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Session LBO2

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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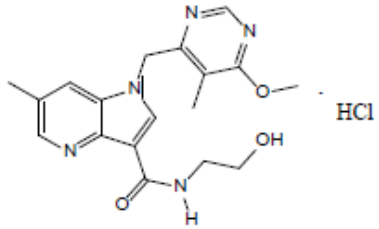
TBA-7371: Preclinical Background



- 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[1]
  - 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

1 - Makarov, 2009; Wang, 2013; Shirude, 2014; Makarov, 2014

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_{max}
  - As a potential AE mitigation strategy, split daily dosing was incorporated into the Phase 2a trial

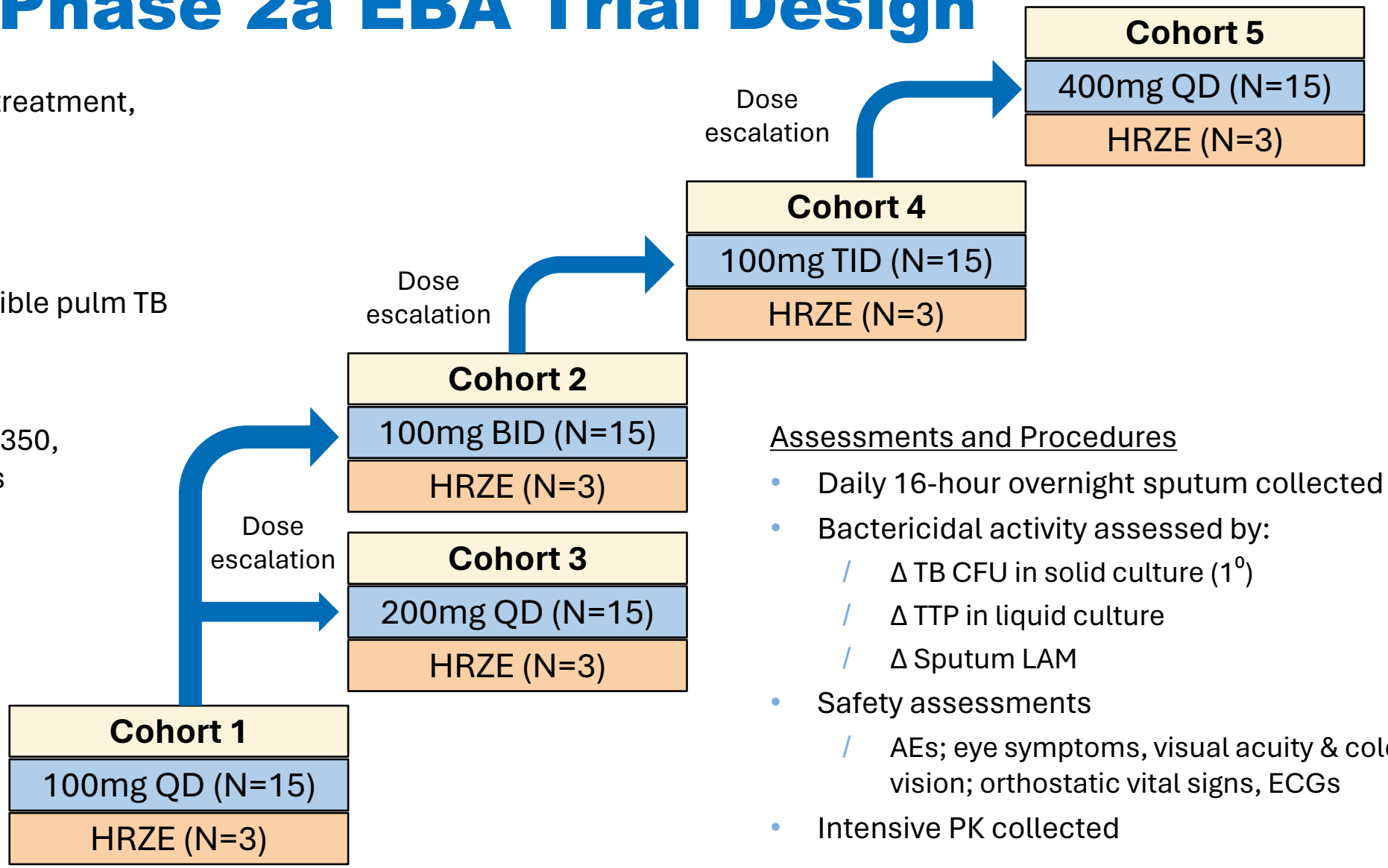
C_{max} = maximum concentration

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 (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

