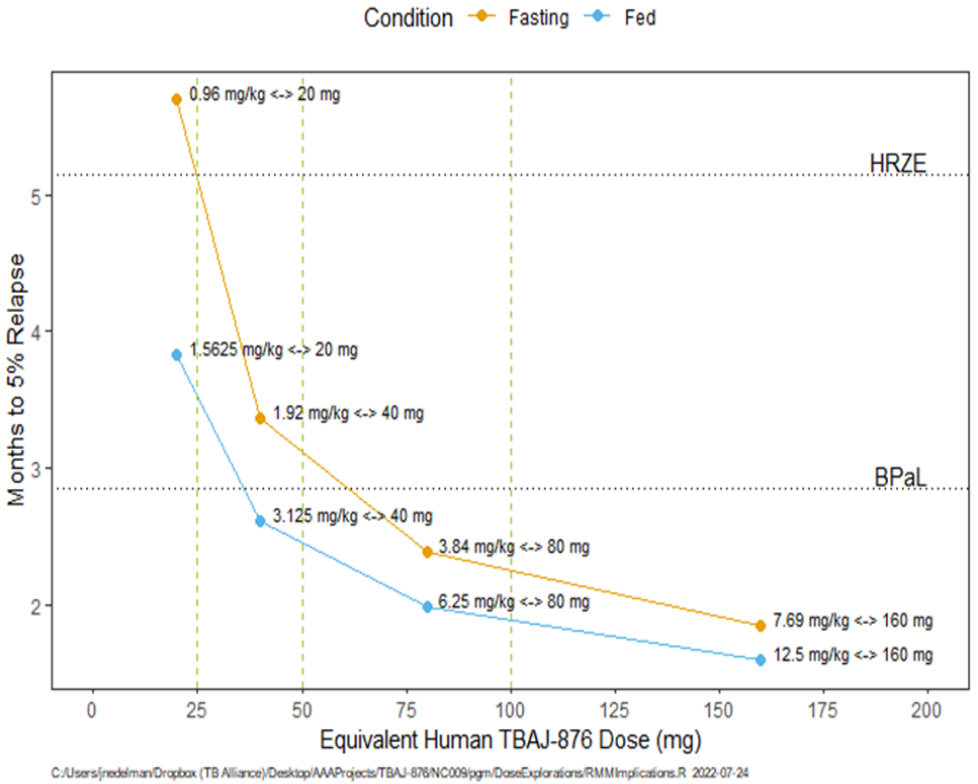
Oral Presentation OA13-299-16:Thur 08:30-10:00, 243 “Enhanced sterilising potential of regimens containing TBAJ-876” (E. Nuermberger)

TBAJ-876 Phase 1 completed

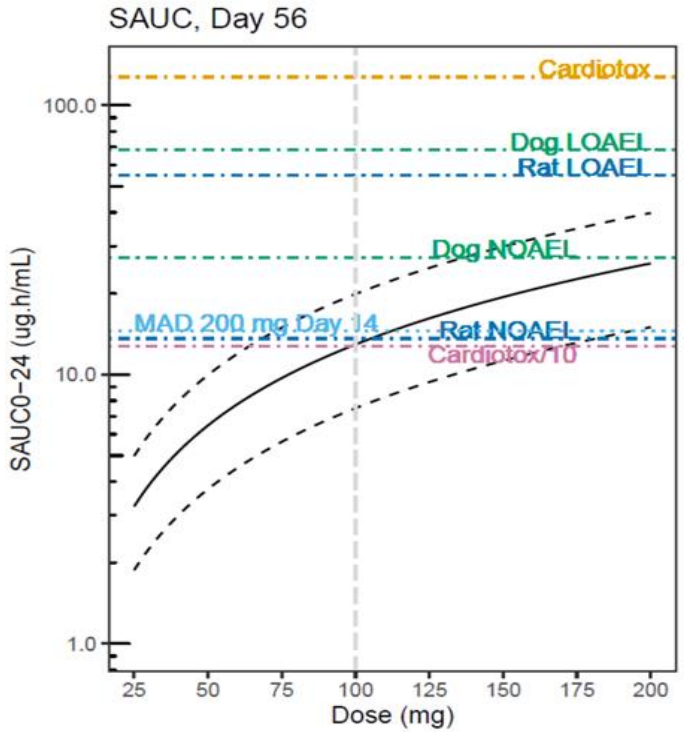
- **Part 1** – SAD (55 on active, 13 on placebo)
  - Oral suspension formulation
  - Placebo, 10, 25, 50, 100, 200, 400 and 800 mg
  - Food effect studied at 100 mg dose
- **Part 2** – MAD (27 on active, 12 on placebo)
  - Placebo, 25, 75 and 200 mg for 14 days taken with food
- **Part 3** – Relative Bioavailability (N= 30)
  - Tablet formulation
  - Single dose of 100 mg (either fasted or fed) or 4 x 25 mg (fasted)

