IPM 018 PROTOCOL AMENDMENT 1

A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED SAFETY AND PHARMACOKINETIC STUDY IN HEALTHY HIV-NEGATIVE WOMEN TO ASSESS DELIVERY OF DAPIVIRINE FROM BOTH MATRIX AND RESERVOIR INTRAVAGINAL RINGS EACH CONTAINING 25 MG OF DAPIVIRINE

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FINAL Version 3.0
10 July 2007

PROTOCOL SYNOPSIS

IPM 018

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BACKGROUND: To date, candidate vaginal microbicides have been formulated predominantly as gels, films, and suppositories. Multiple safety and efficacy studies with various microbicides are currently underway, most of which are evaluating microbicides in gel formulation delivered via a single-use vaginal applicator. However data suggests that compliance may be a critical factor in microbicide efficacy due to issues of gel acceptability and the fact that most gels are coitally dependent. More recently, vaginal rings have been proposed as alternative microbicide delivery methods that may have advantages over other formulations, since use of a ring can circumvent difficulties associated with daily or coitally dependent application of a gel.

OBJECTIVES: The purpose of this study is to evaluate the feasibility of using matrix and reservoir intravaginal rings containing 25 mg of dapivirine to deliver drug for 28 continuous days. Specific objectives are to:

1. Assess the safety and tolerability of intravaginal rings containing dapivirine when used continuously for 28 days compared to placebo.
2. Assess dapivirine concentrations in plasma before, during and after 28 day use of matrix and reservoir silicone elastomer intravaginal rings containing dapivirine.
3. Assess dapivirine concentrations in vaginal fluids before, during and after 28 day use of matrix and reservoir silicone elastomer intravaginal rings containing dapivirine.

ENDPOINTS: To address study objective 1, the following parameters will be assessed:

- Subject-reported genital symptoms
- Pelvic / colposcopic exam findings (including vaginal pH and Nugent scores)
- Laboratory evaluations of hematology, liver function, and renal function

To address study objective 2, the following parameters will be assessed:

- dapivirine concentrations in plasma

To address study objective 3, the following parameters will be assessed:

- dapivirine concentrations in vaginal fluids (collected by Sno-Strips)

DESIGN:

IPM 018 is a double-blind, randomized, placebo-controlled study conducted at one site in Belgium among 24 healthy, HIV-negative women to evaluate dapivirine release for 28 days from matrix and reservoir intravaginal rings, each containing 25 mg of dapivirine, and to assess safety and tolerability compared to placebo.

Women who consent will be invited to screen for the study and if they meet specified inclusion / exclusion criteria, have normal findings based upon a physical and pelvic / speculum examination with colposcopy and medical history, and have negative pregnancy and HIV tests, will be invited to enroll in the study. Upon enrollment, subjects will be randomly assigned in a 1:1:1 ratio to one of three arms; eight subjects will be randomized per arm.

Arm A: A silicone elastomer matrix intravaginal ring containing 25mg of dapivirine;

Arm B: A silicone elastomer reservoir intravaginal ring containing 25mg of dapivirine;

Arm C: Placebo intravaginal ring

Twenty-four (24) healthy, HIV-negative, women will undergo 28 day exposure to a 25mg dapivirine reservoir intravaginal ring, 25 mg dapivirine matrix intravaginal ring, or a placebo intravaginal ring.

After enrollment (Visit 2), the Investigator will insert the dapivirine or placebo intravaginal ring into the vagina. The intravaginal ring will be worn for 28 continuous days, and the subjects will be followed up according to the following table to assess dapivirine concentrations and to monitor safety and tolerability:

Post Intravaginal Ring Insertion and Removal Follow-up																
Pre-Dose	1h	2h	4h	8h	1d	2d	3d	5d	7d	14d	21d	28d	29d	30d	31d	33d

The subject will remain in the clinic for 24 hours after ring insertion and after ring removal (i.e. Visit 2 and Visit 9), at which time blood and vaginal fluids will be collected for measurement of dapivirine concentrations. Blood samples will be taken by vena-puncture; vaginal fluids will be collected through the use of Sno-Strips in the following order: 1) from the surface of the cervix 2) from the surface of the vagina in an area near the introitus, and 3) from the surface of the vagina in an area near where the ring was placed.

The collection of blood and vaginal fluid samples will be completed pre-dose and at 1h, 2h, 4h, 8h, 1d, 2d, 3d, 5d, 7d, 14d, 21d and 28 days post-ring insertion. After ring removal on day 28 (Visit 9) blood and vaginal fluid samples will be collected at 1h, 2h, 4h, 8h, 1d, 2d, 3d, and 5 days. Subjects will be released from the clinic after 24 hours post-ring removal and upon completion of a pelvic / speculum examination but will be asked to return to the clinic during specified time points for specimen collection.

STUDY POPULATION: Healthy, HIV-negative women ≥18≤35 years of age that understand the study and can provide informed consent.

SAMPLE SIZE: 24 women will be enrolled.

REGIMEN: During the 2-month study period, all subjects will undergo a general physical examination at screening (Visit 1), enrollment (Visit 2) and at the last visit (Visit 12), a pelvic / speculum examination at screening (Visit 1), enrollment (Visit 2), Visits 2.1-9 and at the last visit (Visit 12). A colposcopy will also be performed during the pelvic / speculum examinations at enrollment (Visit 2), Visit 9 and at the last visit (Visit 12). Cervico-vaginal swabs for STI testing (Gonorrhea, Chlamydia and Trichomonas) will be collected at screening (Visit 1) and at the last visit (Visit 12). HIV / STI risk reduction counseling will be provided at screening (Visit 1) and at the last visit (Visit 12). HIV testing with pre- and post-test counseling will also be conducted at the screening visit (Visit 1) and at the last visit (Visit 12). Contraceptive adherence counseling will be provided at screening (Visit 1), enrollment (Visit 2) and Visits 2.1-9. Vaginal ring adherence counseling will be provided at the time of ring insertion (Visit 2) and at Visits 2.1-8. Pregnancy testing will be conducted at screening (Visit 1), enrollment (Visit 2) and at the last visit (Visit 12). Adverse events, including vaginal complaints, will be assessed at every visit following enrollment. Complaints at screening and

enrollment will be considered as Medical History. Concomitant medications will be evaluated and captured at every study visit.

STUDY DURATION: The maximum allowable time between screening and enrollment per subject is 28 days. The screening visit (Visit 1) may be conducted over the course of 2 days. Following the screening visit, each subject will be followed for a total of up to 2 months. It is anticipated full enrollment will be completed in 4 weeks (approximately 1 month).

STATISTICAL ANALYSIS: All subjects enrolled in this study will be included in data analyses. Pharmacokinetic and statistical analyses will be done. To address objective 1, tabulations will report each type of endpoint overall and by exposure period (placebo or dapivirine). To address objectives 2 and 3, descriptive statistics of the measured concentrations of dapivirine will be calculated and tabulated.