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

	TBA-7371					HRZE n (%)	Total n (%)
	100mg QD n (%)	100mg BID n (%)	200mg QD n (%)	100mg TID n (%)	400mg QD n (%)		
Screened	--	--	--	--	--	--	271
Screen failure	--	--	--	--	--	--	177* (65)
Randomized	15	15	15	17	16	15	93 (34)
Treated	15	15	15	17	15	15	92 (99)
Completed treatment	15 (100)	14 (93)	14 (93)	15 (88)	15 (100)	13 (87)	86† (94)
Completed study	15 (100)	15 (100)	15 (100)	16 (94)	15 (100)	12 (80)	88‡ (96)
Included in mITT	15 (100)	15 (100)	15 (100)	17 (100)	15 (94)	15 (100)	92 (100)

* 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

	TBA-7371					HRZE (N=15)
	100mg QD (N=15)	100mg BID (N=15)	200mg QD (N=15)	100mg TID (N=17)	400mg QD (N=15)	
Age (mean, min, max)	26 (20, 35)	36 (20, 57)	27 (20, 41)	33 (18, 50)	31 (19, 55)	27 (18, 50)
Male (n, %)	10 (67)	13 (87)	11 (73)	11 (65)	11 (73)	11 (73)
Cavity on CXR (n, %)	14 (93)	12 (80)	14 (93)	15 (88)	15 (100)	13 (87)
BL log_{10}CFU/mL (SD)	6.1 (1.71)	6.2* (1.21)	6.5* (1.05)	6.6 (0.67)	6.5 (1.11)	6.2 (0.69)
BL TTP (hours, SD)	102 (33.8)	110* (58.5)	83 (12.6)	92 (22.5)	93 (53.6)	104 (26.6)
BL log_{10}LAM (pg/mL, SD)	4.8 (1.10)	4.8* (1.52)	5.4 (0.85)	4.9 (0.77)	4.9 (1.18)	4. 8 (0.91)
INH Resistant (n, %)	1 (7)	0	1 (7)	0	1 (7)	0

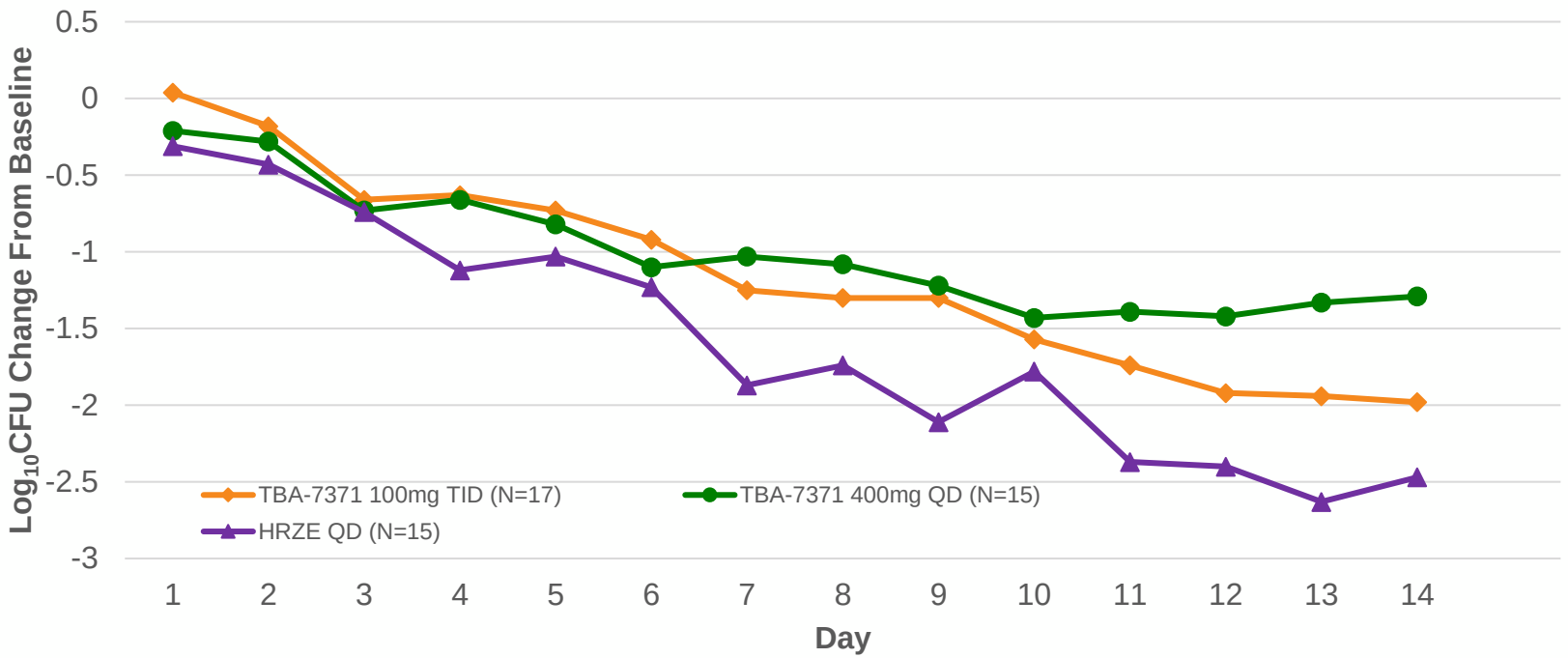
***** 2 participants in 100mg BID cohort were removed from all efficacy analyses, 1 participant in 200mg QD cohort was removed from solid culture CFU analysis, and 1 participant in 100mg TID cohort was removed from liquid culture TTP analysis