Oral Presentation OA12-293-16, Thur 08:30-10:00, 242 A: “TBAJ-876 CL001: pharmacokinetics and safety data from a phase I trial of TBAJ-876” (A. Lombardi)

Phase 2 dose selection guided by PKPD modeling for efficacy and safety

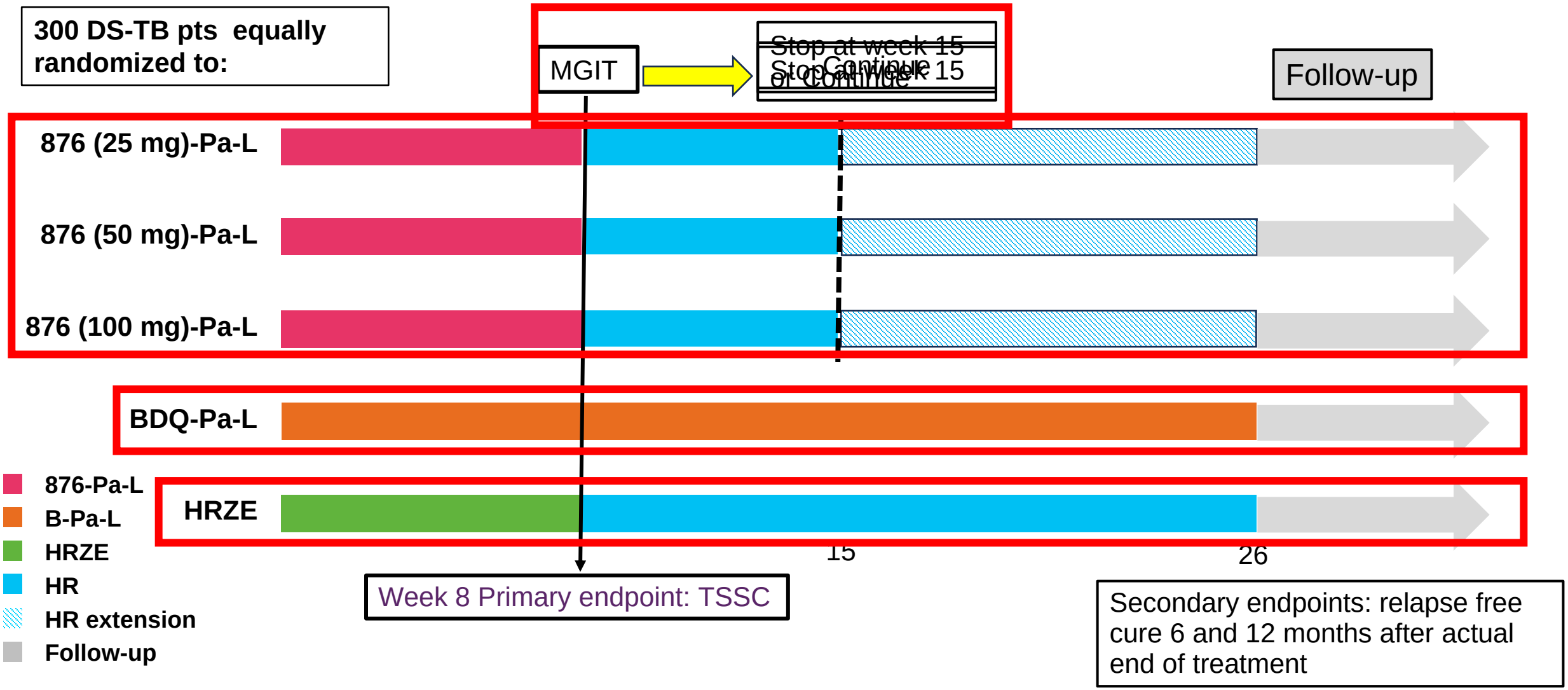


