PAN-TB
PROJECT TO ACCELERATE NEW TREATMENTS FOR TUBERCULOSIS

Overview of PAN-TB Ph 2b/c Treatment Shortening Trial

Gates MRI-TBD06-201 Trial

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Conflict of Interest Disclosure Form

I have no Conflict of Interest to report.

☐ I have the following Conflict of Interest(s) to report:

Please tick the type of affiliation / financial interest and specify the name of the organisation:

☐ Receipt of grants/research supports: _____

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PAN-TB Target Regimen Profile

- Focused on “Test & Treat” Paradigm for TB
- Improve outcomes, enhance case-finding & maximize epidemiologic impact

TRP Criteria	Hypothesis
Pan TB (No DST upfront)	**Simple “Test & Treat”:** Fewer patients lost to the system after diagnosis Decrease time from diagnosis to treatment initiation → Less time to transmit
Shorter: ≤ 3 months	**Clear differentiation from current DS- and DR-TB standards of care (SoCs)** Shorter duration → Improves adherence → Improves outcomes → Reduce transmission
Acceptable Safety Profile	**No baseline or ongoing safety monitoring. Enables Test & Treat.** Well tolerated → Improves adherence → Improves outcomes → Less transmission
Simple	**All oral, once daily** No potential drug-drug interactions to manage, enables Test & Treat approach
Efficacious	**Short, forgiving regimen non-inferior to DS-TB and DR-TB SoCs.** Minimize Efficacy – Effectiveness Gap Forgiving regimen will minimize impact of non-adherence → Improve outcomes → Reduce transmission
Affordable	**Low barrier to uptake → Impact**

Alignment of PAN-TB and WHO pan-TB TRPs

TRP Criteria	PAN-TB TRP	Draft WHO Pan-TB TRP
Indication	No upfront DST required before treatment initiation	First-line treatment initiated even in absence of rapid DST
Duration	≤3 months	≤4 months (minimal); ≤2 months (optimal)
Efficacy	Non-inferior to DS-TB and DR-TB SoCs	Efficacy as good (minimal) or better (optimal) than current rifampicin-susceptible TB SOC treatment
Safety & Monitoring	No baseline or ongoing safety monitoring	• Safety profile no worse (minimal) or better (optimal) than current RS-TB SOC treatment. • Minimal (1x/month) or no (optimal) clinical and laboratory monitoring except special populations
Formulation & Administration	All oral, once daily, no potential drug-drug interactions	All oral, 1-2x a day (minimal) or daily or less (optimal) Fewer than 10 pills (minimal) or 4 pills (optimal) per day
Cost	Affordability important to ensure low barrier to uptake	See Section 4.6 on cost modelling and considerations

Primary Composite Efficacy Endpoint: Unfavorable Outcome

Endpoint = % of participants with unfavorable outcome status (UOS). UOS composed of:

- **Treatment failure**
  - *Clinical*: Based on Investigator assessment during treatment or at end of treatment
  - *Microbiologic*:
    - Sputum culture positive at:
      - Week 17 or after (all arms for Stage 1; SoC for Stage 1 and 2; MDR-TB arm for Stage 2)
      - At end of treatment (XBQS arms in Stage 2)
    - Positive culture at last visit for participants lost to follow-up
- **Permanent treatment discontinuation** due to safety/intolerability
- **Relapse:** re-start of TB treatment during follow-up excluding documented TB re-infection (genotyping used to distinguish between relapse and reinfection)
- **Participant withdrawal**: participant- or investigator-initiated
- **Death** (All-cause)

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Selection of DBQS & PBQS Regimens

Delamanid (D), pretomanid (P), bedaquiline (B), sutezolid (S), and quabodepistat (Q, OPC-167832) represent current Phase 2c-ready agents from PAN-TB Collaboration partners

- DBQS & PBQS as latest stage 4-drug combination regimens to form
- D, P, and B already approved for use in M(X)DR-TB treatment
- Quabodepistat and sutezolid in late Phase 2 development
- Compounds in earlier development within collaboration being evaluated for Phase 2b/c readiness and suitability

Success of BPaL regimen highlights potential of combining B + D/P + sutezolid with potential added value of including a novel cell-wall agent in quabodepistat

- Sutezolid being developed to determine if it has more favorable safety/efficacy profile than linezolid
- Quabodepistat demonstrated meaningful efficacy in nonclinical studies and Phase 2a EBA trial; 4-month Phase 2b trial currently in progress evaluating 4-month DBQ regimen in DS-TB (NCT05221502)