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)



Mean Log_{10}CFU Change from Baseline by Treatment Group over Day 0 to 2 and Day 0 to 14							
		TBA-7371 100mg QD	TBA-7371 100mg BID	TBA-7371 200mg QD	TBA-7371 100mg TID	TBA-7371 400mg QD	HRZE
Day 0-2	Mean Δ log_{10}CFU/mL	0.02	-0.26	-0.33	-0.18	-0.28	-0.43
Day 0-14	Mean Δ log_{10}CFU/mL	-0.46	-1.17	-0.94	-1.98	-1.29	-2.47

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

Estimand	TBA-7371 100 QD	TBA-7371 100 BID	TBA-7371 200 QD	TBA-7371 100 TID	TBA-7371 400 QD	HRZE
Mean Δ MGIT TTP Day 0-14 (hours)	28	39	57	86	57	198
Estimated* Mean Δ MGIT TTP Day 0-14 (hours/day)	2.3	4.1	3.3	5.6	3.8	13.9
Mean Δ Sputum LAM Day 0-14 (log_{10} pg/mL)	-1.1	-1.3	-1.1	-1.6	-1.2	-1.5

***** 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.

QD = once daily; BID = twice daily; TID = thrice daily; MGIT = Mycobacterial Growth Indicator Tube; TTP = time to positivity; LAM = lipoarabinomannan; ANCOVA = analysis of covariance

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

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

* 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).

