INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

Dapivirine Vaginal Ring: Recent Research and Next Steps

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Developing HIV Prevention Products for Women worldwide

Why New HIV Prevention Products for Women?

- Currently available options have not slowed the epidemic among women
  - HIV/AIDS leading cause of death globally among women of reproductive age (15-44)
- Discreet products they can use without male partner consent
- No one product will solve the HIV epidemic
- Women need multiple prevention options that make sense for their lives

IPM's Mission

To develop new products that will give women the tools they need to prevent HIV and protect their sexual and reproductive health

About us

- Nonprofit product development partnership
- Founded in 2002
- Offices in the United States, South Africa and Belgium

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Why Microbicide Vaginal Rings?

- **Long-acting and discreet: monthly or longer**
  - Woman-controlled
- **Easy to use, comfortable**
  - Flexible, can be self-inserted
  - High self-reported willingness-to-use
- **Suitable for developing countries**
  - Relatively low manufacturing cost
  - Stored at room temperature; no cold chain
  - Good safety and acceptability data
- **Potential for ARV drug combinations**

Monthly Dapivirine Ring

- **Flexible silicone vaginal ring developed by IPM**
- **Slowly releases ARV dapivirine**
  - Good safety profile
  - IPM holds exclusive worldwide rights through Janssen Sciences Ireland UC
- **1st long-acting method shown to reduce women's HIV risk** in two Phase III trials: The Ring Study and ASPIRE

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IPM 032/DREAM

- **Phase IIIb open-label follow-on trial to IPM 027/The Ring Study** taking place at 5 research centers in South Africa and 1 in Uganda
- **Objectives:** Continue evaluating safety, and assess adherence
- **Trial design:**
  - All participants receive the active dapivirine ring
  - Trial visits take place monthly up to 3 months after enrollment, then quarterly
- **Timeline**: Interim results as of Sept. 2017; trial ends Dec. 2018
- **Enrollment:** Former Ring Study participants who tested HIV-1 negative and were not pregnant at the time of screening were eligible
  - 985 women screened
  - 900 women enrolled

Timeline

- **Feb. 2016:** The Ring Study reported primary results
- **July 2016:** DREAM initiated
- **Dec. 2017:** DREAM completed enrollment
- **Mar. 2018:** Interim DREAM results reported
  - Data as of Sept. 2017
- **Dec. 2018:** DREAM participant follow-up expected to be completed

Interim Results: Demographics

DEMOGRAPHICS AT ENROLLMENT		n (%)
Age (years)	Median (IQR)	29 (25,34)
Age range (years)	18-21	31 (3.4%)
	>21-25	214 (23.8%)
	>25-30	301 (33.4%)
	>30	354 (39.4%)
Marital status	Married	123 (13.7%)
	Single	724 (80.4%)
	Other	53 (5.9%)
Partners	Main partner	876 (97.3%)
Presence of STI		163 (18.1%)

Interim DREAM Results: Safety

SAFETY	n (%)
Participants reporting any adverse event	461 (51.3%)
Adverse events related to product	3 (0.3%)
Serious adverse events • All unrelated to product	11 (1.2%)
Positive pregnancy tests	15 (1.7%)

ADVERSE EVENTS RELATED TO PRODUCT	3 (0.3%)
Suprapubic Pain, Grade 1	1 (0.1%)
Vulvovaginitis, Grade 2	1 (0.1%)
Vulvovaginal Pain, Grade 1	1 (0.1%)

Interim DREAM Results: Adherence

- **Ring residual levels of ≤ 23.5 mg dapivirine indicate at least some ring use**
- **Proportion of returned rings containing ≤ 23.5 mg dapivirine increased:**
  - 83% in The Ring Study
  - 96% in DREAM

Interim DREAM Results:
HIV-1 Incidence

- **Observed HIV-1 incidence**: 1.8 per 100 PY (95% CI: 0.9-3.2)
- **Expected HIV-1 incidence** in modelled placebo group: 3.9 per 100 PY (95% CI: 2.9-4.9)
  - Based on bootstrap analysis of 10,000 samplings
- HIV-1 incidence of 1.8 per 100 PY observed in DREAM did not occur in these 10,000 samplings.

Key Interim Results and Conclusions

Interim results from DREAM and HOPE were nearly identical:

- Similar safety profile to Phase III trials
- Based on dapivirine ring residual levels, adherence to ring use increased from The Ring Study (83%) to DREAM (96%)
- Observed HIV-1 incidence rate in DREAM is 54% lower than the estimated placebo rate estimated by bootstrap modelling
- These data suggest that ring use and risk reduction increase when participants know the Phase III safety and efficacy results

The DREAM Team

- All participants of IPM 027 and IPM 032

- IPM research center team members at:
  - Madibeng Centre for Research (MCR)
  - MatCH Research Unit (MRU)
  - Qhakaza Mbokodo (QM)
  - MRC/UVRI Uganda Research Unit on AIDS
  - Desmond Tutu HIV Foundation Masiphumelele
  - Ndlovu Care Group (NCG)
- IPM's partners, vendors and collaborators
- Belgium team of Janssen Sciences, Ireland UC
- IPM donors
- IPM staff

Next Steps

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What's Next for the Dapivirine Ring?

