A DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED PHARMACOKINETIC AND SAFETY TRIAL IN HEALTHY HIV-NEGATIVE WOMEN TO ASSESS THE DELIVERY OF DAPIVIRINE FROM A MATRIX VAGINAL RING AND TO EVALUATE THE SAFETY OF A MATRIX VAGINAL RING CONTAINING 25 MG OF DAPIVIRINE
PROTOCOL SYNOPSIS

IPM 013

A DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED PHARMACOKINETIC AND SAFETY TRIAL IN HEALTHY HIV-NEGATIVE WOMEN TO ASSESS THE DELIVERY OF DAPIVIRINE FROM A MATRIX VAGINAL RING AND TO EVALUATE THE SAFETY OF A MATRIX VAGINAL RING CONTAINING 25 MG OF DAPIVIRINE

BACKGROUND: To date, candidate vaginal microbicides have been formulated predominantly as gels. Multiple safety and efficacy trials with various microbicides have been completed or are currently underway, most of which evaluate microbicides in gel formulation delivered via a single-use vaginal applicator. In order for a microbicide to be most effective, it is essential that it is used correctly. Therefore, it is important that a microbicide product is acceptable to users. It is likely that products that can be applied less frequently will be more acceptable and will achieve a higher level of user compliance. Sustained drug release devices such as vaginal rings that need only be replaced monthly may have acceptability, and therefore compliance, benefits over dosage forms that need to be used more frequently. The dapivirine matrix vaginal ring (Ring-004) is an off-white, flexible ring containing 25 mg of drug substance dispersed in a platinum-catalyzed-cured silicone matrix. Ring-004 is designed to provide sustained release of dapivirine over a 28-day period.

OBJECTIVES: The objectives of this trial are:

- To assess the safety of the platinum-catalysed matrix vaginal ring containing 25 mg of dapivirine as compared to placebo ring when used for 56 days (group A) or 57 days (group B) by healthy, sexually active HIV-negative women.
- To examine local and systemic pharmacokinetics of dapivirine concentrations when delivered by the platinum-catalysed matrix vaginal rings containing 25 mg of dapivirine, measured in plasma, vaginal fluids, and cervical tissue during the trial period.

The exploratory objectives are:

- To assess the capacity of a matrix vaginal ring containing 25 mg of dapivirine to protect cervical tissue from infection upon ex vivo challenge with HIV-1.
- To assess the capacity of cervicovaginal fluids taken from women using a matrix vaginal ring containing 25 mg of dapivirine to inhibit HIV-1 infection in an in vitro model of infection.
- To assess local and systemic pharmacokinetics of dapivirine delivered by a matrix vaginal ring, measured in plasma, and vaginal fluids, during menses among women where tampon use is allowed during the trial period.
ENDPOINTS: The safety endpoints are the proportion of women in each of the four vaginal ring regimens (on dapivirine or on placebo ring) with:
- Mucosal abnormalities (as defined in the CONRAD/WHO manual) visible during naked eye examination and/or colposcopy;
- Abnormal vaginal pH and/or abnormal vaginal flora during the course of the trial;
- Positive diagnostic tests for trichomonas, gonorrhoea and/or chlamydia;
- At least one adverse event during the 12-week trial period;
- Any laboratory abnormalities on haematology, electrolytes, liver function, and renal function.

The safety endpoints will be assessed by:
- Gynaecological assessments, including pelvic examination, colposcopy and laboratory STI testing;
- Vaginal flora and vaginal pH analysis;
- Self-reported genital symptoms;
- Adverse Event/Serious Adverse Event reports;
- Safety laboratory evaluations of haematology, electrolytes, liver function, and renal function.

The pharmacokinetic endpoints will be:
- Assessments of local and systemic concentrations of dapivirine in plasma, vaginal fluid and cervical tissue before, during, and after 56 days (Group A) or 57 days (Group B) of use of the vaginal ring containing dapivirine or the placebo ring.

