Population pharmacokinetic modeling of TBA-7371 in healthy participants describes apparent auto-induction of clearance and predicts PK in participants with *Mycobacterium tuberculosis*.

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Introduction

- **Tuberculosis (TB)** is an infectious disease caused by *Mycobacterium tuberculosis* (Mtb) and typically affects the lungs (pulmonary TB).
  - In 2021, there were an estimated 10.6 million new incident cases of TB globally (6.7% co-infected with HIV), and 1.6 million people died from TB (WHO, 2022).
- **Current treatments for TB** have lengthy duration, involve multi-drug regimens, and often have toxicities. Poor adherence, advanced disease severity, significant mortality, and the emergence of drug-resistant strains all complicate the treatment and control of TB (Horsburgh et al., 2015; Zumla et al, 2015, TB Alliance 2015).
  - Current treatment shortcomings combined with prevalent and significant morbidity and mortality of TB make a strong case for the discovery and development of novel TB drugs and regimens.
- **TBA-7371** is a novel non-covalent inhibitor of Mtb decaprenylphosphoryl-β-D-ribose 2′-epimerase 1 (DprE1), an enzyme involved in mycobacterial cell wall synthesis.
  - TBA-7371 demonstrates potent anti-mycobacterial activity in vitro and in mouse models
  - TBA-7371 has been evaluated in a Phase 1 trial in healthy participants and a Phase 2a trial in participants with TB.

Objective

Develop a population pharmacokinetic (pop PK) model that can characterize the apparently complex PK of TBA-7371, in healthy participants (HP) and participants with active TB.

Data

- The data included in this analysis come from a Phase 1, single ascending dose, multiple ascending dose, and drug-drug interaction trial in healthy adults and from a Phase 2a, open-label, interventional, 5-cohort, 3-step dose escalation trial in participants with drug-sensitive pulmonary TB.
- The healthy adults from the Phase 1 trial received either a single dose of 100, 200, 400, or 800 mg or 14 doses of 100, 200, or 400mg once daily (QD) of TBA-7371.
- Participants with TB from the Phase 2 trial received 14 days of 100 mg QD, 100 mg twice daily (BID), 200 mg QD, 100 mg three times daily (TID), or 400 mg QD of TBA-7371.
- A total of 3819 PK samples (1485/2334 from HP/participants with TB) from 125 participants (49/76 from HP/participants with TB) were used in the pop PK analysis
- Median weight was 79/53 kg for HP/participants with TB

Methods

- Modeling and simulations were performed using NONMEM 7.5 and R 4.2.2
- **Population PK model-building** was originally performed on the Phase 1 data in HP
  - Multiple ascending dose Phase 1 data were observed to have apparent **auto-induction** of clearance as evidenced by accumulation of trough PK in the first few days only, followed by a decline in trough PK
  - The PK was described with a 2 compartment Pop PK model with first-order absorption, and parallel linear and non-linear elimination (via Michaelis-Menten kinetics)
  - A hypothetical enzyme compartment was used to drive auto-induction of the non-linear elimination.
    - This was modeled analogously to **indirect-response** modeling of any PD endpoint but was used to scale (induce) non-linear clearance.
  - A limited set of covariates were considered in the modeling:
    - The effect of body weight on distribution and elimination
    - The effects of dose and fed-vs.-fasted state on absorption rate and extent.
- **Simulations** were performed to explore potential dosing regimens for a Phase 2 trial in participants with active TB.
  - After Phase 2 data were available, predictions were compared with data as an external validation visual predictive check (VPC)
- The **Pop PK model** was updated to include both Phase 1 and Phase 2 data
  - The preliminary model structure was tested/confirmed
  - An additional covariate (HP vs participant with TB) was considered

Results (Preliminary Pop PK Model)

- The model schematic for the preliminary (and final) models is shown in Figure 1.
  - Pop PK of TBA-7371 in HP was well characterized using a 2-compartment model with:
    - First-order absorption
      - Absorption was slower for higher doses and slower for Fed vs Fasted
    - Parallel linear and non-linear elimination (via Michaelis-Menten kinetics)
    - Standard allometric exponents on all CL and volume parameters
    - A hypothetical enzyme compartment to drive auto-induction of the non-linear elimination.
- The individual fit for participants in the 400 mg QD cohort is shown in Figure 2. This highlights the induced clearance as well as the model's ability to characterize the PK

Figure 1. PK model schematic

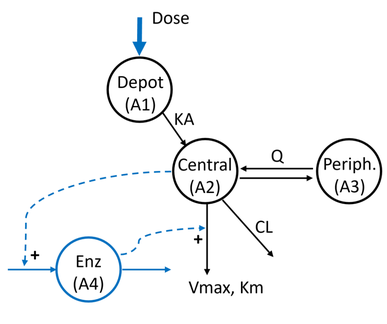
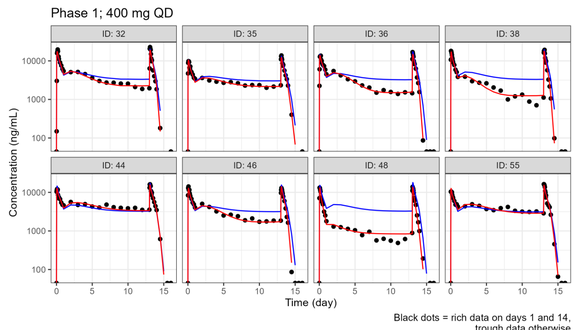