25 mg QD arm is expected to have efficacy at least as good as HRZE



Exposures on Day 56 at 100 mg QD are expected to be safe, based on predicted human SAUC

TBAJ-876 Phase 2: NC-009 study design



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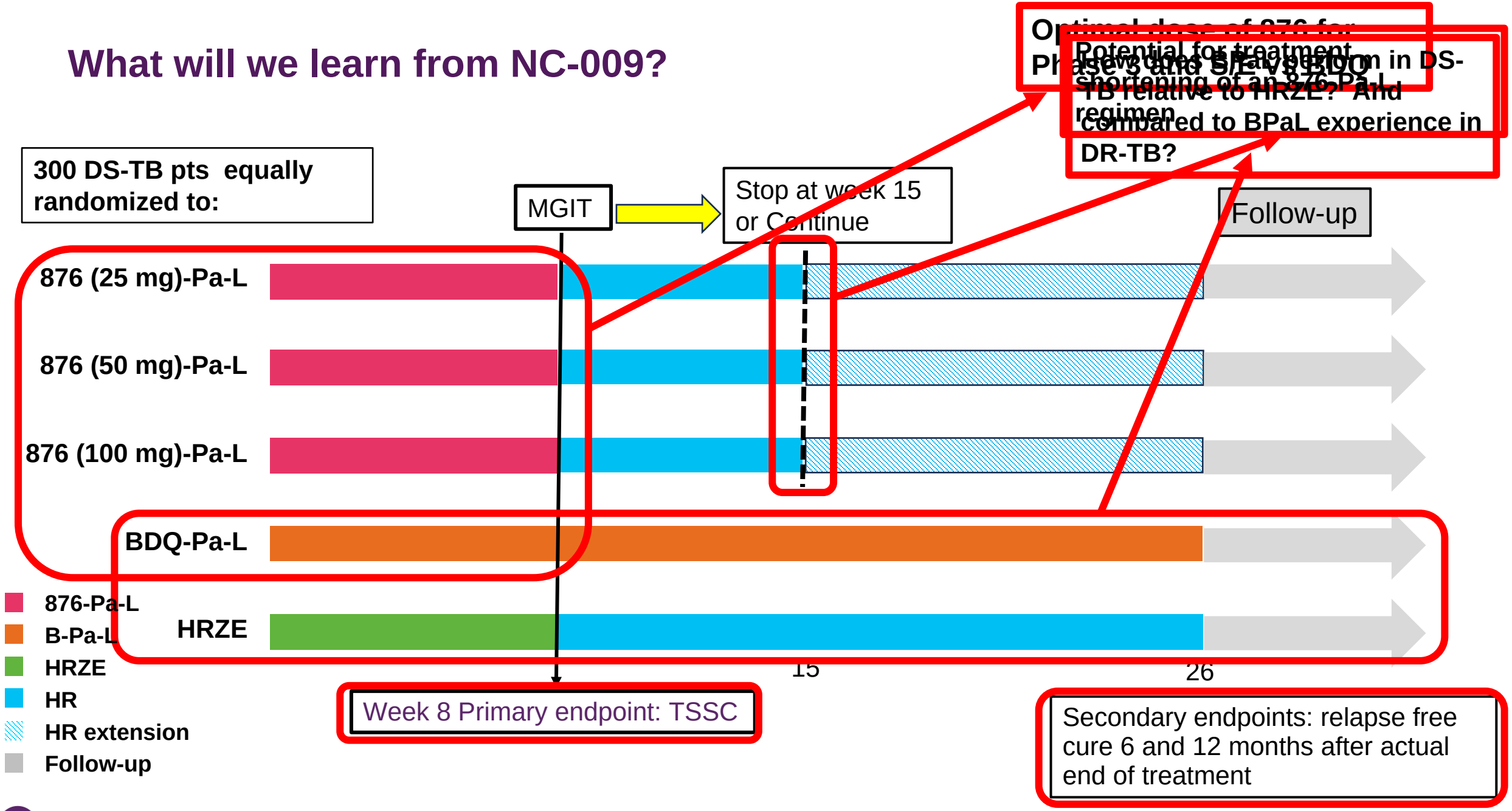
What will we learn from NC-009?



