

**Letter of Amendment #01 to:**

**MTN-013/IPM 026**

**Phase 1 Safety and Pharmacokinetics of Dapivirine/Maraviroc Vaginal Ring**

**DAIDS Document ID: 11772**

**Letter of Amendment date: 14 December 2011**

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*Site Instruction*

The following information impacts the MTN-013/IPM 026 study and must be forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) as soon as possible for their information and review. This must be approved by your IRB/EC before implementation.

The following information also impacts the sample informed consent. Your IRB/EC will be responsible for determining the process of informing subjects of the contents of this Letter of Amendment (LoA).

*Implementation*

Upon receiving final IRB/EC and any other applicable Regulatory Entity (RE) approval(s) for this LoA, sites should implement the LoA immediately. Sites are still required to submit a LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA once the DAIDS PRO verifies that all the required LoA registration documents have been received and are complete. A LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. A copy of the LoA registration notification along with this letter and any IRB/EC correspondence should be retained in the site's regulatory files.

*Summary of Revisions*

This LoA does not impact the overall design or the study visit schedule for MTN-013/IPM 026. The primary reason for this LoA is to address US FDA suggested modifications to the protocol. The protocol team has modified the exclusion criteria to restrict participants who have a Grade 2 or higher white blood count or are infected with Hepatitis B or Hepatitis C from enrolling in MTN-013/IPM 026. In addition, participants who have screened for and/or enrolled in MTN-013/IPM 026 will be tested for hepatitis B and hepatitis C. The protocol also requires a permanent product hold for participants who test positive for Hepatitis B and Hepatitis C and procedures will be slightly modified. Section 7.6, *Pharmacokinetics*, section has been updated. Participants will be provided with information regarding the risk of toxic shock syndrome. Additional edits to the protocol include: modifying the regular menstrual cycle inclusion criterion to allow participants who are currently using continuous hormonal contraceptive methods to enroll in MTN-013/IPM 026; allowing for the treatment of symptomatic Candida vaginitis with a CYP3A inhibitor and requiring a temporary product hold for participants receiving treatment; and updating the vaginal swab collection schedule and evaluations to be completed. Finally, this LoA incorporates changes from Clarification Memo #01.

With the exception of the modifications to the Protocol Team Roster, text to be deleted is noted by ~~strikethrough~~ and text to be added is noted below in **bold** font.

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**DETAILED LISTING OF REVISIONS**

The following items were previously noted in MTN-013/IPM 026, Version 1.0, CM #01, dated 12 July 2011:

1. The following individual was removed from the Protocol Team Roster: Jim Maynard.

- Section 6.4.2, *Storage and Dispensing*, first sentence, has been updated to reflect the current storage requirements for the study products:

The vaginal rings should be stored at a **controlled room temperature, 68°F to 77°F (20°C to 25°C), allowable excursions are between 45°C to 30°C (59°F to 86°F) (15°C to 30°C)**.

- Updates have been made to tables in Section 7.4.2, *Follow-up Visits*, and Appendix I, to streamline the behavioral assessment schedule and clarify the measures utilized:

Table 5: Visit Days 1, 2, 3, 5, 7, 14, 21

Follow-up Visits: Days 1, 2, 3, 5, 7, 14, 21	
Component	Procedures
Behavioral	<ul style="list-style-type: none"> <li>Conduct <b>behavioral adherence—assessments (protocol adherence, product use adherence)</b> ☀</li> </ul>

Table 6: Visit Day 28

Follow-up Visit: Day 28	
Component	Procedures
Behavioral	<ul style="list-style-type: none"> <li>Conduct behavioral assessments <b>(protocol adherence, product use adherence, acceptability)</b></li> <li><del>Conduct adherence assessments</del></li> </ul>

Table 8: Visit Days 31, 35, 42

Follow-up Visits: Days 31, 35, 42	
Component	Procedures
Behavioral	<ul style="list-style-type: none"> <li><b>Conduct behavioral assessment (protocol adherence)</b> ≠</li> </ul>