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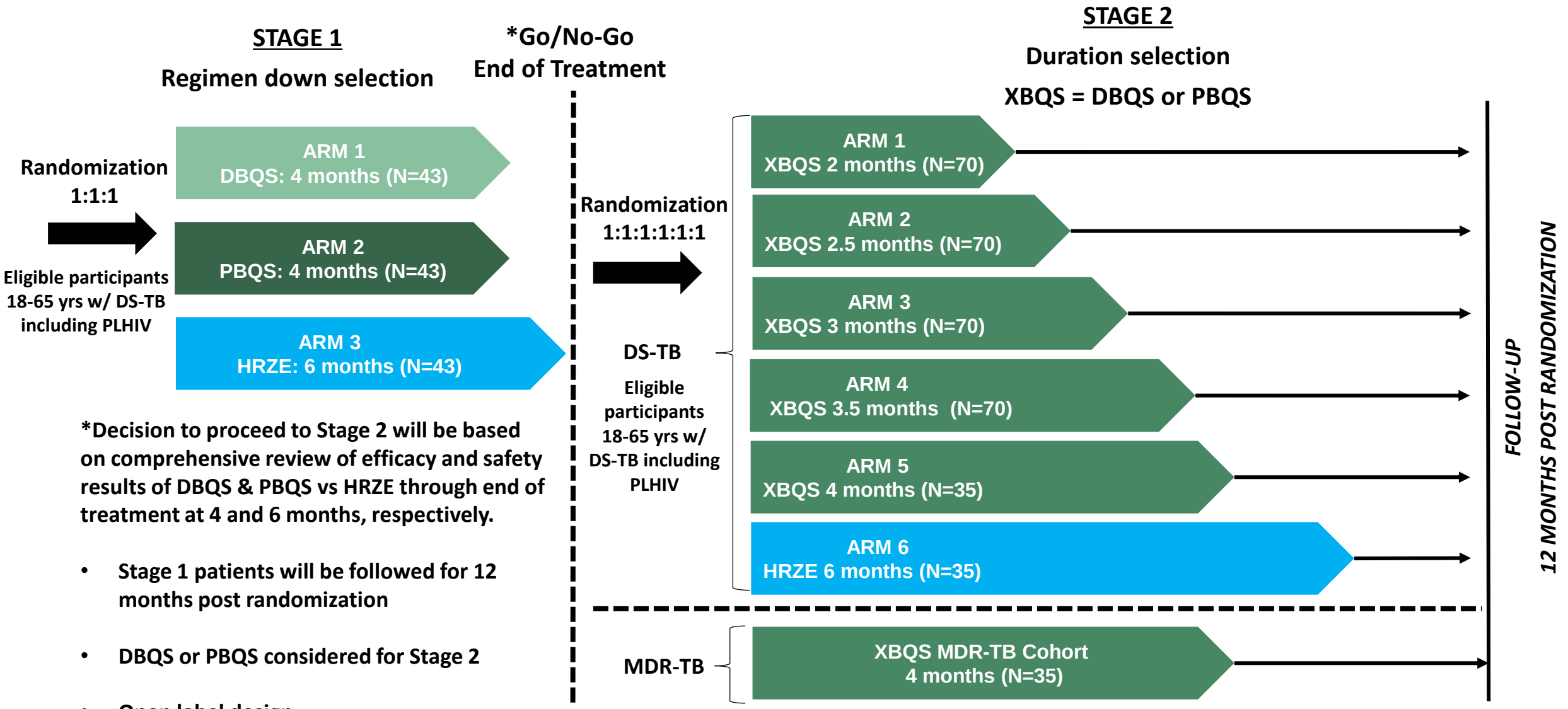
PAN-TB Trial: Ph 2b/c 2-stage, de-risking design



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

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

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

Timing of Primary Endpoint Evaluation

STAGE 1 UOS at end of treatment (W17 for DBQS & PBQS, W26 for HRZE)

STAGE 2 UOS at 12-months post-randomization for all arms

Measures to protect integrity of primary endpoint

- Provide investigators with regular formatted summaries of key clinical, microbiology, adherence, and CXR data throughout participant's treatment to support treatment monitoring
- Institute Concilium* model with required Concilium consultation by investigator when unfavorable outcome assigned (investigator makes final decision on participant UOS and management)

