BRINGING INNOVATION TO THE DEVELOPMENT OF TRANSFORMATIVE TB REGIMENS

NASEM Workshop: Innovations for Tackling Tuberculosis in the Time of COVID-19

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15 September 2021

Progressing Toward a Shorter, Simpler, Safer pan-TB Regimen

1943: Streptomycin (S)
1948: *p*-aminosalicylic acid (PAS)
1952: Isoniazid (H)
1954: Pyrazinamide (Z)
1955: Cycloserine (Cs)
1957: Kanamycin (Z)
1960: Ethionamide (ETO)
1961: Ethambutol (E)
1963: Capreomycin (Cm) & Rifampicin (R)
1998: Rifapentine (P)
2012: Bedaquiline (BDQ)
2014: Delamanid (DLM)
2019: Pretomanid (Pa)

1940s — First randomized trial: S Monotherapy — *Led to S resistance*

1950s — First regimen: S/PAS/H — *24 months of therapy*

1960s — PAS replaced by E: S/H/E — *18 months of therapy*

1970s — Addition of R: S/H/R/E — *9-12 months of therapy*

1980s — S replaced by Z: H/R/Z/E — *6 months, oral therapy*

1990s

2000s

2010s — BPaL — *6-month, all-oral therapy for highly resistant TB*

2020s — 2PHZM/2PHM — *4 months of therapy*

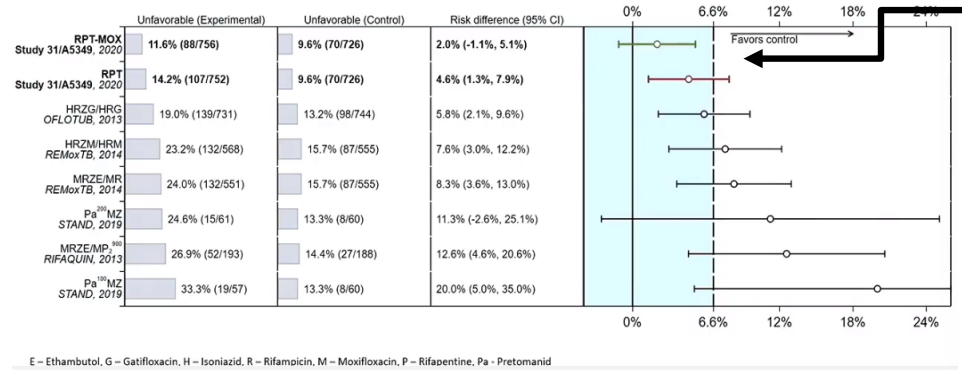
Courtesy of TB Alliance

1 First approvals of novel TB drugs in decades

Steady growth in TB antimicrobial pipeline

2 2019/2020: Regimen Shortening is Feasible (Study 31, NIX)

3 2022/2023: Start Phase 2 Testing of Potential pan-TB Regimens (e.g., P/D+B+O+S)



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SARS-CoV-2 COVID-19 PANDEMIC

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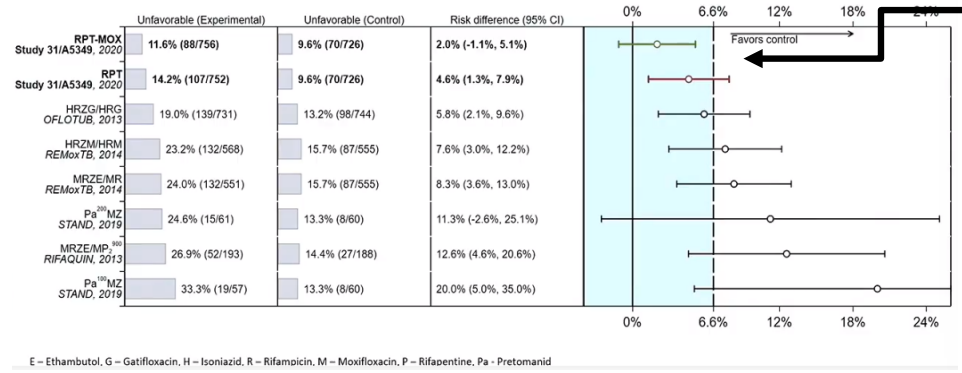


Optimal pan-TB **T**arget **R**egimen **P**rofile (TRP)