The pharmacokinetic endpoints will be assessed through:
- Measurement of dapivirine concentrations in plasma, vaginal fluids and cervical tissue at specified time points throughout the trial duration.

The exploratory endpoints will be:
- The proportion of cervical tissue samples protected from infection upon ex-vivo challenge with HIV-1;
- The proportion of cervicovaginal fluids samples collected from participants demonstrating inhibition of HIV-1 replication in an in vitro model of infection;
- Assessments of local and systemic concentrations of dapivirine in plasma, and vaginal fluid during menses in women allowed to use tampons while using the vaginal ring containing dapivirine or the placebo ring.

The exploratory endpoints will be assessed by:
- Ex vivo challenge with HIV-1 of cervical tissue samples collected by biopsy from women following use of a matrix vaginal ring containing 25 mg of dapivirine or placebo vaginal ring;
• Use of an *in vitro* HIV infection model to determine the inhibitory effects against HIV-1 of cervicovaginal fluids collected from women following use of a matrix vaginal ring containing 25 mg of dapivirine or placebo vaginal ring;
• Measurement of dapivirine concentrations in plasma, and vaginal fluids on Day 3 ± 2 days and at Day 5 ± 2 days of menses throughout the trial duration.

**DESIGN:**
IPM 013 is a double-blind, randomised, placebo-controlled trial conducted over 3 months at one research centre in Belgium among 48 healthy, HIV-negative, sexually active women to assess the pharmacokinetics of dapivirine delivered using a matrix vaginal ring containing 25 mg of dapivirine and to evaluate the safety of a matrix vaginal ring containing 25 mg of dapivirine and placebo vaginal ring.

Women who consent will be invited to screen for the trial and, if they are generally healthy and meet specified inclusion/exclusion criteria, they can be enrolled in the trial. Participants will be assigned, in groups of eight to either Group A or Group B and will be unblinded to their group assignment. Within each group, participants will be randomised in a blinded manner in a 3:1 ratio to either silicone elastomer matrix vaginal ring containing 25 mg of dapivirine or to placebo vaginal ring. There will be a total of four (4) treatment arms:

- A1: Group A (first ring removed Visit 5); matrix vaginal ring containing 25mg dapivirine
- A2: Group A (first ring removed Visit 5) placebo ring
- B1: Group B (first ring removed Visit 7) matrix vaginal ring containing 25mg dapivirine
- B2: Group B (first ring removed Visit 7) placebo ring

Following enrolment, participants will return per their assigned trial groups to the clinic for scheduled visits as indicated in Table 1.1.

**TABLE 1.1: SCHEDULE OF VISITS**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Screen</th>
<th>Enrol</th>
<th>Trial Visits</th>
<th>Exit</th>
<th>Exit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>1a</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Day</td>
<td>n/a</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>A,B</td>
<td>A,B</td>
<td>A,B</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Groups</td>
<td>n/a</td>
<td>A,B</td>
<td>A,B</td>
<td>B</td>
<td>B</td>
</tr>
</tbody>
</table>

At the enrolment visit (Visit 1), the Investigator/physician will insert the vaginal ring and the participant will be instructed to wear it continuously for a period of time dependent on her randomisation group and as illustrated in Diagram 1.1.

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A new ring will be inserted at the following time points:

- **Group A**: Visit 6 (Day 31)
- **Group B**: Visit 8 and 9 (Day 38 and 59)

For participants assigned to Group A, the first ring will be removed during Visit 5, followed by a 3 day period during which no ring will be worn before insertion of the second ring during Visit 6. For participants assigned to Group B, the first ring will be removed during Visit 7, followed by a 3 day period during which no ring will be worn before insertion of the second ring during Visit 8. A third ring will be inserted at Visit 9 immediately after the removal of the second ring and will then be removed at visit 9a.
Diagram 1.1: Randomisation Scheme