Figure 2. Preliminary PK fit for individuals in the 400 mg QD cohort



The ordinary differential equations (ODEs) that describe the model:

- $d/dt(A1) = -KA*A1$
- $d/dt(A2) = KA*A1 - Kel*A2 - K23*A2 + K32*A3 - Vmax*\mathbf{A4}*CC/(KM + CC)$
- $d/dt(A3) = K23*A2 - K32*A3$
- $d/dt(A4) = Kenz*(1 + Emax*CC/(EC50 + CC)) - Kenz*A4$

Where:

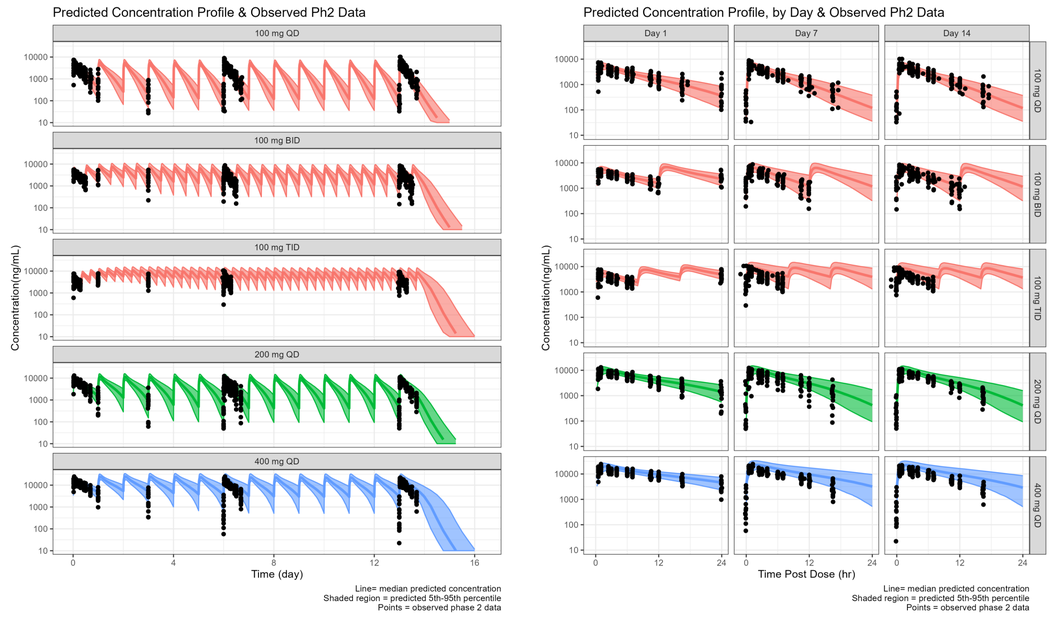
- $A4(t=0) = 1$ (Initial Enz value)
- $A1(0) = A2(0) = A3(0) = 0$
- $CC = A2/V2$
- $Kel = CL/V2$
- $K23 = Q/V2$; $K32 = Q/V3$

V2 and **V3** are the central and peripheral volumes of distribution; **Enz** (A4) is the hypothetical enzyme amount and provides the autoinduction level relative to a starting value of 1; **Vmax** is the maximum non-linear elimination rate when Enz is at normal levels (Enz = 1). **KM** is the concentration of TBA-7371 where half-maximal nonlinear elimination rate occurs; **Kenz** is the zero-order formation rate of enzyme and the first-order enzyme elimination rate constant (due to assumption of that initial Enz=1 at steady state); **Emax** is the maximum effect TBA-7371 has on the rate of formation of the enzyme; **EC50** is the concentration of TBA-7371 of half maximal effect of TBA-7371 on formation rate of the enzyme.

Results (Simulations)

- **Prospective doses**/schedules for the Ph2a study were simulated
  - 100, 200 & 400 mg QD,100 mg BID, and 100 mg TID
- **Assumptions**:
  - The PK of TBA-7371 for participants with TB was simulated under the assumption that it was similar to PK in healthy participants (for similar body weight (WT), dose, and fed/fasted state)
  - Participants with TB have typical WT: 55kg
    - (Assumed; for lower- and middle- income countries vs typical WT of 80 kg for HP in the USA)
  - Fasted
- When the Phase 2 data became available, these simulations were compared with data as an external VPC (Figure 3). The Phase 2 data were generally well predicted.

