AN OPEN-LABEL, RANDOMISED, THREE-PERIOD CROSSOVER TRIAL IN HEALTHY HIV-NEGATIVE WOMEN TO ASSESS THE DRUG-DRUG INTERACTION POTENTIAL BETWEEN DAPIVIRINE VAGINAL RING-004, CONTAINING 25 MG OF DAPIVIRINE, AND MICONAZOLE NITRATE, ADMINISTERED AS A 1200 MG VAGINAL CAPSULE

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PROTOCOL SYNOPSIS
IPM 028

AN OPEN-LABEL, RANDOMISED, THREE-PERIOD CROSSOVER TRIAL IN HEALTHY HIV-NEGATIVE WOMEN TO ASSESS THE DRUG-DRUG INTERACTION POTENTIAL BETWEEN DAPIVIRINE VAGINAL RING-004, CONTAINING 25 MG OF DAPIVIRINE, AND MICONAZOLE NITRATE, ADMINISTERED AS A 1200 MG VAGINAL CAPSULE

BACKGROUND: Dapivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), is a di-amino-pyrimidine (DAPY) derivative with potent antiviral activity against human immunodeficiency virus type 1 (HIV-1). Different vaginal formulations intended for complementary use with condoms have been tested to support a microbicide indication to prevent male-to-female transmission of HIV-1 infection. The dapivirine vaginal ring (Ring-004) is IPM’s lead microbicide formulation, and is currently being tested in a Phase III efficacy and safety program. Ring-004, an off-white, flexible ring, contains 25 mg of dapivirine dispersed in a silicone matrix, and is designed to provide release of dapivirine over a minimum period of 28 days.

Because vaginal yeast infections are quite common in the female population in general this trial will investigate the potential drug-drug interaction between dapivirine vaginal Ring-004 and vaginally administered miconazole nitrate, and will evaluate the safety of co-administration of the dapivirine vaginal ring and miconazole nitrate in healthy, HIV-negative women.

OBJECTIVES:

Primary Objectives:
1. To determine the effect of vaginally administered miconazole nitrate on the local (vaginal fluid, collected at the cervix) and systemic (plasma) pharmacokinetics of dapivirine, delivered by the dapivirine vaginal Ring-004, in healthy, HIV-negative women.

2. To determine the effect of dapivirine, delivered by the dapivirine vaginal Ring-004, on the local (vaginal fluid, collected at the cervix) and systemic (plasma) pharmacokinetics of miconazole, administered as a vaginal capsule in healthy, HIV-negative women.
Secondary Objectives:
1. To assess the local (vaginal fluid, collected at the cervix, introitus and where the ring was placed) and systemic pharmacokinetics of dapivirine, delivered by the dapivirine vaginal Ring-004, containing 25 mg dapivirine.
2. To assess residual levels of dapivirine in used rings.
3. To assess the safety of co-administration of the dapivirine vaginal Ring-004 and vaginal miconazole nitrate in healthy, HIV-negative women.

ENDPOINTS AND ASSESSMENTS:
To address the primary objectives, the following will be assessed:
1. Dapivirine concentrations in vaginal fluid, collected at the cervix, and in plasma, measured at specified time points during each 28-day period that the ring is inserted, and for two weeks following ring removal.

The following pharmacokinetic variables of dapivirine will be determined: $C_{\text{max}}$, $t_{\text{max}}$, $AUC_{0-24h}$, $AUC_{0-48h}$, $AUC_{0-14\text{days}}$, $AUC_{0-28\text{days}}$, $AUC_{\infty}$ and $t_{1/2}$.

2. Miconazole concentrations in vaginal fluid, collected at the cervix, and in plasma, measured at specified time points up to 14 days following administration of a single vaginal capsule, containing 1200 mg miconazole nitrate.

The following pharmacokinetic variables of miconazole will be determined: $C_{\text{max}}$, $t_{\text{max}}$, $AUC_{0-24h}$, $AUC_{\text{last}}$, $AUC_{\infty}$ and $t_{1/2}$.

To address the secondary objectives, the following will be assessed:
1. Dapivirine concentrations in vaginal fluid, collected at the cervix, introitus and where the ring was placed, and in plasma, measured at specified time points during the 28-day period that the vaginal ring is inserted without concomitant miconazole nitrate, and for two weeks following ring removal, for determination of $AUC_{0-28\text{days}}$ and $AUC_{\infty}$.