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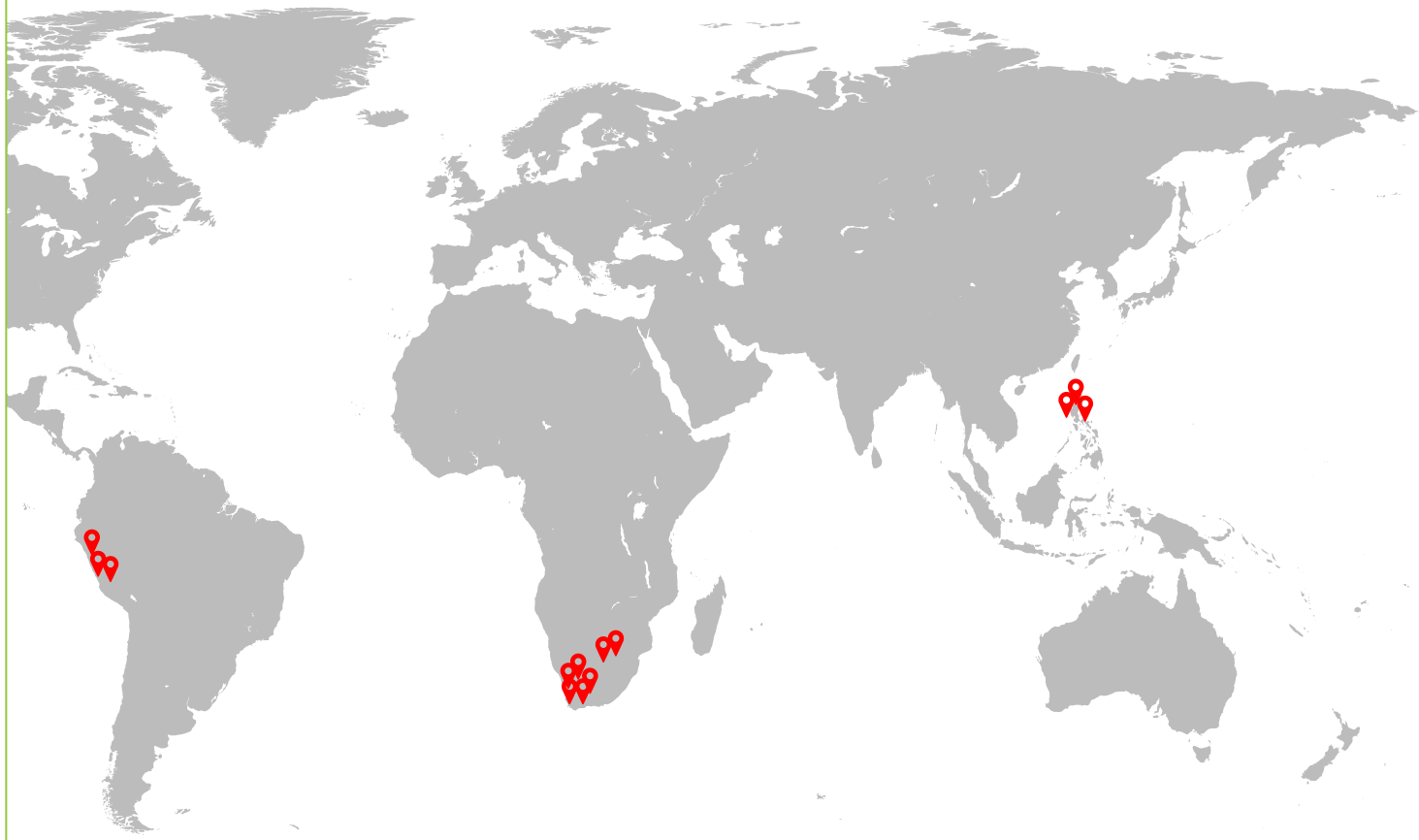
*Concilium consists of 8-9 expert TB clinicians and researchers external to the trial and sponsor

PAN-TB Ph 2b/c Trial Logistics

- Stage 1: 13 planned trial sites in 3 countries
  - South Africa (7)
  - Philippines (3)
  - Peru (3)
- Trial launched July 26, 2023 in South Africa
- Stage 1 completion projected for 2025
- Ongoing regular meetings between PAN-TB & UNITE4TB leadership and clinical, microbiology, and biomarker teams to share plans, improve efficiency of trials



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Stage 1 to Stage 2 transition

- Stage 1 data used to down-select DBQS and PBQS regimens based on their ability to shorten treatment to 4 months
  - Available relapse data will be considered for Stage 1 -> 2 transition

- Plan to expand trial in Stage 2 to additional countries and sites given larger sample size and inclusion of MDR-TB pts in Stage 2

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PAN-TB Collaboration Members

Otsuka

evotec

Johnson&Johnson

BILL & MELINDA GATES foundation

GSK

BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE

TB Alliance

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