BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE

Gates MRI TB Drug Development Activities

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WGND Annual Meeting

14 Nov 23

Gates MRI TB Drug Development Activities

- Regimen development – Phase 2b/2c
  - Pan-TB Target Regimen Profile
  - PAN-TB Collaboration partnership & trial design
    - Gates MRI-TBD06-201 Trial: Evaluation of DBQS† and PBQS† as first 2 regimens

- Individual TB agent evaluation for regimen development readiness
  - TBA-7371
  - TBD09 (MK-7762)
  - TBD10 (MK-3854)
  - TBD11 (CLB073)

† D – delamanid, P – pretomanid, B – bedaquiline, Q – quabodepistat (OPC-167832), S – sutezolid

PAN-TB Target Regimen Profile

Enable "Test and Treat" Paradigm

TRP Criteria	Hypothesis
Pan TB (No DST)	**Simple "test & treat":** Fewer patients lost to the system after Dx Decreases time from Dx to Tx → Less time to transmit (no waiting for DST or failure on HRZE)
Shorter: ⩽ 3mos	**Clear differentiation from SoC** Shorter → Improves Adherence → Improves Outcomes → Less transmission
Acceptable Safety Profile	**No baseline or ongoing safety monitoring. Enables Test & Treat.** Well tolerated → Improves Adherence → Improves Outcomes → Less Transmission
Simpler	**All Oral, Once daily** No DDIs to manage enables Test & Treat
Efficacy (NI to SoC)	**Short, forgiving regimen non-inferior to 6 months.** Minimize Efficacy – Effectiveness gap Forgiving regimen will minimize impact of non-adherence → Improve Outcome → Less Transmission
Affordable	**Low barrier to uptake → Impact**

PAN-TB Collaboration

Project to Accelerate New Treatments for TuBerculosis

Focused on achieving Pan-TB Target Regimen Profile

Gates MRI TBD06-201: PAN-TB Ph2b/2c 2-Stage, De-risking Design

STAGE 1
Regimen Selection

***Go/No-Go**
End of Treatment

STAGE 2
Duration Optimization

Randomization 1:1:1

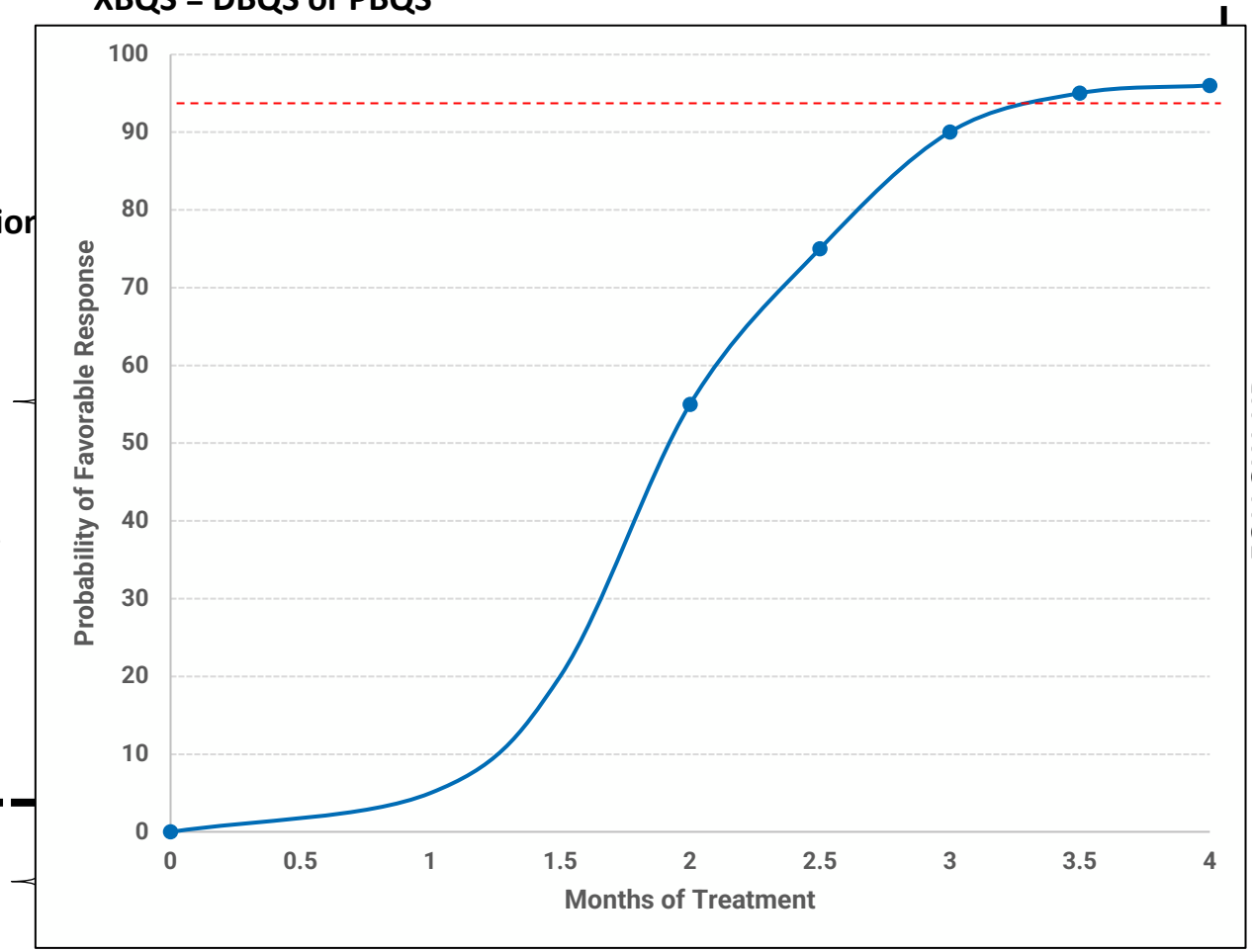
Eligible Participants ≥ 18 to ≤ 65 years with DS-TB (including PLHIV)

