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Dapivirine Vaginal Ring-004 Overview and Regulatory Pathway

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MTN-042 Stakeholder Meeting

Developing HIV Prevention Products for Women worldwide

Scope of Presentation

- Monthly Dapivirine Vaginal Ring
- Phase III to Phase IIIb
- Phase III Results
- Phase IIIb Open-Label Interim Results
- Pregnancy Outcome Data
- Regulatory Pathway

Monthly Dapivirine Vaginal Ring

- IPM holds exclusive worldwide rights for Dapivirine through Janssen Sciences Ireland UC
- Flexible silicone vaginal ring developed by IPM
- Sustained-release of NNRTI ARV drug dapivirine locally to site of potential HIV infection during vaginal sex
  - Minimal systemic absorption
  - Favorable safety profile
- 1st long-acting method shown to reduce women's HIV risk in two Phase III trials

  - IPM 027/The Ring Study and MTN-020/ASPIRE

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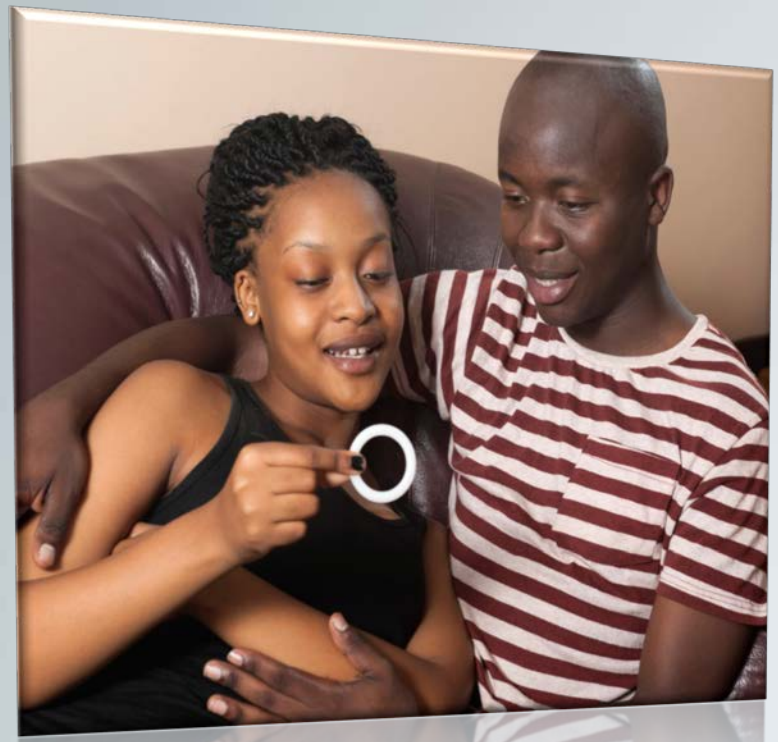
Dapivirine Vaginal Ring: Acceptability



Among women

- Comfortable
- Not felt during daily activities

Among men

- Most did not feel during sex
- No impact on sexual pleasure

Most favorable characteristics to women

- Potential for HIV infection risk reduction
- Does not alter sexual experience
- Continuous use for one month

Involving male partners

- Important that partner accepts ring

Phase III to IIIb (OLE)

IPM 027

A Multi-Centre, Randomised, Double-Blind, Placebo-Controlled Safety and Efficacy Trial of a Dapivirine Vaginal Matrix Ring in Healthy HIV-Negative women

IPM 027

Amendment 5

(all ongoing participants on active drug)

IPM 032 (DREAM)

A follow-on, Opel Label Trial to Access ***Continued Safety*** of and ***Adherence*** to the Dapivirine (25mg) Vaginal Ring-004 in Healthy, HIV- Negative Women

MTN-020

A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase 3 Safety and Effectiveness Trial of a Vaginal Matrix Ring Containing Dapivirine for the Prevention of HIV-1 infection in Women

MTN-025 (HOPE)

An Phase 3B Open-Label Follow-on Trial to Assess the ***Continued Safety*** of and ***Adherence*** to a Vaginal Ring Containing Dapivirine in Women

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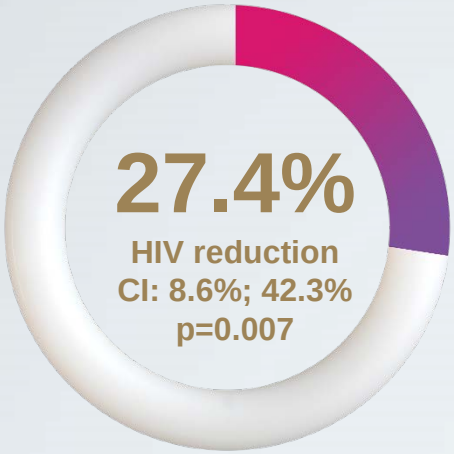
Phase III: Integrated Efficacy Dapivirine Vaginal Ring

Well-tolerated and reduces HIV-1 infection risk in two independent well-controlled Phase III clinical trials, statistically significant in women 18-45 years in sub-Saharan Africa by approximately 30% relative to placebo