SCREENING

RANDOMIZATION (3:1)

Group A
24 participants

Arm A1 *
(18 participants)

Day 0
1st ring inserted

Day 28
1st ring removed

Day 59
2nd ring removed

28 days continuous exposure

Arm A2 #
(6 participants)

Day 31
2nd ring inserted

3 day healing

Group B
24 participants

Arm B1 *
(18 participants)

Day 0
1st ring inserted

Day 35
1st ring removed

Day 38
2nd ring inserted

Day 59
2nd ring removed

Day 60
3rd ring removed

35 days continuous exposure

Arm B2 #
(6 participants)

Day 28
1st ring removed

3 day healing

21 days continuous exposure

RANDOMIZATION (3:1)

24 hour exposure

* Arm A1 and B1 = 25mg Dapivirine Matrix Ring
# Arm A2 and B2 = Placebo Ring
TABLE 1.2: PHARMACOKINETIC AND PHARMACODYNAMIC SAMPLING SCHEDULE

<table>
<thead>
<tr>
<th>Sampling Time</th>
<th>Blood Sample</th>
<th>Cervical Tissue Biopsies</th>
<th>Vaginal Fluids Tear Test Strips</th>
<th>Vaginal Fluids Lavage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0 (Visit 1)</td>
<td>Prior to insertion of first ring</td>
<td>Group A,B</td>
<td>Group A,B</td>
<td>Group A,B</td>
</tr>
<tr>
<td></td>
<td>4 hours after ± 0.5h</td>
<td>Group A,B</td>
<td>Group A,B</td>
<td>Group A,B</td>
</tr>
<tr>
<td></td>
<td>8 hours after ± 0.5h</td>
<td>Group A,B</td>
<td>Group A,B</td>
<td>Group A,B</td>
</tr>
<tr>
<td>Day 1 (Visit 1a)</td>
<td>24 hours after ± 0.5h</td>
<td>Group A,B</td>
<td>Group A,B</td>
<td>Group A,B</td>
</tr>
<tr>
<td>Day 7 (Visit 2)</td>
<td>± 4h</td>
<td>Group A,B</td>
<td>Group A,B</td>
<td>Group A,B</td>
</tr>
<tr>
<td>Day 14 (Visit 3)</td>
<td>± 4h</td>
<td>Group A,B</td>
<td>Group A,B</td>
<td>Group A,B</td>
</tr>
<tr>
<td>Day 21 (Visit 4)</td>
<td>± 4h</td>
<td>Group A,B</td>
<td>Group A,B</td>
<td>Group A,B</td>
</tr>
<tr>
<td>Day 28 (Visit 5)</td>
<td>± 4h</td>
<td>Prior to removal of first ring</td>
<td>Group A</td>
<td>Group A</td>
</tr>
<tr>
<td>Day 31 (Visit 6)</td>
<td>± 4h</td>
<td>Prior to insertion of second ring</td>
<td>Group A</td>
<td>Group A</td>
</tr>
<tr>
<td>Day 35 (Visit 7)</td>
<td>± 4h</td>
<td>Prior to removal of first ring</td>
<td>Group B</td>
<td>Group B</td>
</tr>
<tr>
<td>Day 38 (Visit 8)</td>
<td>± 4h</td>
<td>Prior to insertion of second ring</td>
<td>Group B</td>
<td>Group B</td>
</tr>
<tr>
<td>Day 59 (Visit 9)</td>
<td>± 4h</td>
<td>Prior to removal of second ring</td>
<td>Group A,B</td>
<td>Group A,B</td>
</tr>
<tr>
<td>Immediately after insertion of third ring</td>
<td>Group B</td>
<td>Group B</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 hours after ± 0.5h</td>
<td>Group B</td>
<td>Group B</td>
<td>Group B</td>
</tr>
<tr>
<td></td>
<td>8 hours after ± 0.5h</td>
<td>Group B</td>
<td>Group B</td>
<td>Group B</td>
</tr>
<tr>
<td>Day 60 (Visit 9a)</td>
<td>± 4h</td>
<td>Group B</td>
<td>Group B</td>
<td>Group B</td>
</tr>
<tr>
<td></td>
<td>24 hours after ± 0.5h</td>
<td>Prior to removal of third ring</td>
<td>Group B</td>
<td>Group B</td>
</tr>
<tr>
<td>Day 87 (Visit 10)</td>
<td>± 2 days</td>
<td>Group A</td>
<td>Group A</td>
<td></td>
</tr>
<tr>
<td>Day 88 (Visit 11)</td>
<td>± 2 days</td>
<td>Group B</td>
<td>Group B</td>
<td></td>
</tr>
</tbody>
</table>
NOTE: Participants must notify clinic of the start (first day) of their menses during the trial. Participants will be scheduled to return to clinic for plasma and vaginal fluids sampling on Day 3 ± 2 days and Day 5 ± 2 day of menses; Refer to Table 1.3 for further details.

