Marc Baum, Oak Crest Institute of Science

"TAF implants – Phase 1 Studies" (NIH and collaboration with CAPRISA).

Preclinical studies across implant technologies suggest TAF (double TFV prodrug) implant efficacy for HIV prevention, but heterogenous toxicity.

TAF implants under development by different research groups.

- Reservoir-type polymeric implants: Silicone (Oak Crest); Polyurethane (Northwestern University); Biodegradable polycaprolactone (RTI International).
- Titanium osmotic pump implant (Intarcia Therapeutics).
- Refillable nanofluidic type implant (Houston Methodist Research Institute).

Oak Crest implant.

- Flute-like shaped reservoir device with an exterior silicone sheath containing TAF micro-tablets.
- TAF is released exclusively through delivery channels; release kinetics are determined by the number and diameter of channels and the exterior polymer coating.
- Implant dimensions are based on current contraceptive implants (Human-sized [L 40mm; OD 2.5mm] and mouse-sized [L 10mm; OD 2.5mm]).
- Fabricated using long-term, implantable-grade materials.

Overview of preclinical findings.

- Good-to-high efficacy for HIV prevention.
  Refillable nanofluid implant and biodegradable PCL implant demonstrated rectal and vaginal protection from simian HIV in NHPs.
- Variable local toxicity.
  Expected foreign body reaction and capsule formation (Oak Crest implant) to severe inflammation and tissue necrosis at the implant sit
  This was not observed with their implants, but by others. They did not observe any serious safety signals at TAF release rates below 1 mg/d.

In vivo studies in mice, dogs, and sheep indicate local tolerance of the Oak Crest implant at the predicted target TAF release rate for HIV prevention.

TAF implant PK in beagle dogs (10-year-old study).

- TAF release rate of 0.25 mg/d is expected to achieve prophylactic TFV-DP concentrations.

Local drug exposure in mice after implant removal.

- Semi-quantitative MALDI-MS study of TAF metabolism products (TAF, Met-X, Met-Y, TFV, TFV-MP, and TFV-DP).
- All molecules were present in tissue samples from the implant site, but in different amounts and spatial distributions.
- ***A potential source of toxicity could not be determined*.**

Dose-escalation studies of the TAF implant in mice, dogs, and sheep.

- No apparent local toxicity in mice and sheep at the TAF release rates studied.
- Larger-ranging study in dogs found no toxicity issues at the low end of TAF release rates.
  Began to see local toxicity at extremely high TAF doses (7-8mg/d; well above what would be considered for use in humans)
- ***No concerning local toxicity findings at lower TAF release rates.***

Summary of key preclinical learnings and questions for clinical studies.

Learnings from preclinical studies.

- No concerning drug-related local effects with TAF release rates < 1mg/d in three species.
- *In vivo* release rates of TAF implants from the same batch varied across species.
  *Highlights the importance of preclinical model selection and the difficulty in predicting human release rates.
- Mechanistic PK modeling of implant TAF release in dogs and mice showed unexpected apparent bioavailability >1 relative to IV – suggests a saturable process?

- Predicted target human TAF dose is 0.25mg/day – no other approved drug can compete.

Questions to be answered by clinical studies.

- *in vivo* TAF implant release kinetics and long-term implant stability.
- Do TAF implant release rates correlate with PBMC TFV-DP concentrations? What release rates achieve predicted PBMC TFV-DP concentrations? How does that relate to TAF/TFV plasma concentrations?
- Determine local and systemic safety. Is local tolerance related to local drug exposure?
- **Feasibility of >Q1year TAF implant.**

CAPRISA 018: P1/2 study of Oak Crest TAF implant for HIV PrEP.

Safety, acceptability, and PK of TAF implant (0.25mg/d) in African women at low risk.

- Trial design, implementation, regulatory work, and analysis conducted locally in South Africa (led by CAPRISA).
  Oak Crest collaborated on implant configuration and manufacture in cGMP.
- Study design incorporates stringent local safety vigilance.
  Group 1 lead-in, weekly protocol safety team review, DSMB review prior to Group 2, and safety checkpoints up to one year of use.
- Group 1 (lead-in, n=6): safety and PK to day 28 on product.
  Full safety evaluation before progression to Group 2.
- Group 2 (n=24): randomized, placebo-controlled (4:1) study of safety and PK up to week 52 on product.
  A/B one implant; C/D two implants.
  Safety evaluated at week 12 (to allow use to week 24) and week 24 (to allow use to week 48).

Summary.

- Successful first clinical trial of the Oak Crest TAF implant for HIV prevention – more to come.
  - Accomplished TAF delivery in a clinical trial for an entire year and answered all the key questions – only ISL has done this prior to us, but did not go for a full year.
- CROI 2024 presentations.
  - P1 safety, tolerability and PK of TAF implants in African women: game changers in prevention of HIV and STIs (oral abstract #123).
  - CAPRISA 018 trial: Acceptability of TAF implants for HIV PrEP in African Women (poster #1136).