Regulatory Path

EMA, SAHPRA (S. Af.), FDA and African NRAs

Public Health Path

Open-label studies to provide the ring to women, collect safety data, and understand and support consistent use

Potential Access

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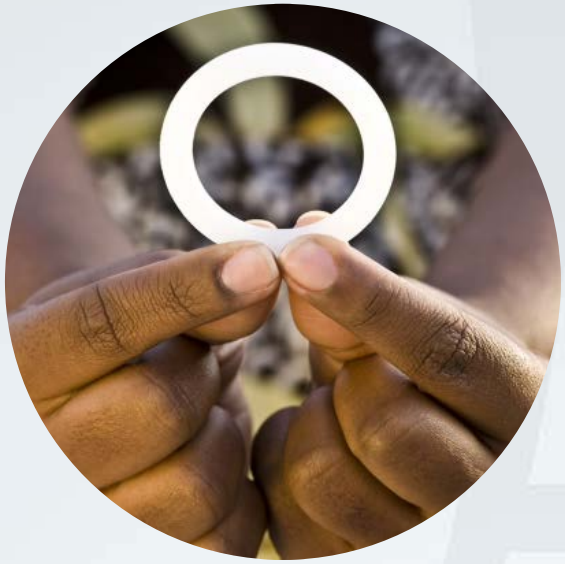
Path to Regulatory Approval

IPM's role: Dapivirine ring's regulatory sponsor

- Ensures all preclinical, clinical and pharmaceutical quality/chemistry, manufacturing and controls (CMC) data meet regulatory requirements
- Formally applying for dapivirine ring approval through European, US and African regulatory authorities



Approval pathway for new HIV prevention drug more complex than for a drug already approved for treatment (e.g., oral Truvada)

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Regulatory Path

European Medicines Agency (EMA)

- Scientific opinion on a product's use in developing countries (via Article 58 procedure)
- Submitted June 2017; currently under review

World Health Organization (WHO)

- EMA Article 58 intended to facilitate process, reduce time to potential PQ
- Standard WHO prequalification (PQ) review can take 6+ months

African National Regulatory Authorities (NRAs)

- Following potential WHO PQ, first submissions to Kenya, Malawi, Rwanda, Tanzania, Uganda, Zambia, Zimbabwe

South African Health Products Regulatory Authority (SAHPRA)

US Food and Drug Administration (FDA)

Why WHO prequalification?

- ✓ Evaluates whether a drug meets global standards for quality, safety, efficacy
- ✓ Many African NRAs consider EMA's scientific opinion and WHO PQ status in their own reviews
- ✓ Could facilitate policy development

Public Health Path

- **REACH adolescent study planned for 2018:** Assess safety of and adherence to dapivirine ring and oral PrEP among 300 young women ages 16-21 in Kenya, South Africa, Uganda and Zimbabwe *(MTN-034)*

- **Ring use study ongoing:** Understand ring use and assess adherence patterns in ASPIRE and HOPE *(MTN-032)*
- **Pregnant and breastfeeding women**: Multiple safety studies planned for 2018-9 to be led by MTN
- **R&D for new women-initiated products continues**

