

# One-Dose Efficacy of Long-Acting Injectable Diarylquinoline in Mouse Model of TB Preventive Therapy

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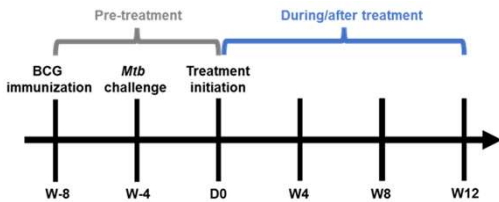
## BACKGROUND

- Use of long-acting injectables (LAIs) has the potential to simplify tuberculosis preventive therapy (TPT), addressing issues such as pill burden and adherence.
- Bedaquiline (BDQ) is a key sterilizing drug in new, shorter regimens for treatment of rifampin-resistant TB and is being studied in novel regimens for drug-susceptible TB. Thus, it could fill the unmet need for a short-course “pan”-TPT option.
- BDQ and other diarylquinolines (DARQs) have physico-chemical and pharmacokinetic (PK) properties amenable to LAI formulations.
- TBAJ-876 is a next-generation DARQ with greater potency and lower potential to prolong the QTc interval than BDQ.
- The aim of this work was to evaluate the PK and efficacy of novel TBAJ-876 formulations prepared by single phase spray drying as LAIs in a validated mouse model of TPT.

## METHODS

- Three reproducible TBAJ-876 LAI formulations (A-C) with 80% (w/w) API and differing excipients were identified.
- Single intramuscular (IM) dose PK profiles were determined in BALB/c mice at doses of 250, 500 and 1000 mg/kg.
- Based on results showing the 250 mg/kg dose produced plasma concentrations  $\geq 36$  ng/mL (the  $EC_{50}$  in a mouse model of active TB) at 8 wks post-dose, formulation B was tested for efficacy in a validated BALB/c mouse model of TPT (Fig. 1) at single IM doses of 62.5, 125 and 250 mg/kg, aiming to maintain plasma concentrations  $\geq 36$  ng/mL for 4-8 wks. Formulations A and C were tested at a single IM dose of 125 mg/kg (n=5 mice/arm). IM dosing was on Day 0 (D0).
- Negative controls went untreated. Positive controls received daily (5 days/wk) oral isoniazid-rifampine (1HP), oral BDQ, or oral TBAJ-876 for 4 wks (D0-W4).

Fig. 1: TPT Model, Drug administration and CFU sampling



## Long-acting injectable formulations for TBAJ-876 demonstrate encouraging exposure profiles and efficacy in a mouse model of tuberculosis preventive therapy

- Bacterial colony-forming units (CFU) were enumerated monthly by quantitative cultures of lung homogenates on 7H11 agar supplemented with 0.4% activated charcoal. Group mean CFU counts were analyzed using 1-way ANOVA.
- Plasma TBAJ-876 concentrations were measured using a validated LC-MS/MS method. Median plasma AUC was calculated using the trapezoid rule.

## RESULTS – TBAJ-876 Plasma Pharmacokinetics

- Each TBAJ-876 LAI formulation demonstrated a sustained release profile in uninfected BALB/c mice in the pilot PK study (Fig. 2) and in infected mice in the efficacy study (Fig 3). Wk 12 results are pending.
- In the pilot PK study, median TBAJ-876  $C_{max}$  was  $<1$   $\mu\text{g/mL}$  for each formulation and dose; and plasma concentrations were  $\geq 36$  ng/mL for  $\geq 8$  wks after 250, 500 and 1000 mg/kg doses of each formulation. Mice receiving formulation A at 1000 mg/kg developed thigh swelling suggesting an excipient-mediated reaction, and required euthanasia. Other doses and formulations were well tolerated.
- In the efficacy study, median plasma  $AUC_{0-6wks}$  values were 143, 206 and 391  $\mu\text{g}\cdot\text{h/mL}$  and plasma concentrations were  $\geq 36$  ng/mL for 4, 6 and  $>6$  wks after the 62.5, 125 and 250 mg/kg doses of formulation B, respectively.

Fig. 2: TBAJ-876 LAI Plasma PK after IM injection in uninfected BALB/c mice

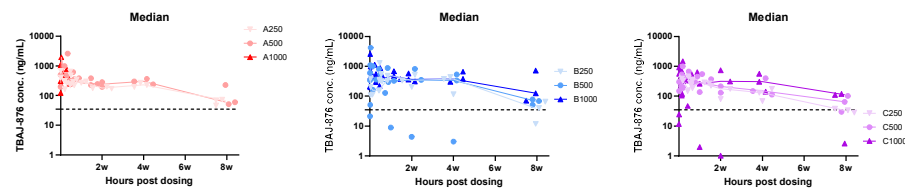
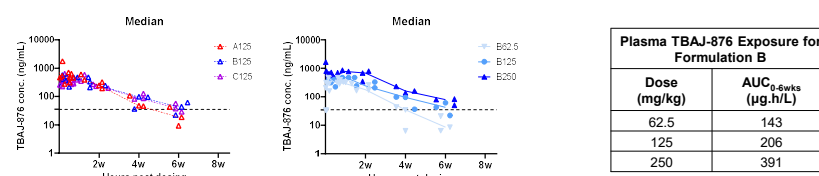


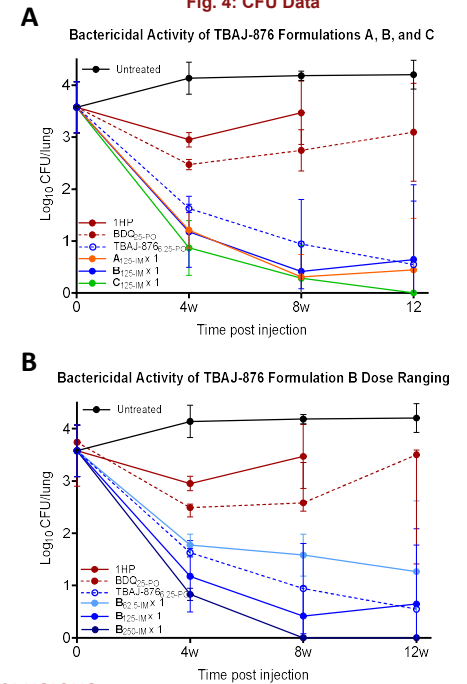
Fig. 3: TBAJ-876 LAI Plasma PK after IM injection in infected BALB/c mice



## RESULTS – TPT Efficacy Study

- All LAI formulations had similar bactericidal activity that was superior to 1HP ( $p < 0.0001$ ) and oral BDQ ( $p < 0.0001$ ) and at least similar in magnitude to the same total TBAJ-876 dose given orally over 4 wks (e.g., 125 mg/kg LAI vs. 6.25 mg/kg orally) (Fig. 4A). Activity was dose-dependent for formulation B (Fig. 4B), and was bactericidal at least as long as plasma concentrations were  $\geq 36$  ng/mL. IM doses  $\geq 125$  mg/kg led to negative 12w cultures, except for 1 mouse ea. in arms A, B.

Fig. 4: CFU Data



## CONCLUSIONS

- These data provide proof-of-concept for a highly efficacious pan-TPT regimen comprised of a single IM dose of a TBAJ-876 LAI formulation.
- Further preclinical development including cross-species PK studies to enable human dose projections, evaluation of injection site safety/tolerability, and assessment of chemistry and manufacturing controls (CMC) procedures is warranted.