A randomized, active-control, open-label phase 2a trial evaluating the bactericidal activity, safety, and pharmacokinetics of TBA-7371 in drug-susceptible pulmonary tuberculosis


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CONFLICT OF INTEREST DISCLOSURE FORM

☒ I have no Conflict of Interest to report.

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  ☐ Spouse/partner: _______________________________________________
  ☐ Other: ________________________________________________________
New anti-TB drugs are needed to provide improved treatment options

TBA-7371 inhibits Mtb growth through non-covalent inhibition of Mtb decaprenylphosphoryl-β-D-ribose 2’-epimerase (DprE1), a key enzyme for mycobacterial cell wall arabinan biosynthesis and a validated Mtb drug target

- No approved DprE1 inhibitors currently, several in development

Anti-TB activity of TBA-7371 demonstrated in vitro and in vivo
- In vitro MIC$_{90}$ = 0.64 µg/mL (range 0.04 – 5.12 µg/mL) against 96 clinical DS- and DR-TB isolates
- Bactericidal in acute mouse TB infection model, less pronounced killing in chronic infection model
- Twice daily dosing showed improved bactericidal activity in acute mouse TB infection model
- Time above MIC demonstrated to be primary PK-PD driver

In vitro, TBA-7371 shows weak phosphodiesterase (PDE) 4, 5, 6, & 11 inhibition

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Mtb = Mycobacterium tuberculosis; MIC$_{90}$ = minimum inhibitory concentration for 90% of isolates; DS = drug-susceptible; DR = drug-resistant; PK-PD = pharmacokinetic-pharmacodynamic
Observations from TBA-7371 Phase 1 Trial Informed Phase 2a Trial Design

- 3-part, first-in-human, healthy volunteer trial conducted by TB Alliance
  - Single dose, multiple dose (14-day dosing), and drug-drug interaction
- Adverse events (AEs) were mild (Grade 1) or moderate (Grade 2)
- Common adverse events observed:
  - Eye-related: symptoms short in duration with resolution before next dose, not recurrent
    - Blurred vision
    - Altered color vision
    - Photophobia
  - Headache
  - Dizziness
  - Orthostatic tachycardia
  - Hypertension
- Eye symptoms found to be associated with $C_{\text{max}}$
  - As a potential AE mitigation strategy, split daily dosing was incorporated into the Phase 2a trial

$C_{\text{max}} = \text{maximum concentration}$
Gates MRI-TBD03-201: TBA-7371 Phase 2a EBA Trial Design

- 14-day inpatient study treatment, 28-day follow-up
- 4 sites in South Africa

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
  - Δ TTP in liquid culture
  - Δ Sputum LAM
- Safety assessments
  - AEs; eye symptoms, visual acuity & color vision; orthostatic vital signs, ECGs
- Intensive PK collected

© 2022, Bill & Melinda Gates Medical Research Institute. All rights reserved. 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
## Participant Disposition

- Screening and enrollment ran from January 2020 – August 2022 with pause for Covid-19 from March – July 2020
- High screen failure rates
  - Most often due to abnormal screening labs (LFTs, Hgb, UDS), positive SARS-CoV-2 PCR, or eye disease/visual deficits
- Good study treatment completion and trial retention rates across all 4 trial sites

### Table: Participant Disposition

<table>
<thead>
<tr>
<th></th>
<th>TBA-7371</th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100mg QD</td>
<td>100mg BID</td>
<td>200mg QD</td>
<td>100mg TID</td>
<td>400mg QD</td>
</tr>
<tr>
<td>Screened</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Screen failure</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Randomized</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Treated</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Completed treatment</td>
<td>15 (100)</td>
<td>14 (93)</td>
<td>14 (93)</td>
<td>15 (88)</td>
<td>15 (100)</td>
</tr>
<tr>
<td>Completed study</td>
<td>15 (100)</td>
<td>15 (100)</td>
<td>15 (100)</td>
<td>16 (94)</td>
<td>15 (100)</td>
</tr>
<tr>
<td>Included in mITT</td>
<td>15 (100)</td>
<td>15 (100)</td>
<td>15 (100)</td>
<td>17 (100)</td>
<td>15 (94)</td>
</tr>
</tbody>
</table>

*1 eligible participant withdrew from the trial prior to randomization.
†6 participants discontinued treatment: 3 due to adverse events, 2 due to positive SARS-CoV-2 result, 1 due to participant withdrawal
‡4 treated participants withdrew from the trial: 1 due to adverse event, 1 due to being lost to follow-up, 2 due to participant withdrawal

LFT = liver function tests; Hgb = hemoglobin; UDS = urine drug screen; QD = once daily; BID = twice daily; TID = thrice daily; mITT = modified Intention to Treat
Baseline Demographics & Disease Characteristics

- Baseline demographic characteristics and markers of TB disease severity & burden similar across all cohorts
- Higher degree of baseline TB disease severity and burden reflective of trial inclusion criteria enriching for individuals likely to have positive cultures for CFU analysis