ENABLE A SIMPLER "TEST & TREAT" PARADIGM TO DRIVE IMPACT

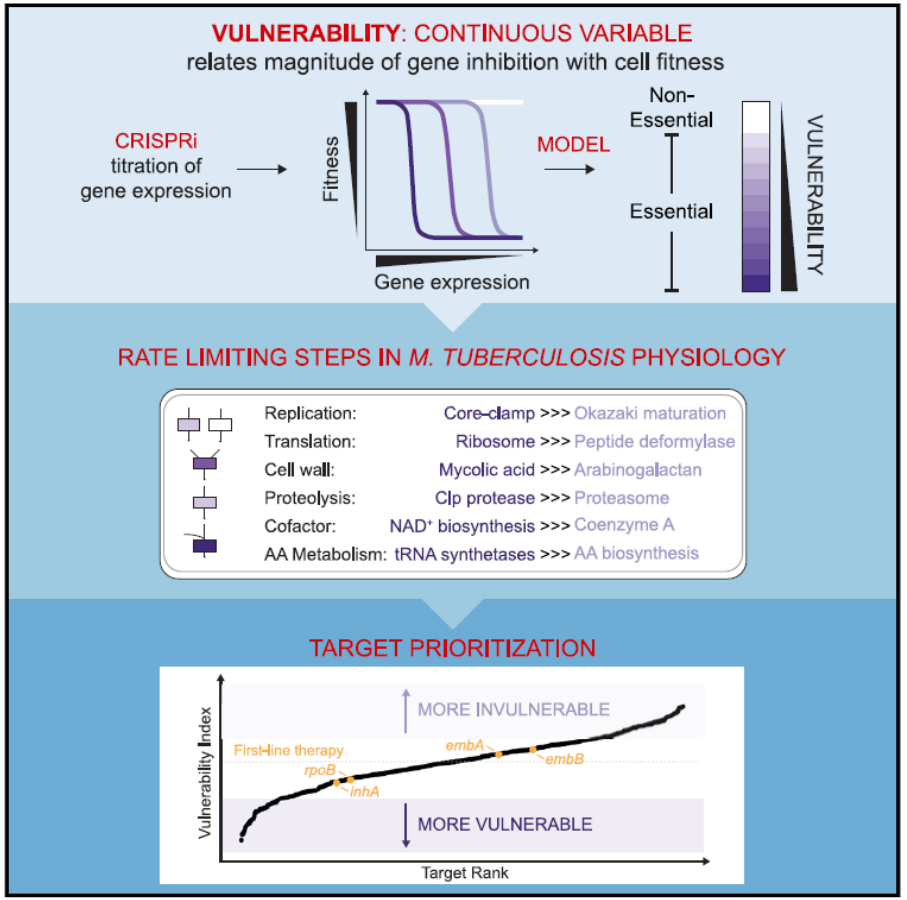
TRP Criteria	Hypotheses
pan-TB	No DST required. Fewer patients lost to the system after diagnosis
Shorter (<2-3mos)	Shorter → Improves Adherence → Improves Outcome → Less transmission
Safe and Well Tolerated	No baseline or ongoing safety monitoring. Well-tolerated → Improves Adherence
Simpler	All oral, QD, no drug-drug interactions to manage
Efficacy	Short, forgiving regimen non-inferior to SoC to minimize efficacy – effectiveness GAP
Affordable	Low barrier to uptake

Challenges in Meeting the pan-TB TRP

Challenges	Actions and Approach
Too few antimicrobial candidates	Drive discovery efforts, innovation to efficiently identify vulnerable targets and optimal combinations
Limited translational science	Innovation in biomarkers, dose selection, & efficient experimental design. Leverage quantitative translational modelling.
No single organization will own the best candidates to build the best regimen	Embrace collaboration. TBDA, PAN-TB, ERA4TB, UNITE4TB, etc…
Meeting the “aspirational” pan-TB TRP	Don’t let ***PERFECT*** be the enemy of the ***GOOD***

Innovation in *Mtb* Antimicrobial Discovery

- CRISPR interference platform used to titrate *Mtb* gene expression
- VULNERABILITY index is derived from relationship between magnitude of gene expression and *Mtb* fitness estimated
- VULNERABLILTY index contributing to *Mtb* antimicrobial target identification