TABLE 1.3: MENSES SAMPLING SCHEDULE

<table>
<thead>
<tr>
<th>Sampling Time</th>
<th>Blood Sample</th>
<th>Vaginal Fluids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 3 of menses ± 2 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If applicable, after removal of tampon</td>
<td>Group A,B</td>
<td>Group A,B</td>
</tr>
<tr>
<td>Day 5 of menses ± 2 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If applicable, after removal of tampon</td>
<td>Group A,B</td>
<td>Group A,B</td>
</tr>
</tbody>
</table>

Samples must be collected at a minimum of 48 hours apart. Participants must notify clinic of the first day of menses. If participant is using a tampon, the tampon is to be removed prior to vaginal fluid sample collection time point.

Blood samples will be taken by venipuncture and vaginal fluids will be collected through the use of Tear Test Strips. (See Study Operations Manual for details regarding procedures.)

Vaginal fluids will also be collected by cervicovaginal lavage at the time points indicated above in Table 1.2 for participants in the specified groups at the specified visits. Cervicovaginal lavage fluids will be collected prior to ring removal.

Cervical tissue biopsies, measuring approximately 2mm by 4mm, will be obtained under topical anaesthesia if necessary, after cervicovaginal lavage and vaginal ring removal at the time points as indicated in Table 1.2.

TRIAL POPULATION: Healthy, HIV-negative, sexually active women ≥18 to ≤40 years of age that understand the trial and can provide informed consent.

SAMPLE SIZE: 48 women will be enrolled.

REGIMEN: During the 3-month trial period, all participants will undergo the following examinations. Please refer to Table 1.1 to note which groups of participants are scheduled to attend each visit.
General physical examination will be performed at screening, pre-enrolment (Visit 1/Day 0), and at trial exit (Visit 10/Day 87 for Group A and Visit 11/day 88 for Group B).


Colposcopy will be performed in conjunction with the pelvic examination at pre-enrolment (Visit 1/Day 0), Visit 5/Day 28 for Group A, Visit 7/Day 35 for Group B, and at Visit 9/Day 59.


STI testing (for Gonorrhoea, Chlamydia and Trichomonas) will be conducted at screening, pre-enrolment (Visit 1/Day 0), at Visit 5/Day 28 for Group A, Visit 7/Day 35 for Group B, at Visit 9/Day 59, and at trial exit (Visit 10/Day 87 for Group A and Visit 11/Day 88 for Group B). Syphilis testing will be conducted at screening and as clinically indicated at any other visit.

Safety laboratory testing (haematology and chemistry) and urinalysis will be conducted at screening, pre-enrolment (Visit 1/Day 0), at Visit 5/Day 28 for Group A, Visit 7/Day 35 for Group B, at Visit 9/Day 59, and at trial exit (Visit 10/Day 87 for Group A and Visit 11/Day 88 for Group B).

Testing for Hepatitis B and C will be conducted at the screening visit.

