Vivian Cox MD, Clinical Lead of R&D for TB at Jannsen

"Current Status of Janssen LA/ER TB pipeline"

Background – LAI formulations of tuberculosis (TB) drugs.

Uses.

- Latent TB infection (LTBI) treatment vs incorporation into treatment regimens for TB disease (TBD).
- Companion LA drug for prevention or treatment.

Potential for improved adherence.

- Critical to consider the acceptability of injectable agents (IM or SC), especially in younger children who benefit from TPT.
- Patient preference studies and patient reported outcomes should be incorporated into clinical development.

Possible TB indications.

- Single-dose or intermittent TPT would fit well into current service delivery models for ART.
- Shortened-course TBD treatment (e.g., oral lead-in with culture conversion, then one or two doses of LAI formulation).

Key attributes for an ideal parenteral LTBI regimen (TPP).

- Activity against drug-susceptible (DS) and drug-resistant (DR) TB.
- Single injection (volume 2mL; ≤25gauge needle) or implant.

Considerations for development of LAI Bedaquiline (BDQ) for TPT.

Favorable Chemistry Manufacturing and Controls (CMC) properties.

- Low aqueous solubility (0.0002mg/mL); Low plasma clearance (0.04mcg/h/kg); and Low MIC for *Mtb* (0.03mcg/mL; High efficacy at lower drug exposures).

Activity against DS and DR-TB.

- Potential for a "pan-TPT" indication as monotherapy.

Potential for a one-time IM injection.

- TPT completion rate ensured with a single clinic visit; could be easily integrated into existing service delivery.

Oral formulation has extensive safety evidence.

- Reduced concern about QT prolongation and other side effects from earlier studies.

LA formulation is targeted for ambient temperature storage conditions (TPP).

- No cold chain required.

Target BDQ exposure in humans is not known (lowest dose that yields an adequate CFU decline).

- Preclinical studies of oral BDQ used a CFU target equivalent to 1HP (-2.5 log reduction at 12 weeks).
  - Low-dose oral BDQ (5mg/kg) and 1HP (SOC) have similar bactericidal effects at 12 weeks.
  - Estimated target BDQ exposure is 0.3mcg/mL over 3 months.
- Translatability of preclinical data to humans is uncertain.

Uncertainties in preclinical data mitigate the translatability of PKPD to humans.

Preclinical PK uncertainties.

- Target BDQ exposure (0.3mcg/mL) is based on **oral BDQ AUC x 2** to correct for the M2 metabolite.
- Additional drivers of CFU decline may warrant consideration.
  - Translational PKPD modeling of HP and rifapentine showed change in concentration over time drives CFU decline, not only AUC.
- Similar average concentrations of LAI and oral formulations might have differential effects due to distinct PK profiles and M2 metabolite contributions.

Preclinical PD uncertainties.

- M2 metabolite contribution in humans.
- Impact of short-term CFU decline on long-term sterilization.

- Contribution of BDQ exposure beyond 3 months to long-term success (BDQ has a uniquely very long half-life).
- Where does the CFU target (-2.5 log reduction at 12 weeks) fit as a target at "treatment end" (1M, 3M, 6M or longer).

Ongoing translational PKPD modeling is needed.

- To refine the target PD endpoint and corresponding target dose.

TB prevention pipeline – single-dose LAI BDQ.

P1 single ascending dose study will begin Summer 2024.

- PK, safety, and tolerability of a LAI BDQ formulation (single ventrogluteal IM dose) in 32 healthy participants.
- Dose will be escalated between Groups A, B, and C.
  - Safety and tolerability of each dose will be assessed at 2 weeks before moving to higher doses.
- Planned interim analysis of all three groups at 23 months.

Development priorities for LAI formulations of TB drugs.

- Improve the reliability of PD models and translatability from preclinical models to humans.
- Consider new chemical entities in the development pipeline for early development of a LA/ER formulation.
- Collaborations are needed to advance two-drug TPT and combination TBD treatment.
  - Rich collaborations have enabled co-formulation of two drugs in the LA HIV space.
- Engagement with diverse TB stakeholders.
  - Input from patients, providers, and National TB programs on the role of LAIs for TB prevention and treatment would set the scene for successful product introduction for either indication.