Bosch et al., 2021, Cell *184*, 1–14
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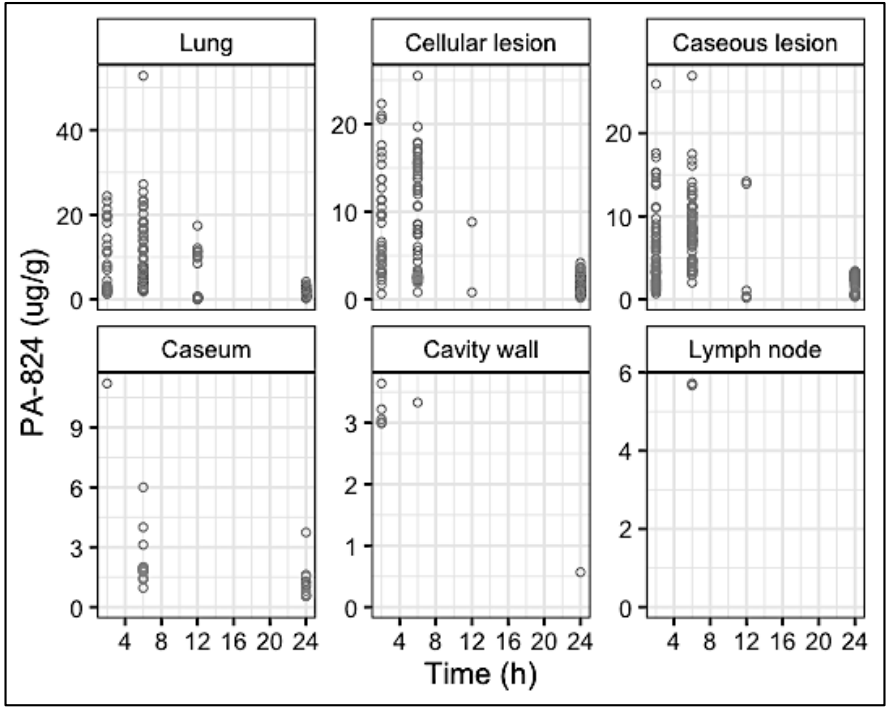
Innovation in Dose selection

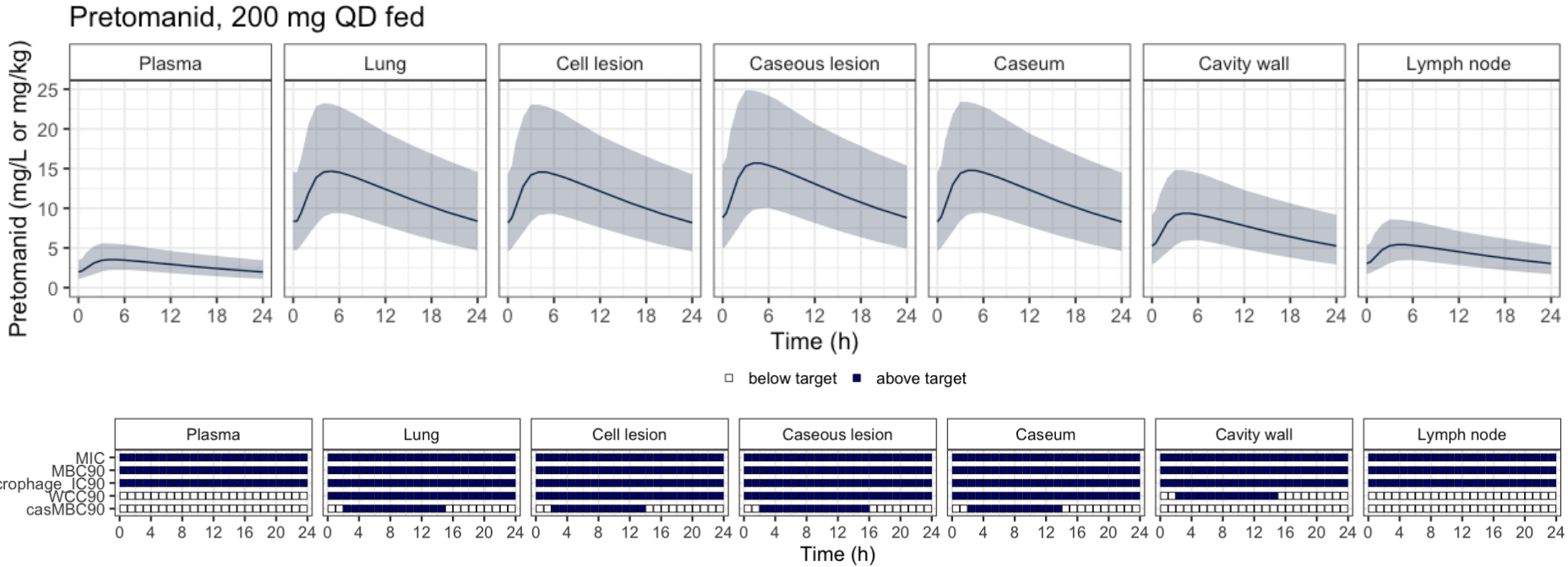
- Non-clinical platform (rabbit) to measure PK and PD across sites of infection
- Time-series samples collected from blood and heterogenous sites of infection
- Tissues:
  - Uninvolved lung
  - Cellular lesions
  - Caseous lesions
  - Caseum
  - Cavity wall
  - Lymph node