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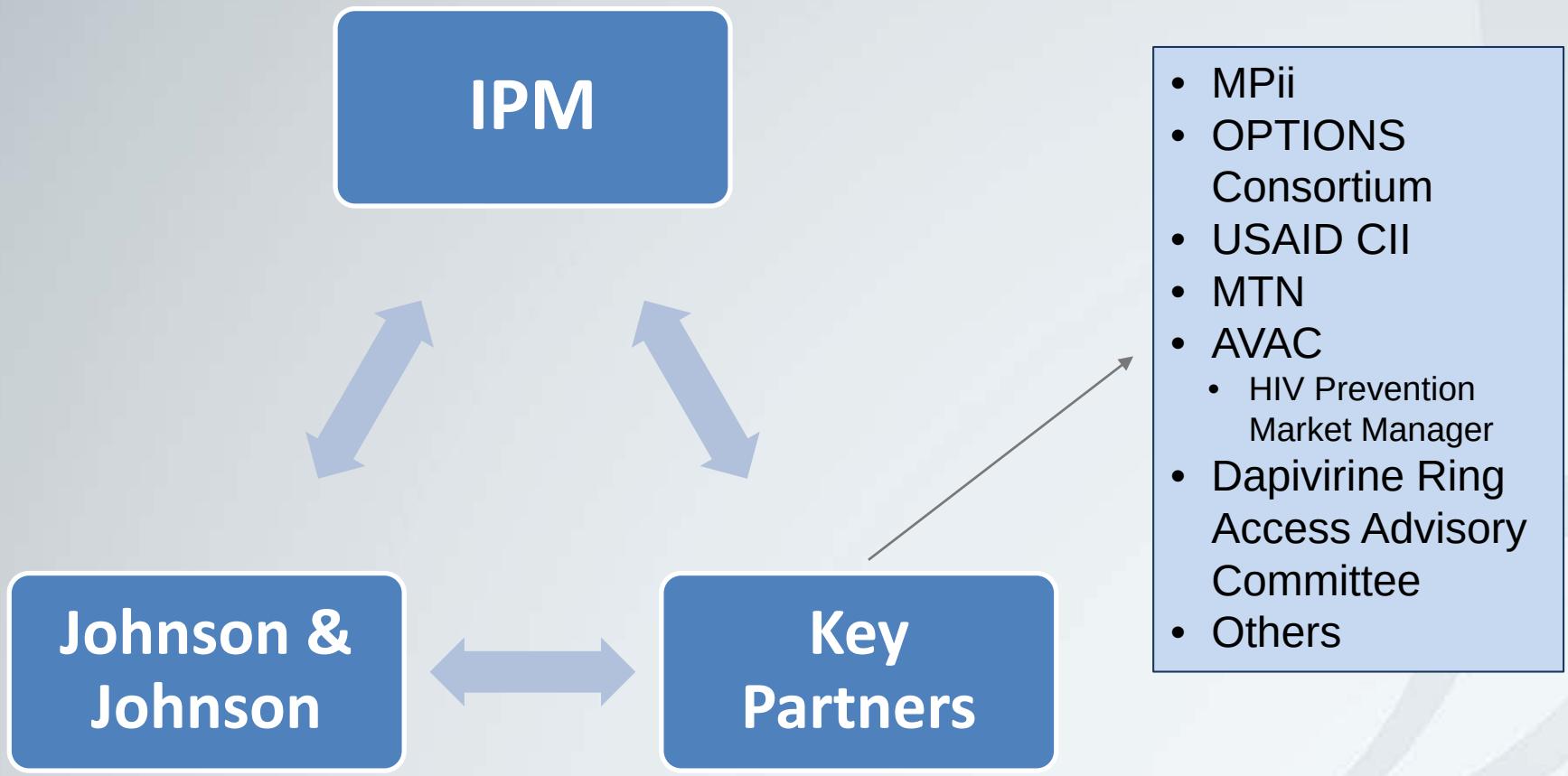
Access Collaboration to Drive Successful Product Introduction



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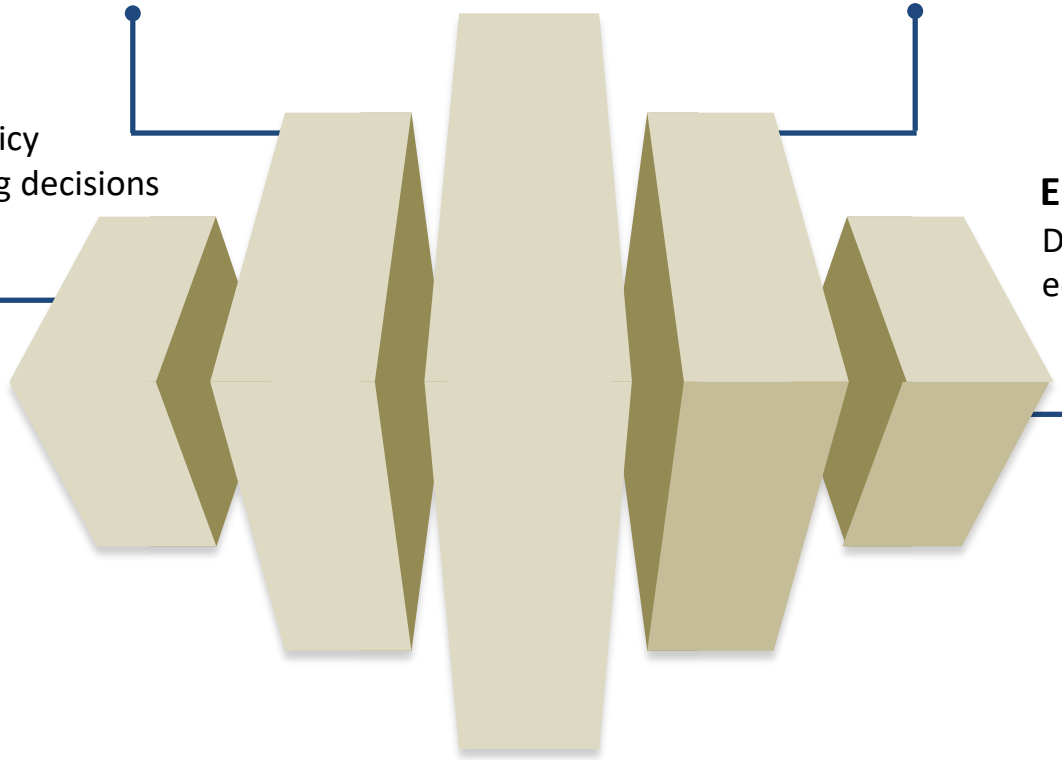
Access Strategy: Goals

Clinic/Public Hospital Access
Drive ring awareness/education to encourage provider referrals to patients

Operations & Logistics
Deliver the ring to clinics/hospitals via approved channels and partnerships

Government & Donor Support
Include the ring in policy guidelines and funding decisions

End-User Access
Drive women's awareness, education and use of the ring



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