Table 9: Visit Day 52, Final Clinic/Early Termination Visit

Final Clinic/ Early Termination Visit: Visit Day 52	
Component	Procedures
Behavioral	<ul style="list-style-type: none"> <li>Conduct behavioral assessments <b>(protocol adherence) (acceptability ▲)</b></li> <li><del>Conduct adherence assessment ▲</del></li> </ul>

Appendix I: Schedule of Study Visits and Evaluations

	SCR	ENR Day 0	VISIT DAYS 1, 2, 3, 5, 7, 14, 21	VISIT DAY 28	VISIT DAYS 29, 30	VISIT DAYS 31, 35, 42	DAY 52 Final Clinic/ Early Term.	Interim
<b>BEHAVIORAL</b>								
<del>Conduct adherence assessment(s)</del>			☀	✗		≠	▲	
Conduct behavioral assessment	X	X		✗			✗	
<b>Conduct acceptability assessment</b>				X			▲	
<b>Conduct protocol adherence assessment(s)</b>			☀	X		≠	X	
<b>Conduct product use adherence assessment(s)</b>			☀	X				

- Section 7.9, *Laboratory Evaluations*, Vaginal and Cervical sub-bullets, the protocol has been updated to reflect that biopsies will be obtained from the cervix not the vagina.

- Vaginal
  - ~~Biopsy for PK assessment~~

- Cervical
  - Biopsy for **PK and PD** assessment
- 5. Section 10.6, *Randomization*, first paragraph, fourth sentence has been removed to eliminate the requirement to stratify the randomization by site to the end of study period PK/PD sampling times given the number of sampling time points, number of sites and sample size:

~~This randomization will be stratified by site to ensure balanced assignment of PK/PD end of study period sampling timing.~~

Modifications new to LoA #01:

1. As a result of suggested modifications to the protocol by the FDA, the Exclusion Criteria has been updated to revise the exclusion criteria to restrict participants with abnormal laboratory values, including excluding participants who have Hepatitis B or Hepatitis C. This has resulted in subsequent changes to Table 3, the addition of Section 9.9, and updates to Appendix I, Appendix III, and Appendix IV:

- Section 5.3, Exclusion Criteria, 4 e), f), and g) have been added:

**e. White blood count Grade 2 or higher as per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0, December, 2004 (Clarification dated August 2009)**

**f. Positive HBsAg test result**

**g. Positive Anti-HCV test result**

- Table 3: Screening Visit, Laboratory, Blood, under the first bullet, fifth and sixth sub-bullets have been added:

Laboratory	Blood	- HBsAg ◊ - Anti-HCV ◊
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\* If indicated, ◊= Mandatory at the Screening Visit, however if not previously completed at the Screening Visit prior to LoA #01 approval, perform at the next study visit.

- **NEW Section 7.5.3, Participants Who Are Found to be Infected with Hepatitis B or C,**

**All protocol-specified procedures will continue except the following:**

- **Provision of study product and instructions**
- **Acceptability and adherence assessments**
- **Pelvic exams**
- **PK specimen collection (blood and pelvic samples)**
- **Provision of counseling**
  - **Protocol and product use adherence**
- Subsequent protocol numbering following 7.5.3 has been updated.
- Section 9.9, *Hepatitis B or C Infection*, has been added to assist with the management of participants who are found to be infected with Hepatitis B or C.

### **9.9 Hepatitis B or C Infection**

**A participant who is found to be Hepatitis B and/or Hepatitis C positive, will be permanently discontinued from study product.**

- Appendix I, Study Procedures, HBsAg and Anti-HCV testing have been added:

	SCR	ENR Day 0	VISIT DAYS 1, 2, 3, 5, 7, 14, 21	VISIT DAY 28	VISIT DAYS 29, 30	VISIT DAYS 31, 35, 42	DAY 52 Final Clinic/ Term.	Interim
<b>LABORATORY</b>								
<b>HBsAg</b>	◊							
<b>Anti-HCV</b>	◊							