Cervicovaginal samples will be collected for BV testing and for vaginal flora and pH testing at screening, pre-enrolment (Visit 1/Day 0), at Visit 5/Day 28 for Group A, Visit 7/Day 35 for Group B, at Visit 9/Day 59, and at trial exit (Visit 10/Day 87 for Group A and Visit 11/Day 88 for Group B). Cervicovaginal sample will also be collected for Pap test at the screening visit, unless a Pap test was done up to 3 months prior to screening, and the results are available and normal.

Pregnancy testing will be conducted at screening, pre-enrolment (Visit 1/Day 0), at Visit 5/Day 28 for Group A, Visit 7/Day 35 for Group B and at Visit 9/Day 59.

Vaginal ring adherence counselling will be provided at the time of first ring insertion (Visit 1/Day 0), and at Visit 2/Day 7, at Visit 3/Day 14, at Visit 4/Day 21, Visit 6/Day 31 for Group A, and at Visit 8/Day 38 for Group B and at Visit 9/Day 59 for Group B.

**NOTE:** Any of the above procedures may be performed at a visit if deemed necessary by the Investigator.

Adverse events, including vaginal complaints, will be assessed at every visit except screening and pre-enrolment. Complaints at screening and pre-enrolment will be considered as Medical History. Concomitant medications will be evaluated and captured at every trial visit following the screening visit.

Vaginal fluid, cervical tissue and plasma samples will be collected at visits as specified in Table 1.2.

**TRIAL DURATION:** The maximum allowable time between screening and enrolment per participant is 28 days. Following the enrolment into the trial, each participant will be followed for a total of approximately 3 months, approximately 8 weeks of ring use and a follow up visit 4 weeks post final ring removal. It is anticipated full enrolment will be completed in approximately 4-5 months for a total of up to approximately 8 months of trial duration.

**STATISTICAL ANALYSIS:** The safety analysis will focus on safety assessments, using the intent-to-treat population. Comparison will be made between the women using a matrix vaginal ring containing 25 mg of dapivirine (Groups A1 and B1) and the women using a placebo ring containing no dapivirine (Groups A2 and B2). Exploratory analyses using a per-protocol population may also be performed.

The pharmacokinetic analysis will summarize the dapivirine concentration measured in plasma, vaginal fluids, and cervical tissue over time with descriptive statistics.

The exploratory analysis will assess whether the use of the matrix vaginal ring containing 25 mg of dapivirine for 28 or 35 days, protects cervical tissue from infection upon ex-vivo challenge with HIV-1 virus; and
whether cervicovaginal fluids collected from women following use of a matrix vaginal ring containing 25 mg of dapivirine or a placebo ring demonstrate inhibitory effects against HIV-1 in vitro. Plasma and vaginal fluid samples will also be collected in the absence of the tampon on Day 3 and Day 5 of menses (anticipated to be days of heaviest flow) to assess the effect of menses and tampon use on dapivirine levels during menstruation.

Participant safety will be monitored by a Safety Evaluation Committee (SEC). The SEC will review safety data (adverse events and other relevant data) from this trial approximately every six weeks while the trial is ongoing. Specific details regarding the operation of the SEC will be described in the SEC charter.

PHARMACODYNAMIC METHOD EVALUATION SUB-TRIAL:

An additional 5 to 8 women who are willing to provide informed consent and meet all eligibility criteria, as specified in Section 5.14, will participate in a pharmacodynamic method evaluation sub-trial of IPM 013. These volunteers will have a cervical tissue biopsy, by which one tissue sample, measuring approximately 2mm by 4mm, will be collected under topical anaesthesia if necessary. The cervical tissue specimens obtained during this sub-trial will be used to evaluate the laboratory procedures being used to assess the effects of the HIV-1 virus on the tissue prior to treatment with dapivirine. These volunteers will only participate in the sub-trial portion of the IPM 013 protocol.