2. The residual amounts of dapivirine in used vaginal rings, removed on Day 28.

3. Safety will be assessed through the reporting of adverse events, including serious adverse events, laboratory safety assessments (haematology, biochemistry and urinalysis) if clinically indicated, physical and gynaecological examinations, and vaginal flora and pH assessments at specified time points throughout the trial.
TRIAL DESIGN: This will be an open-label, randomised, 3-period, 2-sequence, crossover trial, conducted at one research centre in Belgium among 36 healthy, HIV-negative women to assess the drug-drug interaction potential between the dapivirine vaginal Ring-004, containing 25 mg dapivirine, and a single dose of 1200 mg miconazole nitrate, delivered as a vaginal capsule formulation (Gyno-Daktarin®).

Eligible participants will be randomly assigned to one of two treatment sequences (ABC or BAC). During two consecutive 28-day treatment periods (treatment periods 1 and 2), separated by a washout period of 3 weeks, the participants will receive each of the following treatments according to their assigned treatment sequence: dapivirine vaginal Ring-004 for 28 days (Treatment A), followed by dapivirine vaginal Ring-004 for 28 days along with a single dose of miconazole nitrate on Day 0 (Treatment B); or dapivirine vaginal Ring-004 for 28 days along with a single dose of miconazole nitrate on Day 0 (Treatment B), followed by dapivirine vaginal Ring-004 for 28 days (Treatment A). Following a further washout period of 3 weeks, all participants will receive a single dose of miconazole nitrate (Treatment C) on Day 0 of treatment period 3. Participants will be admitted to the Phase I Unit on Day 0 of all treatment periods (Treatments A, B and C) and on Day 28 of Treatments A and B, and will remain in the Unit for at least 8 hours for blood and vaginal fluid sample collection. Participants will return to the Unit at regular intervals for blood and vaginal fluid sampling for the remainder of the treatment period, in accordance with the schedule of clinical procedures (Appendix A).

Safety evaluations will be performed throughout the conduct of the trial at specified time points. Safety laboratory assessments may be performed at the Investigator’s discretion at any time point when clinically indicated.

TRIAL DURATION: The maximum allowable time between screening and enrolment per participant will be 28 days. Following enrolment into the trial, each participant will be followed for two 28-day treatment periods (treatment periods 1 and 2), and one single dose treatment period (treatment period 3), separated by two washout periods of three weeks each. Following completion of the last treatment period, participants will be followed for two weeks for collection of blood and vaginal fluid samples and follow-up safety evaluations. It is anticipated that full enrolment will be completed in approximately 4 months, for an approximate total trial duration of 10 months.
**POPULATION:** Healthy, HIV-negative women, $\geq 18$ and $\leq 40$ years of age, who understand the trial and can provide informed consent.

**SAMPLE SIZE:** 36 women will be enrolled; 18 participants will be randomised to each treatment sequence.

**INCLUSION CRITERIA:**

Women must meet all of the following criteria to be eligible for enrolment:

1. Women $\geq 18$ and $\leq 40$ years of age who can give written informed consent
2. Available for all visits and consent to follow all procedures scheduled for the trial
3. Healthy, based on medical history, vital signs, physical examination, urinalysis (dipstick and microscopy (if indicated)), laboratory evaluations for genital infections (bacterial vaginosis, gonorrhoea, chlamydia and trichomonas), and laboratory evaluations for haematology and chemistry
4. HIV-negative as determined by an HIV test at the time of enrolment
5. On a stable form of contraception, defined as:
   - A stable oral contraceptive regimen for at least 2 months prior to enrolment, OR
   - Transdermal contraceptive patch for at least 3 months prior to enrolment, OR
   - Long-acting progestins for at least 6 months prior to enrolment, OR
   - An IUD inserted (with no vaginal or gynaecological complaints associated with its use) at least 3 months prior to enrolment, OR
   - Have undergone surgical sterilisation at least 3 months prior to enrolment,
   AND willing to use oral contraceptives if necessary to delay menstruation during the vaginal sampling period
6. Upon pelvic examination at the time of enrolment, the cervix and vagina appear normal as determined by the Investigator/Physician
7. Asymptomatic for genital infections at the time of enrolment (if a woman is diagnosed with any treatable STI, either clinically or by laboratory test at the time of screening, she must receive treatment at least 2 weeks prior to enrolment)
8. Willing to refrain from the use of topical medications, vaginal products or objects, including female condoms, tampons, cotton wool, rags, diaphragms, cervical caps (or any other vaginal barrier method), douches, lubricants, vibrators/dildos, and drying agents for 14 days prior to enrolment and for the duration of the trial.

