Overview of PAN-TB Ph 2b/c
Treatment Shortening Trial
Gates MRI-TBD06-201 Trial

David Holtzman, MD, MSc
Clinical Development Leader
Bill & Melinda Gates Medical Research Institute
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: _______________________________

☐ Receipt of honoraria or consultation fees: ___________________________

☐ Participation in a company sponsored speaker’s bureau: ______________

☐ Tobacco-industry and tobacco corporate affiliate: _________________

☐ Stock shareholder: _____________________________________________

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☐ Other: _______________________________________________________
# PAN-TB Target Regimen Profile

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

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

<table>
<thead>
<tr>
<th>TRP Criteria</th>
<th>PAN-TB TRP</th>
<th>Draft WHO Pan-TB TRP</th>
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<tr>
<td><strong>Indication</strong></td>
<td>No upfront DST required before treatment initiation</td>
<td>First-line treatment initiated even in absence of rapid DST</td>
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<td><strong>Duration</strong></td>
<td>≤3 months</td>
<td>≤4 months (minimal); ≤2 months (optimal)</td>
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<td><strong>Efficacy</strong></td>
<td>Non-inferior to DS-TB and DR-TB SoCs</td>
<td>Efficacy as good (minimal) or better (optimal) than current rifampicin-susceptible TB SOC treatment</td>
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</table>
| **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)
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)
PAN-TB Trial: Ph 2b/c 2-stage, de-risking design

**STAGE 1**
Regimen down selection

- **Randomization 1:1:1**
- **Eligible participants** 18-65 yrs w/ 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)

*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

**STAGE 2**
Duration selection
XBQS = DBQS or PBQS

- **Randomization 1:1:1:1:1:1**
- **DS-TB**
  Eligible participants 18-65 yrs w/ DS-TB including PLHIV

**ARM 1**
XBQS 2 months (N=70)

**ARM 2**
XBQS 2.5 months (N=70)

**ARM 3**
XBQS 3 months (N=70)

**ARM 4**
XBQS 3.5 months (N=70)

**ARM 5**
XBQS 4 months (N=35)

**ARM 6**
HRZE 6 months (N=35)

- MDR-TB
  XBQS MDR-TB Cohort 4 months (N=35)

**FOLLOW-UP 12 MONTHS POST RANDOMIZATION**

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)

*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
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
PAN-TB Collaboration Members

- Otsuka
- evotec
- Johnson & Johnson
- Bill & Melinda Gates Foundation
- GSK
- Bill & Melinda Gates Medical Research Institute
- TB Alliance