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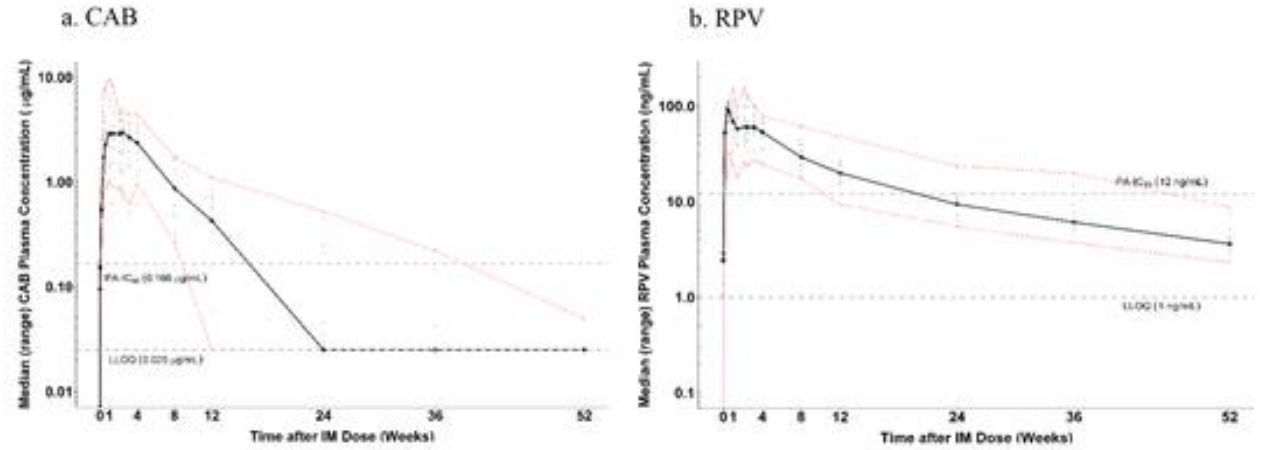
TBAJ-876 as a candidate for Long-Acting Injectable

LAI treatment of TB should be achievable, particularly for latent TB

- Advances in formulation technology
- Drugs with favorable physicochemical properties
- More potent drugs, meaning lower drug load
- TBAJ-876 meets these criteria

HIV can be treated with a 2-drug long-acting injection (LAI) every 2 months

Figure. Preliminary median (range) of plasma concentration-time profiles of CAB (a) and RPV (b) after single IM administration of (a) CAB LA 600 mg (3 mL) and (b) RPV LA 900 mg (3 mL) to the lateral thigh muscle in healthy adult participants.



Plasma concentrations below the lower limit of quantification (LLOQ) were imputed as the value of LLOQ. Black solid line represents the median and dotted red lines represent min and max of the observed data. Grey open circles represent individual observed data. PA-IC_{90}: in vitro protein-adjusted concentration resulting in 90% of the maximum inhibition of viral growth.












This work would not be possible without clinical trial participants, investigators and site staff, DSMB Members, funders, consortia partners, and many other collaborators, to whom we are incredibly thankful.

TB Alliance