<table>
<thead>
<tr>
<th></th>
<th>TBA-7371</th>
<th>HRZE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100mg QD (N=15)</td>
<td>100mg BID (N=15)</td>
</tr>
<tr>
<td>Age (mean, min, max)</td>
<td>26 (20, 35)</td>
<td>36 (20, 57)</td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>10 (67)</td>
<td>13 (87)</td>
</tr>
<tr>
<td>Cavity on CXR (n, %)</td>
<td>14 (93)</td>
<td>12 (80)</td>
</tr>
<tr>
<td>BL log_{10}CFU/mL (SD)</td>
<td>6.1 (1.71)</td>
<td>6.2* (1.21)</td>
</tr>
<tr>
<td>BL TTP (hours, SD)</td>
<td>102 (33.8)</td>
<td>110* (58.5)</td>
</tr>
<tr>
<td>BL log_{10}LAM (pg/mL, SD)</td>
<td>4.8 (1.10)</td>
<td>4.8* (1.52)</td>
</tr>
<tr>
<td>INH Resistant (n, %)</td>
<td>1 (7)</td>
<td>0</td>
</tr>
</tbody>
</table>

* 2 participants in 100mg BID cohort were removed from all efficacy analyses, 1 participant in 200mg QD cohort was removed from solid culture CFU analysis, and 1 participant in 100mg TID cohort was removed from liquid culture TTP analysis.

QD = once daily; BID = twice daily; TID = thrice daily; BL = baseline; CFU = colony forming units; TTP = time to positivity; LAM = lipoarabinomannan
Primary Analysis: Bactericidal Activity of TBA-7371 Greatest in 100mg TID Cohort

- Dose-dependent increase in bactericidal activity (BA) observed up to 300mg daily dose (100mg TID)
- Greater BA seen with dose fractionation
  / 100mg TID > 400mg QD
  / 100mg BID > 200mg QD
- Apparent “plateauing” of BA in QD dosing arms in 2nd week
  / 200mg QD & 400mg QD showed greater BA than 100mg BID & 100mg TID over 1st two days, lower BA by Day 14
- BA of HRZE cohort comparable to other EBA trials

### Mean Change from Baseline of Solid Culture Log_{10}CFU over 14-Day Treatment Period by Treatment Group (Select Cohorts)

<table>
<thead>
<tr>
<th>Day</th>
<th>TBA-7371 100mg QD</th>
<th>TBA-7371 100mg BID</th>
<th>TBA-7371 200mg QD</th>
<th>TBA-7371 100mg TID</th>
<th>TBA-7371 400mg QD</th>
<th>HRZE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0-2</td>
<td>Mean Δ log_{10}CFU/mL</td>
<td>0.02</td>
<td>-0.26</td>
<td>-0.33</td>
<td>-0.18</td>
<td>-0.28</td>
</tr>
<tr>
<td>Day 0-14</td>
<td>Mean Δ log_{10}CFU/mL</td>
<td>-0.46</td>
<td>-1.17</td>
<td>-0.94</td>
<td>-1.98</td>
<td>-1.29</td>
</tr>
</tbody>
</table>

CFU = colony forming units; (E)BA = (early) bactericidal activity; QD = once daily; BID = twice daily; TID = thrice daily
Similar Dose Differentiation in Bactericidal Activity w/ MGIT, Less Discrimination w/ LAM

• Same observation of greatest TBA-7371 BA in 100mg TID also seen with MGIT TTP and LAM

• Similar efficacy seen for 100mg BID, 200mg QD, and 400mg QD with MGIT and LAM

• Less discrimination with LAM: 100mg TID and HRZE had similar BA in sputum LAM, and minimally improved over other TBA-7371 cohorts

<table>
<thead>
<tr>
<th>Estimand</th>
<th>TBA-7371 100 QD</th>
<th>TBA-7371 100 BID</th>
<th>TBA-7371 200 QD</th>
<th>TBA-7371 100 TID</th>
<th>TBA-7371 400 QD</th>
<th>HRZE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Δ MGIT TTP Day 0-14 (hours)</td>
<td>28</td>
<td>39</td>
<td>57</td>
<td>86</td>
<td>57</td>
<td>198</td>
</tr>
<tr>
<td>Estimated* Mean Δ MGIT TTP Day 0-14 (hours/day)</td>
<td>2.3</td>
<td>4.1</td>
<td>3.3</td>
<td>5.6</td>
<td>3.8</td>
<td>13.9</td>
</tr>
<tr>
<td>Mean Δ Sputum LAM Day 0-14 (log₁₀ pg/mL)</td>
<td>-1.1</td>
<td>-1.3</td>
<td>-1.1</td>
<td>-1.6</td>
<td>-1.2</td>
<td>-1.5</td>
</tr>
</tbody>
</table>

* Estimated mean average daily change in MGIT TTP in hours/day derived from ANCOVA with treatment as a factor and baseline MGIT TTP as covariate.
Acceptable Overall Safety Profile, Increased AE Frequency in 400mg QD Cohort