Dartois Lab. Center for Discovery & Innovation. Hackensack Meridian Health.

Innovation in Dose selection

Animal PK/PD data used to estimate human “lesion coverage”

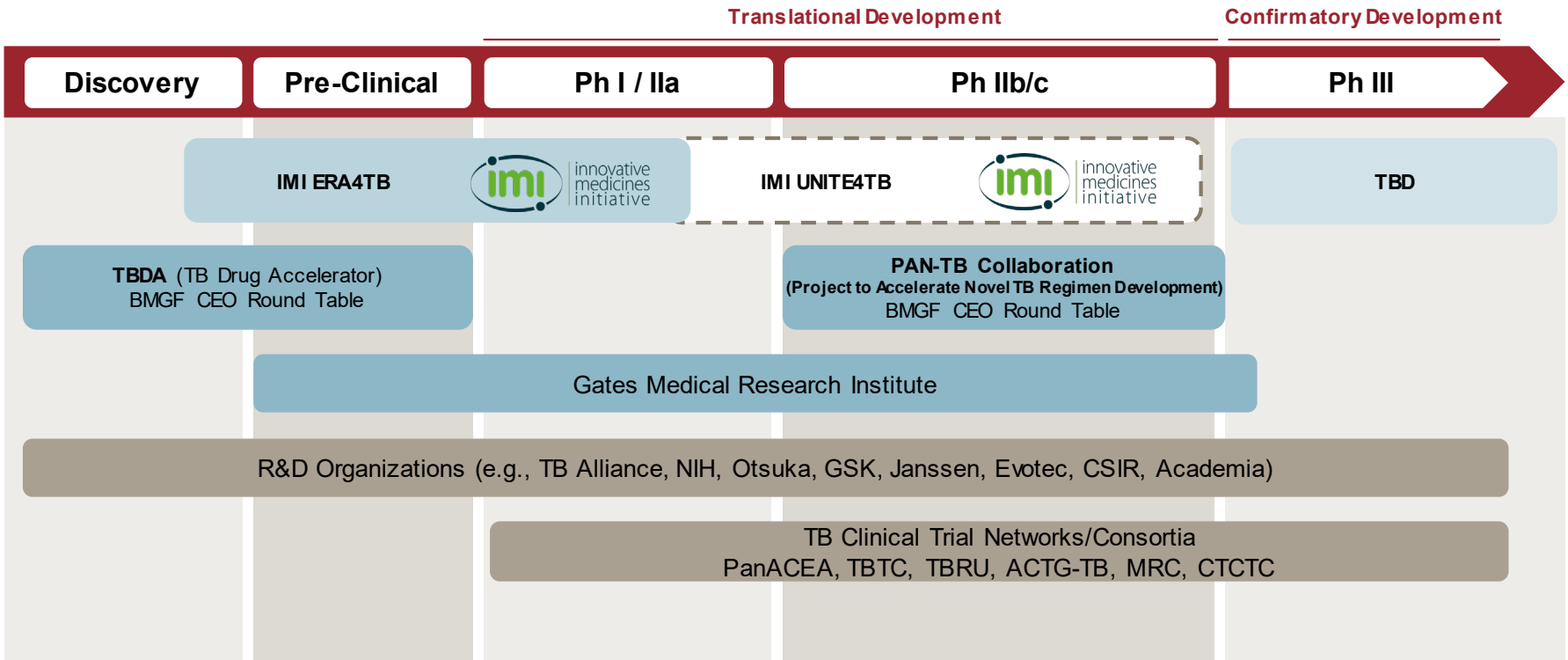


In vitro targets (mg/L)	MIC50	MBC90	Macrophage IC90	WCC90	casMBC90
	0.3	0.23	0.45	7.19	11.8

