Next-generation Islatravir/Etonogestrel/Ethinyl Estradiol MPT Intravaginal Ring

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BACKGROUND

- Condoms are the only available multipurpose prevention technology (MPT) but eliciting poor user adherence and require partner cooperation.
- Current intravaginal ring (IVR) technologies have limited ability to achieve target drug release kinetics and do not elicit 100% drug release.
- Unmet Need: (1) Long-acting MPTs with high user adherence and acceptability for all women. (2) IVRs with the ability to fine-tune drug release and provide complete drug release.

INNOVATION

3D-printed geometrically complex IVRs for the prevention of HIV and unplanned pregnancy

Structural and geometric complexity elicits tunable and complete drug release.

Continuous Liquid Interface Production (CLIP™) for 3D-Printed IVRs

- CLIP implements computer aided design (CAD) and a photoactive resin that solidifies upon selective UV exposure via free radical photopolymerization mechanisms.
- Incorporation of oxygen to inhibit polymerization, creating a "dead zone" for continuous and layerless production.

Geometrically complex IVR CAD design

- CLIP can overcome limitations with manufacturing due to its wide design space eliminating the ring's solid cross-section for targeted, tunable, and complete drug release.

METHODS

Solid human-sized IVRs were manufactured using CLIP 3D-printing and Islatravir (EFdA), ethnoestrone (ENG), and ethinyl estradiol (EE) were formulated individually or in combination (Fig.1)

RESULTS

First-in-line 3D-printed MPT IVR demonstrates sustained drug release and was well-tolerated in sheep and macaques

- 3D CLIP IVRs were loaded with EFdA, ENG, and EE (3.7 wt%, 0.19 wt%, and 0.04 wt%, respectively) for in vitro release study in SVF (sheep pH 7). Release samples were collected and drugs quantified by HPLC. All drugs exhibited low burst in the first 24 h (<10%) and sustained zero order release over 180 day (Fig.2).
- MPT IVRs were administered to 4 female sheep (4.03-6.48 mg/kg EFdA, 0.2-0.3 mg/kg ENG, and 0.05-0.07 mg/kg EE) for a 21-day pharmacokinetic study. Plasma, vaginal biopsies, and fluids were collected (Fig.3).
- Macaque-sized IVRs (25 mm OD 6.0 mm CSD) with Islatravir were administered to 3 female non-human primates for a 30-day pharmacokinetic study. Plasma, PBMCs, vaginal biopsies, and fluids were collected. (Fig.4).

CONCLUSIONS

- Plasma EFdA levels (1-10 ng/mL) were maintained over 14 days in sheep and 28 days in macaques.
- EFdA-TP levels were above oral benchmark of 50-100 fmol/10^6 PBMCs in macaques (green shaded region in Figures 6 & 7).
- MPT IVRs were well-tolerated in sheep and VEC cultures (Figures 8).
- Plasma ENG/EE levels were maintained over 14 days and comparable to NuvaRing levels.