- Increase in proportion of participants reporting AEs in 400mg QD cohort, including TBA-7371-related AEs
- Severe and serious AEs occurred infrequently in TBA-7371 cohorts, only 1 severe AE considered related
- Cardiac, visual, and headache AEs occurred more often in TBA-7371 cohorts than HRZE cohort

<table>
<thead>
<tr>
<th>Number of participants experiencing adverse event (n, %)</th>
<th>TBA-7371 100 QD (N=15)</th>
<th>TBA-7371 100 BID (N=15)</th>
<th>TBA-7371 200 QD (N=15)</th>
<th>TBA-7371 100 TID (N=17)</th>
<th>TBA-7371 400 QD (N=15)</th>
<th>All TBA-7371 (N=77)</th>
<th>HRZE (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Event (AE)</td>
<td>11 (73)</td>
<td>14 (93)</td>
<td>13 (87)</td>
<td>12 (71)</td>
<td>15 (100)</td>
<td>65 (84)</td>
<td>11 (73)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>6 (40)</td>
<td>11 (73)</td>
<td>7 (47)</td>
<td>6 (35)</td>
<td>3 (20)</td>
<td>33 (43)</td>
<td>8 (53)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>5 (33)</td>
<td>2 (13)</td>
<td>5 (33)</td>
<td>4 (24)</td>
<td>12 (80)</td>
<td>28 (36)</td>
<td>0</td>
</tr>
<tr>
<td>≥ Grade 3*</td>
<td>0</td>
<td>1 (7)</td>
<td>1 (7)</td>
<td>2* (12)</td>
<td>0</td>
<td>4 (5)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Study Drug-Related AE</td>
<td>5 (33)</td>
<td>3 (20)</td>
<td>7 (47)</td>
<td>9 (53)</td>
<td>15 (100)</td>
<td>39 (51)</td>
<td>7 (47)</td>
</tr>
<tr>
<td>Study Drug Discontinuation Due to AE*</td>
<td>0</td>
<td>1 (7)</td>
<td>1 (7)</td>
<td>1 (6)</td>
<td>0</td>
<td>3 (4)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Serious Adverse Event*</td>
<td>0</td>
<td>1 (7)</td>
<td>1 (7)</td>
<td>0</td>
<td>0</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>AE of Special Interest†</td>
<td>2 (13)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (7)</td>
<td>3 (4)</td>
<td>0</td>
</tr>
</tbody>
</table>

* One participant in HRZE cohort discontinued study treatment due to study drug-related AE (elevated ALT/AST). No participant in any TBA-7371 cohort had a study drug-related treatment discontinuation or SAE. One (1.3%) participant in 100mg TID cohort had 1 severe AE (Grade 3 orthostatic hypertension) assessed as related to TBA-7371. Three (20%) participants in HRZE cohort had 4 severe AEs assessed as related to HRZE (Grade 3 or 4 elevated ALT/AST).

† All three AEs of special interest were Grade 2 and assessed as related to TBA-7371: orthostatic hypotension (100mg QD and 400mg QD) and syncope (100mg QD)

QD = once daily; BID = twice daily; TID = thrice daily; AE = adverse event; SAE = serious adverse event; ALT/AST = alanine/aspartate aminotransferase
Identification of Therapeutic Window to Maximize Efficacy, Reduce Adverse Events

- Higher time over MIC$_{90}$, C$_{\text{min}}$, and AUC$_{0-24}$ correlated with greater ↓ in log$_{10}$CFU and ↑ in MGIT TTP
- Occurrence of tachycardia AEs and TBA-7371-related eye AEs correlated with higher C$_{\text{max}}$ values
  - Blurred vision, color vision change & photophobia most common
- PK-PD model projects:
  - Day 14 C$_{\text{min}}$ > 2500 ng/mL expected to achieve 90% of observed maximal BA
  - If C$_{\text{max}}$ <10,000 ng/mL, cardiac AEs expected to be <10% and eye AEs <25%

© 2022, Bill & Melinda Gates Medical Research Institute. All rights reserved. MIC = minimum inhibitory concentration; C$_{\text{min}}$ = minimum concentration; C$_{\text{max}}$ = maximum concentration; AUC = area under the concentration curve; PK-PD = pharmacokinetics – pharmacodynamics; CFU = colony forming units; TTP = time to positivity
Summary and Conclusions

• Significant, dose-dependent bactericidal activity of TBA-7371 was observed, providing further clinical validation of DprE1 as an anti-TB drug target

• Fractionated daily dose of 300mg (100mg TID) provided maximal bactericidal activity with an acceptable safety profile
  / Increased AEs and lower BA at 400mg QD produced less favorable benefit-risk profile for that dose

• Time over MIC, $C_{\text{min}}$, and AUC identified as the key PK drivers of efficacy and $C_{\text{max}}$ as the main PK driver for safety
  / Provides opportunity for further development of TBA-7371 focused on optimizing $C_{\text{min}}$ and exposure while minimizing $C_{\text{max}}$ to best balance efficacy and safety
  / Potential for long-acting injectable or extended oral release formulation development
Acknowledgments

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