9. Documentation of no abnormality on cervical cytology, including grossly bloody smear, within 90 days prior to screening.

10. Willing to refrain from participation in any other research trial for the duration of this trial.

11. Willing to provide adequate locator information for trial retention purposes and be reachable per local standard procedures, e.g. by home visit or telephone, or via family or close neighbour contacts (confidentiality to be maintained).

12. Willing to agree to abstain from all the following for a total of 2 days (48 hours) prior to each trial visit:
   - Penile-vaginal intercourse
   - Oral contact with her genitalia

13. Hepatitis B and C negative at the time of enrolment.

EXCLUSION CRITERIA:

Women who meet any of the exclusion criteria below are not eligible:

1. Currently pregnant or had their last pregnancy outcome within 3 months prior to screening

2. Currently breast-feeding

3. Currently or within two months of participation in any other clinical research trial involving investigational or marketed products prior to screening

4. Untreated symptomatic urogenital infections, e.g. urinary tract or other sexually transmitted infections, or other gynaecological conditions such as vaginal itching, pain, or discharge, within 2 weeks prior to enrolment.

5. Have a Grade 2 or higher pelvic examination finding, according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events; Addendum 1 Female Genital Grading Table for Use in Microbicide Studies.

6. History of significant urogenital or uterine prolapse, undiagnosed vaginal bleeding, urethral obstruction, incontinence or urge incontinence.

7. Current vulvar or vaginal symptoms/abnormalities that could influence the trial results.
8. Cervical cytology at screening that requires cryotherapy, biopsy, treatment (other than for infection), or further evaluation

9. Symptomatic genital herpes simplex virus (HSV) infection or a history of genital herpetic infection

10. Any Grade 2, 3 or 4 haematology, biochemistry or urinalysis laboratory abnormality at baseline (screening) according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events; Addendum 1 Female Genital Grading Table for Use in Microbicide Studies

11. Unexplained, abnormal bleeding per vagina during or following vaginal intercourse, or gynaecologic surgery within 90 days prior to enrolment

12. Any history of anaphylaxis or severe allergy resulting in angioedema; or a history of sensitivity/allergy to latex or silicone

13. Any serious acute, chronic or progressive disease (e.g. any known history of neoplasm, cancer, diabetes, epilepsy, cardiac disease, autoimmune disease, HIV, AIDS, or blood dyscrasias), or signs of cardiac disease, renal failure, or severe malnutrition

14. Have undergone a hysterectomy

15. Any condition(s) that, in the opinion of the Investigator, might interfere with adherence to trial requirements or evaluation of the trial objectives.

METHODS:

All participants who consent to participate in the trial, and who meet the specified inclusion/exclusion criteria, will be enrolled into the trial.

Eligible participants will be randomly assigned to one of two treatment sequences (ABC or BAC). During two consecutive 28-day treatment periods (treatment periods 1 and 2), and one single dose treatment period (treatment period 3), separated by two washout periods of three weeks each, all participants will receive each of the three treatments (specified below) in accordance with their assigned treatment sequence.

Treatment A: Dapivirine Vaginal Ring-004.

The Investigator/Physician will insert the dapivirine vaginal ring on Day 0. Women will be instructed to keep the ring inserted until Day 28.

Treatment B: Dapivirine Vaginal Ring-004 plus a single 1200 mg dose of miconazole nitrate, administered as a vaginal capsule.
formulation (Gyno-Daktarin®).
The Investigator/Physician will insert the dapivirine vaginal ring on Day 0. Women will be instructed to keep the ring inserted until Day 28. Immediately following ring insertion on Day 0, the Investigator/Physician will administer a single dose of vaginal miconazole nitrate.

Treatment C: A single 1200 mg dose of miconazole nitrate, administered as a vaginal capsule formulation (Gyno-Daktarin®).
The Investigator/Physician will administer the vaginal capsule on Day 0.

Participants will be admitted to the Phase I Unit on Day 0 of all treatment periods (Treatments A, B and C) and on Day 28 of Treatments A and B, and will remain in the Unit for at least 8 hours for blood and vaginal fluid samples (by tear test strip). Thereafter, participants will return to the Unit at regular intervals for blood and vaginal fluid sampling for the remainder of the treatment period.

During treatment periods, participants will not be allowed to have sexual intercourse:

- within 48 hours prior to Day 0 until the Day 7 vaginal fluid sample collection for Treatments A and B, and the Day 3 vaginal fluid sample collection for Treatment C
- within 48 hours prior to each subsequent trial visit for Treatments A, B and C
- within 48 hours prior to Day 28 until the Day 31 vaginal fluid sample collection for Treatments A and B.