Figure 3. Preliminary PK model simulations compared with Phase 2 data



Results (Final Pop PK Model)

- The preliminary model was fit to the combined Phase 1 and Phase 2 data
  - **Model structure** and assumptions were re-tested and confirmed
    - Figure 1 provides the final model schematic
    - HP vs participant with TB was tested as a covariate on absorption and distribution parameters
- **Absorption**
  - Slower for HP (vs participant with TB)
    - KA for HP 40% [32, 48; 95% CI] of that for participant with TB
  - Slower for fed (vs fasted)
    - KA for fed 4.7% [3.9, 5.5] of that for fasted
  - Slower for higher doses
- **Central Volume** (V2)
  - Lower for HP (vs participant with TB)
    - V2 for HP 75% [69, 81] of that for participant with TB
- **Saturable elimination and auto-induction**
  - Vmax 2700 µg/hr [2060, 3530]
    - Max pathway elimination of 65 mg/day initially
    - Increased via induction (up to ~8x, depending on sustained concentration levels)
- A **VPC** (Figure 4) shows that the model fits the Phase 2 data well

Figure 4. VPC of Phase 2

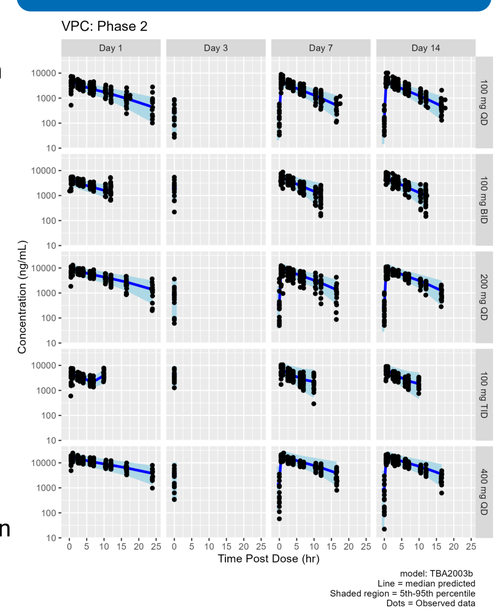


Table 1. Final Pop PK model parameters

Parameter	Value	95% CI
KA[a] (1/hr)	3.39	2.92 – 3.93
CL[b] (L/hr)	1.09	0.970 – 1.22
V2[c] (L)	24.5	22.8 – 26.4
Q[b] (L/hr)	3.12	2.4 – 4.05
V3[b] (L)	9.31	8.06 – 10.8
VMAX (µg/hr)	2700	2060 – 3530
KENZ (1/hr)	0.0114	0.0096 – 0.0136
EMAX	7.11	4.15 – 12.2
EC50 (ng/mL)	5720	2310 – 14100
KM (ng/mL)	1130	863 – 1480
KA~Dose/200	-0.226	-0.378 – -0.734
KA~FED	0.0470	0.0391 – 0.0549
KA~HP	0.401	0.324 – 0.477
V2~HP	0.748	0.686 – 0.810

Random Effect	Value	95% CI	Shrinkage
VMAX (%CV)	41.4	34.2 – 47.5	7.3%
CL (%CV)	43.1	34.6 – 50.1	9.9%
V2 (%CV)	20.6	16.6 – 24.0	7.5%
KA (%CV)	42.9	32.1 – 51.5	20%
corr(VMAX,CL)	-0.213	-0.393 – -0.0327	
corr(VMAX,VC)	0.396	0.221 – 0.571	
corr(CL,VC)	0.153	-0.0556 – 0.373	

Residual Error	Value	95% CI	Shrinkage
PROP (%CV)	18.0	16.5 – 19.4	5.1%
ADD (µg/L)	27.0	17.7 – 33.8	5.1%

a = Typical KA for participant with TB administered 200 mg TBA-7371 in a fasted state. Note: All participants with TB were black/African descent, so participant with TB, race and body weight may be confounded
b = Typical values for participant of WT = 70 kg; with standard allometric scaling
c = Typical V2 for participant with TB and WT = 70 kg;

Conclusions

- Pop PK of TBA-7371 in healthy participants was well characterized using a 2-compartment model with first-order absorption, parallel linear and non-linear elimination and a hypothetical enzyme compartment to drive auto-induction of the non-linear elimination.
  - The hypothetical enzyme and auto-induction was modeled as an indirect response, with feedback to the nonlinear elimination rate
- The preliminary pop PK model described the PK in participants with active TB well.
- The updated pop PK model described the PK in healthy participants and participants with active TB as well.
  - A covariate analysis found small differences in PK between healthy participants and those with TB.
- The model was deemed fit for the purposes of
  - Informing selection of dosing and schedules for further study
  - Providing individual exposure measures for analysis of exposure-response

WHO 2022.WHO.Global Tuberculosis Report 2022. Geneva: World Health Organization. Available from: https://www.who.int/publications/i/item/9789240061729; **Horsburgh et al. 2015 Horsburgh** CR, Jr., Barry CE, 3rd, Lange C.Treatment of Tuberculosis. N Engl J Med. 2015;373(22):2149-60; **Zumla et al. 2015** Zumla A, Chakaya J, Centis R, et al.Tuberculosis treatment and management--an update on treatment regimens, trials, new drugs, and adjunct therapies. Lancet Respir Med. 2015;3(3):220 34. ;**TB Alliance.** Inadequate Treatment. Available from: https://www.tballiance.org/why-new-tb-drugs/inadequate-treatment