- ARM 1: DBQS: 4 months (N=43)
- ARM 2: PBQS: 4 months (N=43)
- ARM 3: HRZE: 6 months (N=43)

Randomization

- DS-TB: Eligible Participants ≥ 18 to ≤ 65 years with DS-TB (including PLHIV)
- RR/MDR-TB

XBQS = DBQS or PBQS



FOLLOW-UP
12 MONTHS POST RANDOMIZATION

***Decision to proceed to Stage 2 will be based on a comprehensive review of efficacy and safety results of DBQS & PBQS vs. HRZE through 4, and 6 months of treatment, respectively**

- **Stage 1 patients will be followed for 12 months post randomization**
- **DBQS or PBQS considered for Stage 2**

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Gates MRI-TBD06-201/PAN-TB Trial Update

- Launched in South Africa on July 26, 2023
- 6 sites in South Africa currently enrolling
- Trial launch in Philippines imminent
- Clinical Trial Application under regulatory review in Peru
- Stage 1 results anticipated in 2025

PAN-TB Trial Launch

Evaluation of Individual TB Agents for Entry into Regimen Development

Gates MRI-TBD03-201: TBA-7371 (DprE1 Inh) Phase 2a EBA Trial

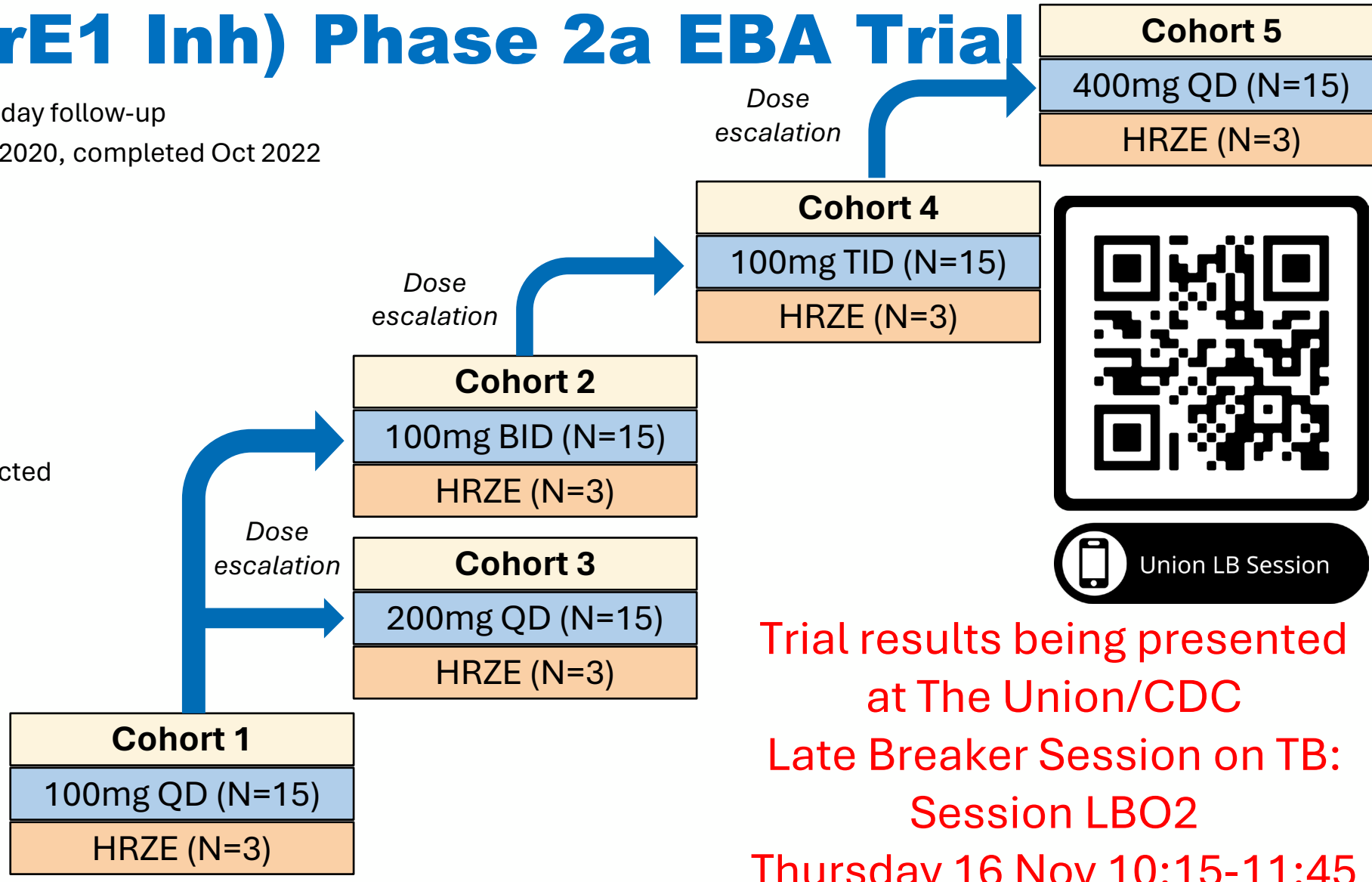
- 14-day inpatient study treatment, 28-day follow-up
- 4 sites in South Africa; Launched Jan 2020, completed Oct 2022

Eligibility criteria

- Untreated, RIF-susceptible pulm TB
- ≥1+ smear positivity
- Adults 18-60 years
- PLHIV eligible if CD4+ ≥350, no AIDS-defining illness

Assessments and Procedures

- Daily 16-hour overnight sputum collected
- Bactericidal activity assessed by:
  - Δ TB CFU in solid culture (1^0)
  - Δ TTP in liquid culture
  - Δ Sputum LAM
- Safety assessments
  - AEs; eye symptoms, visual acuity & color vision; orthostatic vital signs, ECGs