- ***3.7% HIV-1 incidence/100 PY*** in dapivirine ring group
- ***5.0% HIV-1 incidence/100 PY*** in placebo ring group

p < 0.05, statistically significant

Based on HIV-1 Seroconversion (HIV Rapid Test Result)

Phase III: Integrated Safety Dapivirine Vaginal Ring

- Majority of reported adverse events (AEs) were Grade 1(mild) or Grade 2 (moderate) in intensity
  - proportions were similar between dapivirine and placebo ring groups
- No product related SAEs and permanent product discontinuation due to an AE was rare
- No clinically relevant differences between groups in terms of impact on vaginal pH and flora
- NNRTI Resistance:
  - similar proportions between groups in terms of mutations associated with resistance to nevirapine and efavirenz
  - not fully characterised, analyses ongoing

Phase IIIb OLE Enrollment

	IPM 032/DREAM	MTN-025/HOPE
Number of research centres	6	14
Countries	South Africa and Uganda	Malawi, South Africa, Uganda, Zimbabwe
Enrolled	941	1441

- Majority of women from South Africa
- Major reasons for screening failures are:
  - HIV-positive
  - Currently pregnant/planning to become pregnant or breastfeeding
  - Not available for all visits
  - Not using contraception

Interim Results:
HIV-1 Incidence

	IPM 032/DREAM	MTN-025/HOPE
HIV-1 seroconversions	11 in 623 PY	12 in 616 PY
HIV-1 incidence	**1.8 per 100 PY** **95% CI: 0.9-3.2**	**1.9 per 100 PY** **95% CI: 1.2-3.0**
Based on 10,000 bootstrap samples, HIV-1 incidence in the modelled placebo group is	3.9 (95% CI: 2.9-4.9) per 100 PY	4.1 (95% CI 3.2-5.1) per 100 PY

Data cut-off 29 Sep '17 and 06 Oct '17 respectively

The HIV-1 incidence of 1.8 per 100 PY observed in DREAM, and 1.9 per 100 PY observed in HOPE, did not occur in these 10,000 samplings

OLE Conclusions

- Interim results indicate a similar safety profile as in Phase III trials
- Based on dapivirine ring residual levels, adherence to ring use appears to be higher
- Observed HIV-1 incidence rate has been half of the expected placebo rate estimated by bootstrap modelling
- Although based on modelling, these interim data support the hypothesis that increased risk reduction occurs when participants know the safety and efficacy results from Phase III trials

Dapivirine: Safety in Pregnancy – Nonclinical findings

- No effects on embryo-foetal development in rabbits up to 90mg/kg or maternally non-toxic doses up to 20mg/kg in rats
  - Exposure levels > 1000-fold higher than expected human systemic exposure
  - Oral dapivirine (doses ≥ 80mg/kg) embryo-foetal development studies showed toxicity at maternally toxic doses in rats
- In rats oral dapivirine prenatal and post-natal development studies no effects were seen at 20mg/kg
- No maternal or embryo-foetal toxicity observed with dapivirine vaginal gel up to 3.3 mg/mL

Phase III Pooled Analysis: Pregnancy

Outcome data as at 30 Sept 2017

Pregnancy Outcome	Dapivirine Vaginal Ring n (%)	Placebo Vaginal Ring n (%)
Number of pregnancies	137	117
Live birth	80 (58.4%)	72 (61.5%)
Spontaneous abortion	28 (20.4%)	24 (20.5%)
Non-therapeutic abortion/elective termination of pregnancy	22 (16.1%)	15 (12.8%)
Stillbirth/intrauterine death	2 (1.5%)	3 (2.6%)
Ectopic Pregnancy	2 (1.5%)	1 (0.9%)
Maternal death	None	1 (0.9%)
Unknown	3 (2.2%)	1 (0.9%)

Phase III Data: Congenital Anomalies

Outcome data as at 30 Sept 2017

Anomaly Medical Concept	IPM 027		MTN-020	
	DPV Ring N=45 n (%)	PLA Ring N=21 n (%)	DPV Ring N=92 n (%)	PLA Ring N=96 n (%)
• Congenital inguinal hernia (bulge in the groin area)			1 (1.1%)	
• Congenital umbilical hernia (bulge at the belly button)			3 (3.3%)	3 (3.1%)
• Multiple congenital abnormalities		1 (4.8%)		
• Plagiocephaly (flattening of the head)			1 (1.1%)	
• Polydactyly (extra fingers or toes)	1 (2.2%)			1 (1%)
• Skeletal dysplasia (short legs and arms)			1 (1.1%)	

Abbreviations:
DPV = dapivirine
PLA = placebo
N = overall number of pregnancies per treatment group
n = number of pregnancies with anomaly

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Phase IIIb OLE Interim Pregnancy Data: as at 20 March 2018

- 22 pregnancies reported in IPM 032/DREAM
- 53 pregnancies reported in MTN-025/HOPE
- Less than 50% of pregnancy outcomes available
- No new safety signals in respect of available pregnancy outcome data
- No congenital anomalies reported to date

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Regulatory Pathway

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

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Questions

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