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Long-acting Bedaquiline

Considerations for LA TB drug formulations

Possible indication for LTBI and TBD treatment.

- Once-off or intermittent TPT.
- Opportunity to "shorten" TBD treatment by incorporating LA formulation(s) into the continuation phase.
- Role as a companion drug for either indication.

Need to understand acceptability of IM and SC injections.

- Important to consider patient preference studies and patient reported outcomes.

Potential to improve adherence and easy to integrate into established ART service delivery.

BDQ as a LA formulation for TPT

Favorable CMC properties for LA.

- Low aqueous solubility (0.0002 mg/mL).
- Low plasma clearance (0.04 L/h/kg).
- Efficacy at low drug exposures (MIC for *Mtb* = 0.03 mcg/mL).

Could lead to a pan-TB indication as monotherapy.

- Active against DS and DR forms of TB.
- A single IM injection would ensure TPT completion.
- Could further shorten TPT – a single injection at a single visit vs SOC (3HP or 1HP).

Oral formulation has a favorable side effect profile.

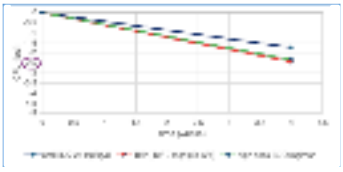
- Years of data are reassuring regarding QTc prolongation.

Target formulation would have ambient storage conditions.

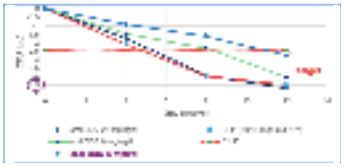
Existing data on LA BDQ in a TPT mouse model

Bactericidal effect is similar to oral SOC (1HP).

- High-exposure BDQ vs 1HP (Kaushik 2019):
  Similar CFU decline at 4 weeks (-2.5 $\log_{10}$CFU).



- Low-dose BDQ vs 1HP (Kaushik 2021):
  CFU decline matched 1HP at 12 weeks (-2.5 $\log_{10}$CFU).
  Estimated target exposure: 0.3 mcg/mL over 3 months.



Uncertainties in preclinical data limit translation to humans

Pharmacokinetic uncertainties.

- Preclinical target exposure (0.3 mcg/mL) is based on oral BDQ AUC x 2 (correction for M2 metabolite).
  - Translational PKPD modeling of 1HP suggests that change in concentration over time also drives CFU decline, not AUC alone (Radtke et al 2021).
  - LAI and oral formulations may have different effects despite similar average concentration due to different PK profiles and M2 contribution.

Pharmacodynamic uncertainties.

- What is the contribution of the M2 metabolite?
- Does short-term CFU decline translate to long-term sterilization?

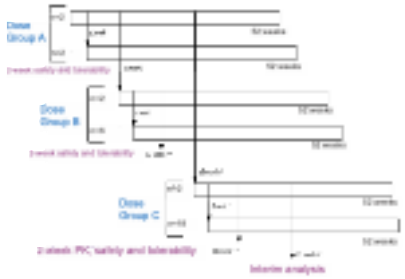
- What is the contribution of exposure beyond 3 months? A unique consideration given the long BDQ half-life.

Ongoing translational PKPD modeling is needed.

- Refine the target PD endpoint and target dose based on that endpoint.

LAI BDQ will soon be in Phase 1

Single ascending-dose study design:



- PK, safety, & tolerability of IM dosing in 32 healthy volunteers.
- Lower-dose PK assessed before proceeding with the ascending dosing strategy.
- Planned interim analysis at Group C enrollment to inform next steps.

Considerations for future use of LAI BDQ for prevention and treatment

- **Improve the reliability of PD models**, our assumptions, and the translatability of preclinical models to humans.
- **Consider new chemical entities** in our pipeline for early development of LA/ER formulations.
- **Pursue collaborations** to develop two LAI drugs for TBD treatment (as has been done for HIV).
- **Engage TB stakeholders** to understand patient, provider, and National TB Program views on the role of LAI for prevention and treatment indications.