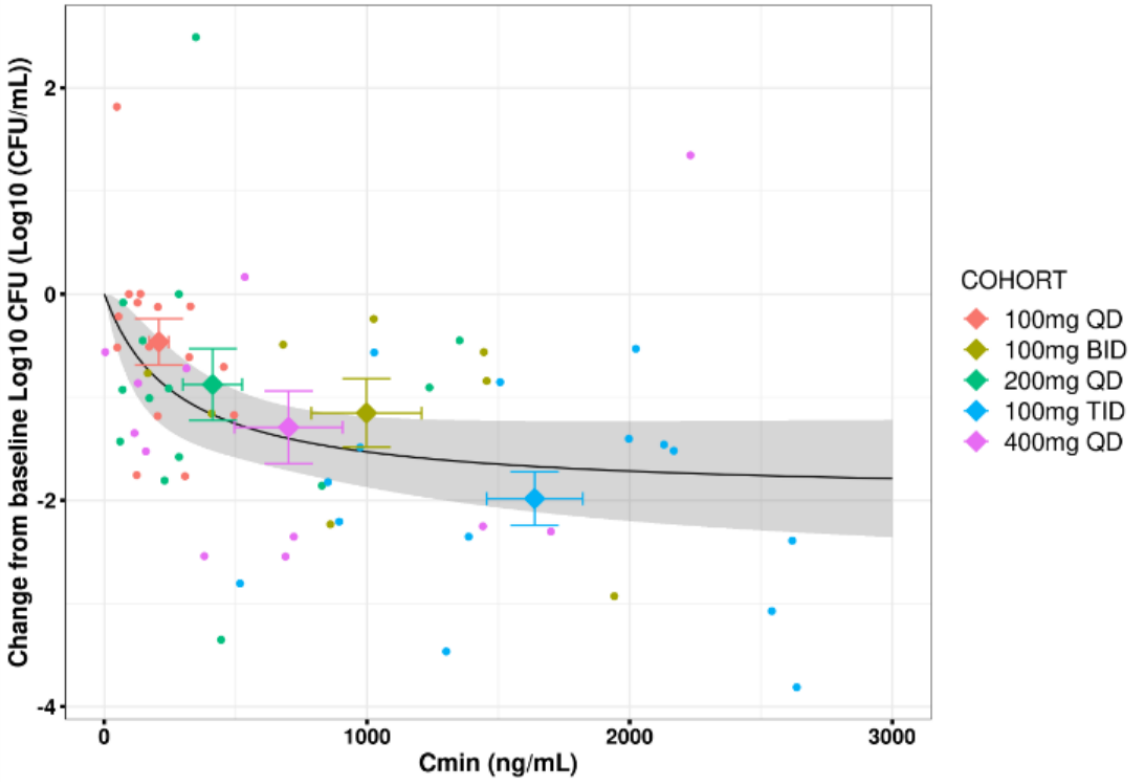
† All three AEs of special interest were Grade 2 and assessed as related to TBA-7371: orthostatic hypotension (100mg QD and 400mg QD) and syncope (100mg QD)

QD = once daily; BID = twice daily; TID = thrice daily; AE = adverse event; ; SAE = serious adverse event; ALT/AST = alanine/aspartate aminotransferase

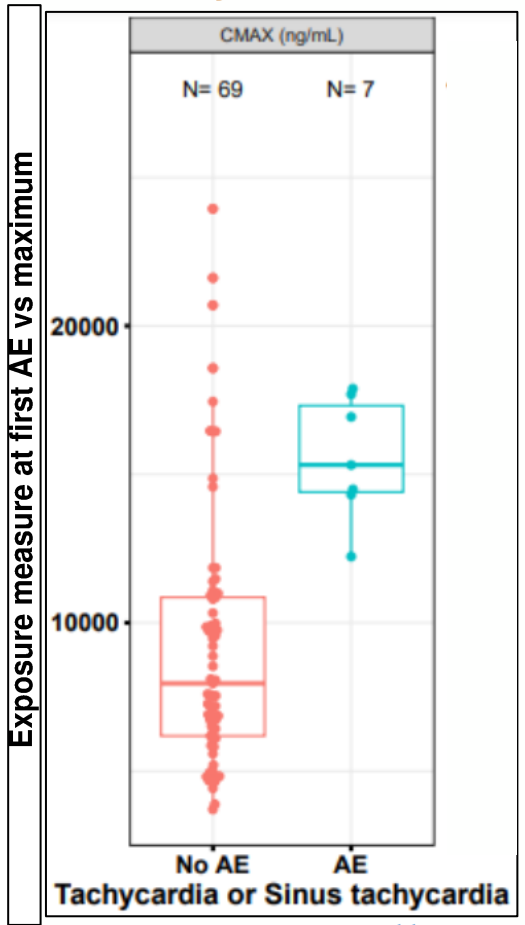
Identification of Therapeutic Window to Maximize Efficacy, Reduce Adverse Events

- Higher time over MIC_{90}, C_{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_{max} values
  - Blurred vision, color vision change & photophobia most common
- PK-PD model projects:
  - Day 14 C_{min} > 2500 ng/mL expected to achieve 90% of observed maximal BA
  - If C_{max} <10,000 ng/mL, cardiac AEs expected to be <10% and eye AEs <25%

Higher C_{min} Correlated with Greater Reduction in CFU



Higher C_{max} Correlated with Increased Occurrence of Tachycardia AE



MIC = minimum inhibitory concentration; C_{min} = minimum concentration; C_{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_{min}, and AUC identified as the key PK drivers of efficacy and C_{max} as the main PK driver for safety
  - Provides opportunity for further development of TBA-7371 focused on optimizing C_{min} and exposure while minimizing C_{max} to best balance efficacy and safety
  - Potential for long-acting injectable or extended oral release formulation development

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