Lakshminarayana, et al., J Antimicrob Chemother 2015; 70: 857–867

UCSF

Collaboration - Evolving TB Drug Development landscape



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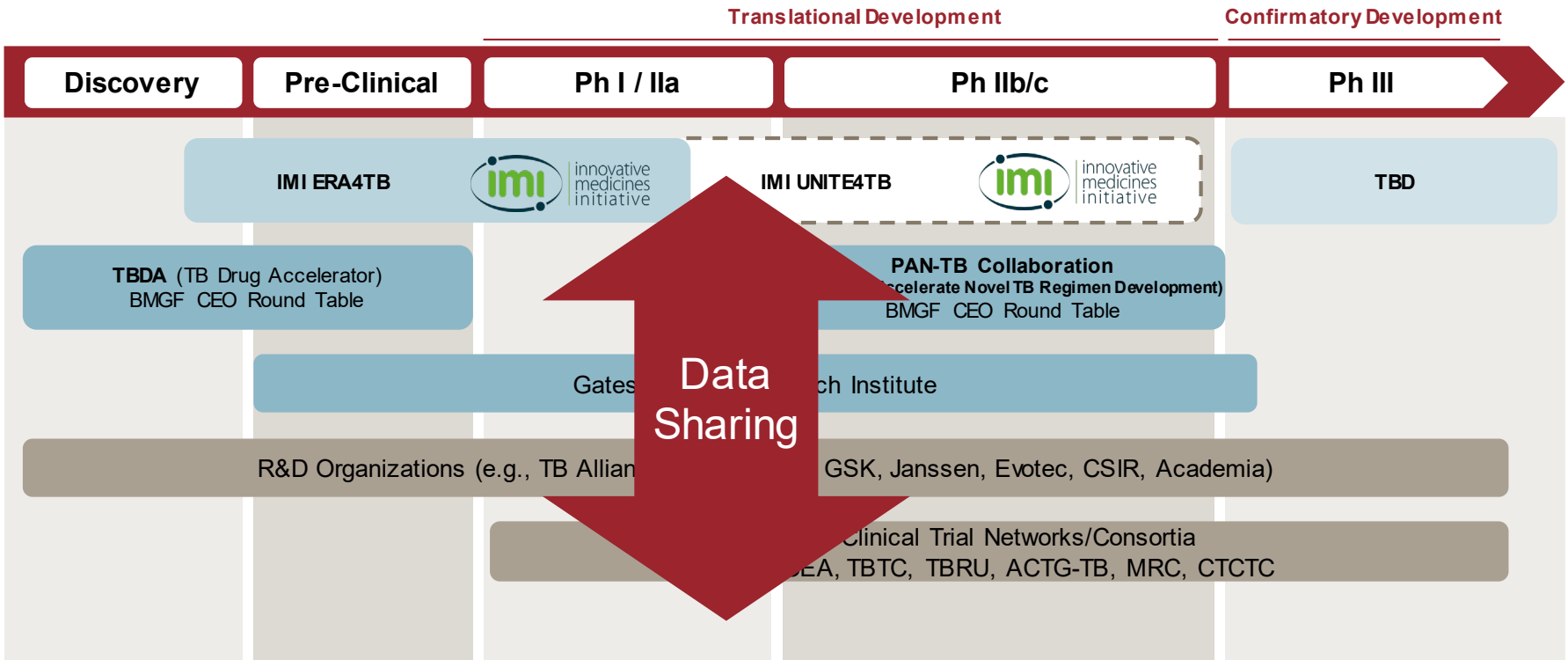


Collaboration - The TB Drug Accelerator

The TBDA, est. 2012, is a collaboration between six pharmaceutical companies, a biotech, fifteen research institutions, and a product development partnership to facilitate early TB drug discovery.

