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**Press Briefing: Monday, May 24, 11:15 a.m., ET**

**Microbicides that do More than Gel: Vaginal Rings, Tablets and Films**

### **Vaginal ring with two anti-HIV drugs nears benchmark for clinical testing of its safety in women**

An intravaginal ring formulated with two anti-HIV drugs – dapivirine and maraviroc – can deliver therapeutic levels of both drugs for as long as a month, according to laboratory studies. Based on these and other findings, the ring is a good candidate for testing in clinical safety trials, reported Andrew Loxley, Ph.D., from Particle Sciences, Inc., of Bethlehem, Pa. Vaginal rings are small, flexible devices designed to allow for the slow delivery of a drug or multiple drugs over time. As a potential method for preventing sexual transmission of HIV, rings are seen as an alternative to microbicide gels that must be used every day or at the time of sex. Dapivirine, also known as TMC-120, belongs to a class of anti-HIV drugs called non-nucleoside reverse transcriptase inhibitors that bind to and disable HIV's reverse transcriptase enzyme, a protein that HIV needs to make more copies of itself. Maraviroc is a type of drug called an entry inhibitor that prevents HIV from entering a healthy cell. The current study indicates that inside the vaginal ring, the two drugs work well side-by-side with the activity and structure of each drug not being affected by the presence of the other. High amounts of each drug were still being released from the ring at 15 days and continued to be delivered for up to 30 days. Even after being stored in harsh conditions for six months, both drugs maintained their stability and structure, suggesting that under more normal temperature conditions, the rings remain viable for a year or even longer. The rings are made of a type of plastic called ethylene-vinyl acetate copolymer (EVA) and share many of the same properties as rings currently used for contraception. They are manufactured using standard processes called hot metal extrusion and injection molding. If clinical trials prove the rings safe and effective, manufacturing and scale-up should be relatively easy, say the researchers who made the rings with the support of the International Partnership for Microbicides located in Silver Springs, Md.

***Presentation: Monday, May 24, 9:45 a.m., Rooms 403-405***

***Session 22 – Oral Abstracts: Preclinical studies of Ring and Film Formulations (9:30-11 a.m.)***

***(Abstract #185)***

***Combination Ethylene Vinyl Acetate Intravaginal Vaginal Rings Containing Dapivirine and Maraviroc***

(see following page for full abstract)

Abstract # 185

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**Background:** Microbicides have historically been incorporated into daily use vaginal gels. We report here the development of combination intravaginal rings (IVRs), based on ethylene-vinyl acetate copolymer (EVA), containing the microbicides Dapivirine (Tibotech, 25 mg) and Maraviroc (Pfizer, 200 mg or 300 mg). These IVRs are designed for 30 day use and are considered a viable non-coitally dependent dosage form for the prolonged release of Dapivirine and Maraviroc.

**Methods:** IVRs were prepared by hot-melt batch mixing or hot-melt extrusion, followed by injection molding. Durometer hardness, and flexibility were measured and IVRs were assayed by HPLC. To determine API-release kinetics, IVRs were incubated in 100 mL isopropanol-water mixture at 37 °C. The medium was replaced periodically over 30 days to maintain sink conditions, and aliquots were analyzed by HPLC. The stability of compounded API/EVA blend, and finished IVRs, was tested for up to six months at 40 °C.

**Results:** IVRs have similar properties to currently marketed contraceptive IVRs (4 mm cross-sectional diameter and 54 mm overall diameter, shore hardness 20D – 25D, and 0.74 – 1.07 N bending force). API assays show ~100% recovery of both APIs, with minimal related substances formed during processing. Dapivirine release follows approximately first-order kinetics, whereas after an initial peak release, Maraviroc follows close to zero-order release kinetics. The *in vitro* release of each API is loading-dependent (linearly in the case of Maraviroc), independent of the loading of the other API, and relatively insensitive to EVA type. The day 15 *in vitro* release of APIs from optimally formulated IVRs is on the order 500 mg/d (Dapivirine) and > 1000 mg/d (Maraviroc). IVRs and EVA/API compound was stable at 40 °C for at least three and six months respectively. IVRs made with pilot-scale equipment showed equivalent properties and performance to lab-scale IVRs.

**Conclusions:** A viable, non-coitally dependent Dapivirine/Maraviroc combination microbicide device has been developed as an alternative to daily use vaginal gels, and the IVRs have similar physical properties to marketed contraceptive devices, assuring good tolerability. The production processes are facile and scalable, and can be performed at any suitably equipped location. The *in vitro* API release from the IVRs is considered sufficiently high over a 30 day period to be practical, and clinical trials for these devices are planned for 2010.