Eugene Sun, Senior Vice President of Research and Development at TB Alliance
Rajneesh Taneja, Vice President of Pharmaceutical Product Development at TB Alliance
Long-acting injection formulations for TB drugs

"Science is not advanced in a linear way … this is a watershed [moment]."

Development of LAIs for TB

Represents a confluence of fortuitous circumstances.

- Formulation technology has advanced.
- Success of Cabenuva for HIV perhaps sparked competitiveness.
- Robust TB drug pipeline and high level of collaboration in the TB field.
- Multiple drugs have suitable physicochemical properties for LAI.

TB Alliance (TBA) approach.

- LTBI is the most obvious early target. A single LA injection would enable diagnosis and treatment on the same day/visit.
- TBD treatment requires more drugs and longer duration (≥3 drugs as LAIs). Oral lead-in (OLI) + single-dose (SD) LAI or LAI (3 drugs) + second injection in 2 months.
- Select TB drugs could have other applications. Examples include: BDQ for Leprosy and Q-203 for Buruli ulcer.

Compound and technology platform selection

Searched the TBA portfolio for compounds with suitable LAI properties.

- Compounds searched (19 in Discovery; 11 in P1 to P3; and 3 marketed products).
- Focused on TBAJ-587 (P1), TBAJ-876 (P2), Q-203 (P2), BDQ (P3), Pretomanid (Market).
- Considerations for compound selection: Crystalline; Low aqueous solubility; High potency; Long PK half-life; Low local irritation potential (Int J Tuberc Lung Dis, 2018); No pre-existing resistance.

Focused on two LA technologies that are available, affordable, and adoptable.

- Nanoparticle suspension: Ready-to-use suspensions (no reconstitution); Drug release ≥ 8-12w per dose; Each dose ≤ 2 x 3mL IM injections; Administration via ≤25G needle; Stability ≥2y at room temp.
- Implant: Biodegradable, subdermal, rod-shaped device (L ≤ 40mm and OD ≤ 2mm); Reasonable COGs for formulation and insertion; Non-surgical insertion (similar to subdermal contraceptive implants); Stability ≥ 2y at room temp.
- Commercialization considerations for technology selection: Established technology with approved products; Max possible drug load and lowest drug excipient load; Simple equipment and manufacturing process; Established CMC regulatory pathways; Easy to scale up and transfer to global partners/CDMOs.

Collaborative development of LAI formulations

PK modeling informs the most desirable release profile.

- In silico simulation of TBAJ-876 PK (Certara). OLI + SD LAI (4, 8, or 12w release) vs OLI + QD oral

Efficacy studies of individual formulations are needed to determine target exposures.

- A standard target cannot be used across LAIs (e.g., 3xMIC or ECOFF).

Translation to humans.

- High plasma concentration and tissue penetration are promising LAI properties for translation to larger animals (Kovarova, 2022).

Collaborative programs.

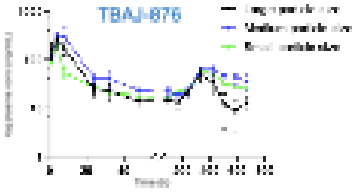
External Partner	LA Technology	Compound
Southern Denmark University (SDU) Bill & Melinda Gates Foundation (BMGF))	NP suspension	TBAJ-587 TBAJ-876 Pretomanid Q-203*
Inflammasome Therapeutics BMGF	Subdermal rod implant	TBAJ-876 Pretomanid
University of Liverpool Johns Hopkins University (JHU)	Solid drug NP	TBAJ-876
University of North Carolina NIH	In-situ forming implant	TBAJ-587 TBAJ-876

***PK analysis performed by DAIDS.**

Status of LAI diarylquinolines (TBAJ-587 and TBAJ-876)

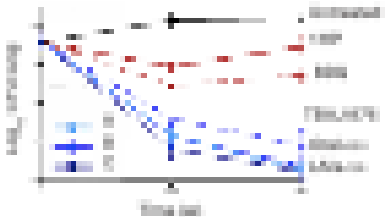
SDU/BMGF program. Sustained release of three LAI TBAJ-876 formulations in vivo (PBP World Meeting 2024).

- Generated three NP suspension TBAJ-587 & TBAJ-876 formulations using established, scalable technology.
  - Small, medium, and large particle size.
- Single-dose PK in rats.
  - TBAJ-876 formulations are expected to sustain desirable Css >2m. **Dose and formulation optimization under discussion.**
  - Encouraging preliminary PK data for TBAJ-587 (week 2 and 4)



Univ of Liverpool/JHU program. Proof of concept for single-dose LAI TBAJ-876 IM formulation as an efficacious pan-TPT regimen (CROI 2024).

- Identified three reproducible solid drug NP TBAJ-876 formulations.
  - Formulations A, B, and C comprise 80% TBAJ-876 plus different excipients.
- PK of TBAJ-876 IM formulations in mice (A, B, C at 250, 500, and 1000 mg/kg).
  - Plasma concentration > EC50 for ≥ 8 weeks after a single dose of each formulation.
- Efficacy of TBAJ-876 IM formulations in a BALB/c TPT mouse model (TBAJ-876 IM x1 vs QD oral 1HP, BDQ, or TBAJ-876 x 4 weeks).
  - TBAJ-876 IM Formulations A, B, and C (125 mg/kg)
    - **Similar bactericidal activity across TBAJ-876 IM formulations.**
    - **TBAJ-876 LAIs > oral 1HP ($p<0.0001$) and BDQ ($p<0.0001$), and at least similar to the equivalent total oral TBAJ-876 dose given over 4 weeks.**



  - TBAJ-876 IM Formulation B (62.5, 125, and 250 mg/kg).
    - **Dose-dependent bactericidal activity of Formulation B.**
    - **Further pre-clinical development is warranted:** Cross-species PK for human dose projections, safety and tolerability, and assessment of CMC procedures.