How it works…

NIH National Institute of Allergy and Infectious Diseases · Seattle Children's Hospital · Research · Foundation · Drug Discovery Unit · MERCK & CO., INC. Kenilworth, N.J., U.S.A. · gsk · evotec · Weill Cornell Medicine · CDI Center for Discovery & Innovation, Member of Hackensack Meridian Health · Eisai · Tufts University · Colorado State University · Cornell University College of Veterinary Medicine · IDM · TB Alliance · H3D · GHDDI · Janssen · abbvie · LEENIA · HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH · Calibr at Scripps Research

With Participation From: BILL & MELINDA GATES *foundation*

NATURE MEDICINE | VOL 27 | AUGUST 2021 | 1329–1337 | www.nature.com/naturemedicine

Collaboration - **P**roject to **A**ccelerate **N**ovel **TB** Regimen Development (PAN-TB; est. 2019)

Objective

The goal of the Collaboration is to develop a shorter, simpler, safer regimen aligned with the pan-TB TRP.

- Data Sharing
- Global Access

BMGF Funding

- Non-clinical regimen evaluation

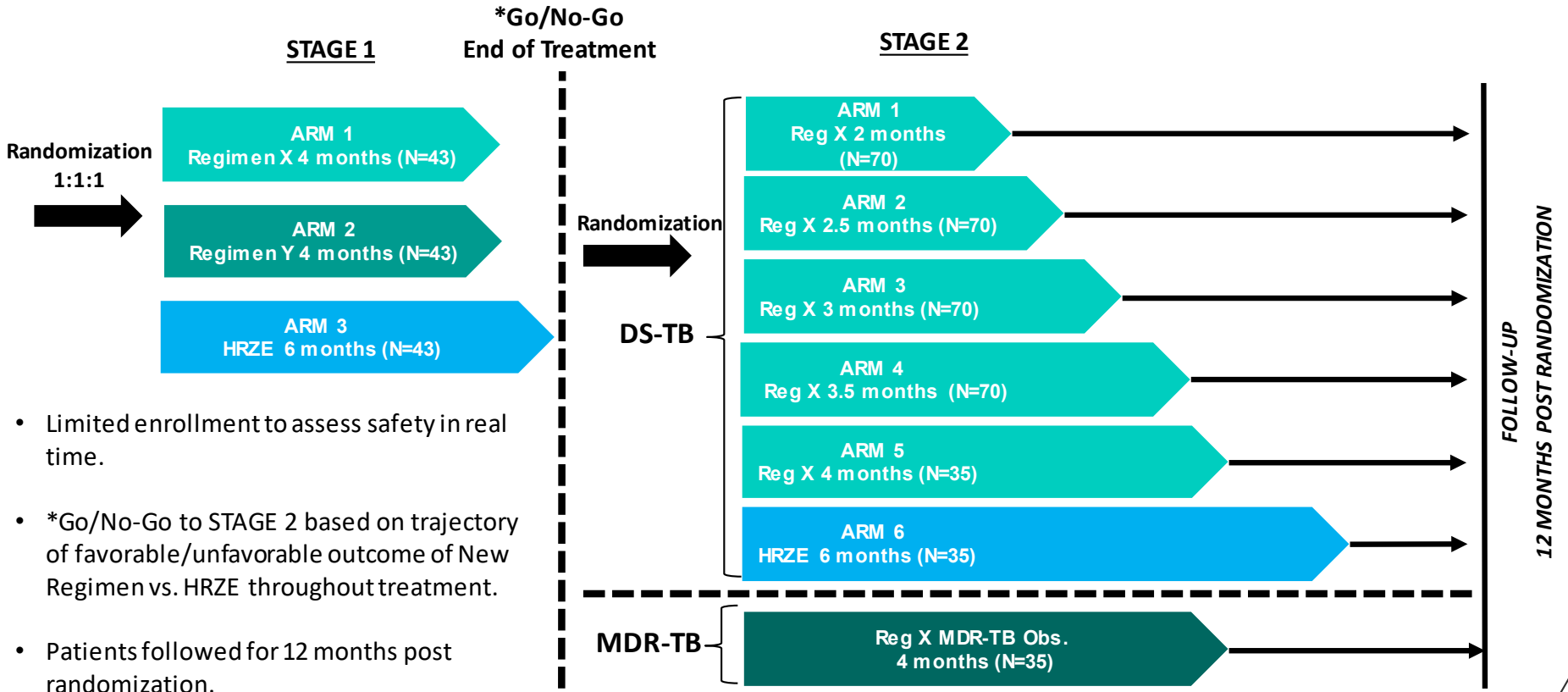
  and

- Phase 2b/c clinical studies executed by the Gates MRI

GATES MRI

Responsible for execution of the clinical studies within PAN-TB

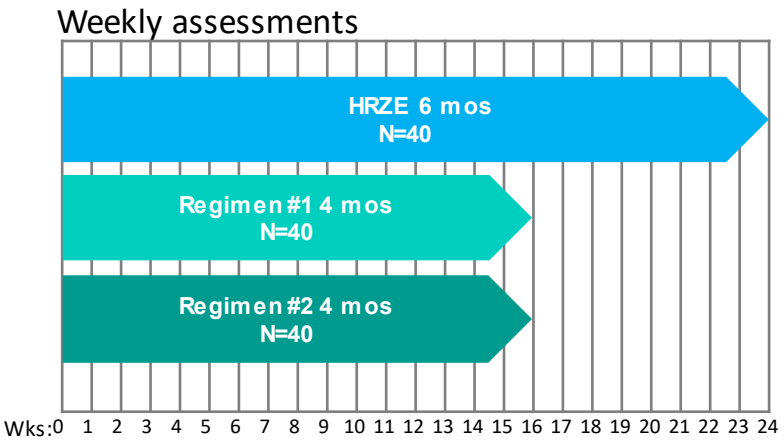
Innovation in Phase 2 Trial Design, Duration-Finding

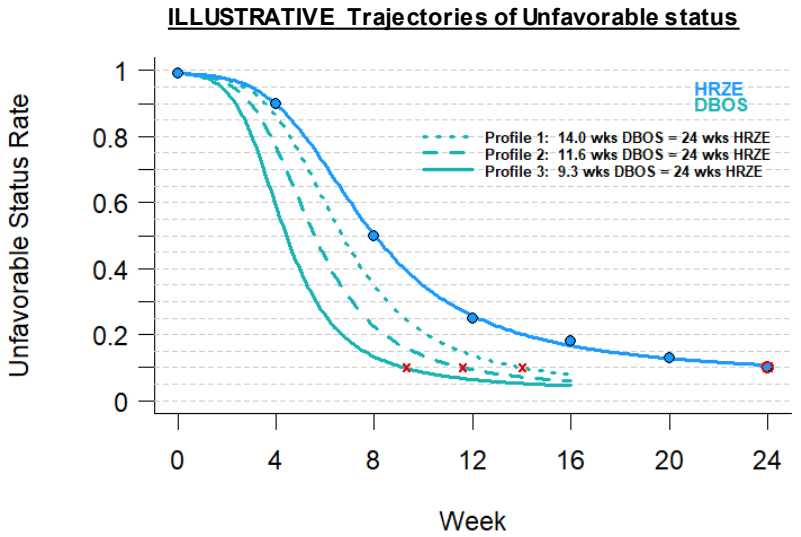