For those treatment periods where miconazole nitrate is administered, participants will be advised to refrain from using condoms for 7 days post-insertion of the vaginal capsule, based on instructions in the miconazole nitrate labelling that the antimycotic can interfere with condom integrity.

STATISTICAL CONSIDERATIONS:

Sample size:
No accurate estimates of the within-individual variability of the pharmacokinetic variables $C_{\text{max}}$ and $AUC_{\infty}$ of dapivirine, delivered via Ring-004, are available. Between-individual coefficients of variation (CVs) for these variables, determined for plasma and vaginal fluids, ranged between 25% and 37%.
in IPM 024, and between 20% and 50% in IPM 013. As with individual variability can be expected to be lower than between-individual variability, the within-individual CV is estimated at 30%. Based on this estimate, and under the assumption of no difference in the mean pharmacokinetic parameters (\(C_{\text{max}}\) and AUC\(_{\infty}\)) of dapivirine between Ring-004 + miconazole nitrate ("test" treatment) and Ring-004 alone ("reference" treatment), for a power of 80% and significance level of 0.05, 32 participants would be needed to demonstrate a lack of interaction between the "test" and "reference" treatments, if no drug-drug interaction exists\(^9\).

To allow for an expected discontinuation rate of 10%, 36 participants will be enrolled, i.e. 18 per treatment sequence.

**Statistical Analysis:**

Individual and mean plasma and vaginal fluid concentrations of dapivirine and miconazole will be listed, summarised, and presented graphically. Standard pharmacokinetic parameters, including \(C_{\text{max}}\), \(t_{\text{max}}\), AUC\(_{0-24h}\), AUC\(_{0-48h}\), AUC\(_{0-14\text{days}}\), AUC\(_{0-28\text{days}}\), AUC\(_{\infty}\) and \(t_{1/2}\) for dapivirine in plasma and vaginal fluids, and \(C_{\text{max}}\), \(t_{\text{max}}\), AUC\(_{0-24h}\), AUC\(_{\text{last}}\), AUC\(_{\infty}\) and \(t_{1/2}\) for miconazole in plasma and vaginal fluids (if possible) will be calculated and summarised descriptively.

To address the primary objectives, natural log-transformed \(C_{\text{max}}\) and AUC values for plasma and vaginal fluids (collected at the cervix) will be subjected to an analysis of variance (ANOVA), with treatment, period, and sequence as fixed effects and participant as random effect (for the miconazole analyses, period and sequence effects are not applicable). The point estimates of test versus references ratios (Ring-004 + miconazole versus Ring-004 ratios for dapivirine, and Ring-004 + miconazole versus miconazole ratios for miconazole), and corresponding 90% confidence intervals (CIs) will be calculated to assess the effect of concomitant miconazole on dapivirine, and the effect of concomitant dapivirine on miconazole, respectively. The confidence intervals will be compared with the standard equivalence range of 0.80 to 1.25.

To address the secondary objectives, the following analyses will be performed:

For the treatment arm where the dapivirine vaginal Ring-004 is administered alone, AUC\(_{0-28\text{days}}\), AUC\(_{\infty}\) and \(C_{\text{max}}\) of dapivirine in plasma and vaginal fluids (collected at the cervix, introïtus and where the ring was placed) will be used as estimate of the systemic and local pharmacokinetics of dapivirine from Ring-004, for comparison with the corresponding values obtained in IPM 013 and IPM 024. These parameters will be natural log-transformed and subjected to an ANOVA with treatment as fixed effect. Point
estimates and 90% CIs will be calculated for the comparison of IPM 028 with IPM 013 and IPM 024.

The amount of residual dapivirine in used vaginal rings removed on Day 28 will be listed, summarised, and presented graphically. To evaluate whether the amount of dapivirine released from the rings over 28 days was affected by concomitant administration of miconazole nitrate, the residual amounts for Ring-004 alone and for Ring-004 + miconazole will be compared by ANOVA, with treatment, period, and sequence as fixed effects and participant as random effect (untransformed data). A point estimate and 90% CI will be calculated for the ratio “Ring-004 + miconazole versus Ring-004”. The relationship between the amount of residual dapivirine in the used rings and the plasma and vaginal fluid levels of dapivirine (AUC_{0-28days}) will be investigated graphically.

Safety assessments will be listed and summarised by treatment group, where appropriate. Descriptive statistics will include the mean, standard deviation, median, minimum, and maximum for continuous data; categorical data will be summarised with frequency and relative frequency.