- Intensive PK collected



Trial results being presented at The Union/CDC Late Breaker Session on TB: Session LBO2 Thursday 16 Nov 10:15-11:45

EBA = early bactericidal activity; RIF = rifampicin; PLHIV = persons living with HIV
QD = once daily; BID = twice daily; TID = thrice daily; CFU = colony forming unit; TTP = time to positivity; LAM = lipoarabinomannan; ECG = electrocardiogram

TBD09 (MK-7762)

- Oxazolidinone (protein synthesis inhibitor)
- Discovered by Merck with NIAID through TB Drug Accelerator
- Phase 1 first-in-human trial launched 23 Feb 2023
  - Single ascending dose and food effect portion completed
  - 28-day multiple ascending dose portion of trial launching Q4 ’23
- Planning underway for Phase 2a trial evaluating TBD09 in TB patients

Ph1 CT.gov

TBD10 (MK-3854) and TBD11 (CLB073)

TBD10

- Protein synthesis inhibitor but structurally diverse from oxazolidinones
- Discovered by Merck with NIAID through TB Drug Accelerator
- IND-enabling studies nearing completion

TBD11

- Gates MRI licensed from Calibr in February 2023
- Discovered by Calibr with Cornell through TB Drug Accelerator
- Activates adenylyl cyclase (Rv1625c) ultimately blocking Mtb's ability to metabolize cholesterol
- Significantly enhanced CFU decline of BPaL at 8 weeks in mouse TB model
- IND-enabling studies currently underway

Acknowledgments

Partnerships, Collaboration & Coordination as Key Ingredient for Success

- PAN-TB – BMGF, Otsuka, TB Alliance, Janssen, GSK, Evotec
- IMI – ERA4TB, UNITE4TB
- Merck
- Calibr
- Foundation for Neglected Disease Research
- TB Drug Accelerator