- Limited enrollment to assess safety in real time.
- *Go/No-Go to STAGE 2 based on trajectory of favorable/unfavorable outcome of New Regimen vs. HRZE throughout treatment.
- Patients followed for 12 months post randomization.

Innovation in Phase 2 Trial Design, STAGE 1

Rule-Out Poorly Performing Regimens





Treatment Endpoint:

- Favorable / Unfavorable status across time (binary Microbiological + clinical + tolerability assessment)

Analysis:

- Estimate and compare time-response trajectories between regimens

Go/No-go:

- New Regimen time-response profile is shifted favorably (e.g., to the left and lower) relative to HRZE supporting treatment shortening potential and a "Go" to Stage 2

PAN-TB
PROJECT TO ACCELERATE NEW TREATMENTS FOR TUBERCULOSIS

Perspectives

- Progress and growth in TB antimicrobial R&D slowed by COVID-19.
- The TB R&D community is poised to launch late-stage clinical trials of potential pan-TB regimens.
- Innovation in target identification, dose-selection, biomarkers, and trial design is happening now. More innovation is needed to efficiently design and test the best regimens.
- The technical/scientific "substrate" for potentially impactful pan-TB regimens is here and more is coming. Accelerating R&D progress and patient impact - warrants global engagement and funding comparable to the COVID-19 response.

THANK YOU!