X required; \*if indicated; ◆ on Day 3 only; ☆ Day 7, Day 14 and Day 21 visits only; ◊ Day 7 only; ☒ Required at Day 14; † to be completed on randomization Day 31, Day 35, or 42 only; ▣ Day 31 only; ▲ if early termination visit and not previously collected, ◊= **Mandatory at Screening, however if not previously completed at the Screening Visit prior to LoA #01 approval, perform at the next study visit.**

- Appendix III, Sample Informed Consent Document (Screening), second sub-bullet after “Take a blood sample” has been modified:

- Take a blood sample [Sites to insert amount]:
  - To test the health of your blood, liver and kidneys
  - To test for infections passed through sex, including HIV, **Hepatitis B and Hepatitis C**

- Appendix IV: *Sample Informed Consent Document (Enrollment)*, *What do I have to do if I Decide to Take Part in MTN-013/IPM 026*, *At other study visits you will, Provide a sample of blood subsection*, new third sub-bullet:

- **If you did not have Hepatitis B or Hepatitis C tests at your Screening Visit you will need to have these tests performed at an upcoming visit. These tests will require a blood sample [Sites to insert amount].**

2. Section 5.2, *Inclusion Criteria*, Item 10, has been clarified to allow participants who use continuous contraceptive methods who are found to meet the eligibility criteria to enroll in MTN-013/IPM 026.

- 10.) Per participant report at Screening, regular menstrual cycles with at least 21 days between menses (does not apply to participants who report using a progestin-only method of contraception at screening, e.g., Depo-Provera or levonorgestrel-releasing IUD)

***Note: This criterion is not applicable to participants using continuous combination oral contraceptive pills, as the absence of regular menstrual cycles is an expected, normal consequence in this context.***

3. Section 6.8, *Prohibited Medications and Practices* second and third sentences and the third bullet of Section 9.5, *Other Clinical Events* have been clarified to allow for the use of a CYP3A inhibitor to treat yeast vaginitis and to allow for a product hold while participants are receiving treatment.

- Section 6.8, *Prohibited Medications and Practices*, first paragraph second and third sentences:

Several concomitant medications/practices will not be permitted. Participants are asked to refrain from using CYP3A inhibitors and CYP3A inducers, **however allowances will be made to treat symptomatic Candida vaginitis**. These medications are ~~not~~ **allowed** because both dapivirine and maraviroc are CYP3A substrates.

- Section 9.5, *Other Clinical Events*, Abnormal vaginal discharge (judged to be unrelated to cervicitis) Section, third bullet:

- Provide or prescribe treatment and continue study VR use for all cases of Trichomoniasis, ~~symptomatic Candida vaginitis~~, and symptomatic BV. **Study product should be temporarily held for the treatment of symptomatic Candida vaginitis.**

4. Updates have been made to tables in Section 7.4.2, *Follow-up Visits*, and Appendix I, to clarify the timing of the vaginal swab collection and the evaluations to be completed:

- Table 5: Visit Days 1, 2, 3, 5, 7, 14, 21, first bullet, fourth sub-bullet clarified:

Follow-up Visits: Days 1, 2, 3, 5, 7, 14, 21		
Component		Procedures
<b>Laboratory</b>	<b>Vaginal</b>	- <b>Vaginal swabs for validation testing</b> and <del>vaginal biomarker assessment</del>

\* If indicated ♦ Day 3 only; ☼ Day 7, Day 14, and Day 21 visits only; ☹ Day 14 only; ◇ Day 7 only

- Table 6: Visit Day 28, first bullet, third sub-bullet clarified:

Follow-up Visit: Day 28		
Component		Procedures
<b>Laboratory</b>	<b>Vaginal</b>	- Vaginal swabs for <b>validation testing</b> , vaginal biomarker assessment and PD

\* if indicated

- Appendix I, Schedule of Study Visits and Evaluations

		SCR	ENR Day 0	VISIT DAYS 1, 2, 3, 5, 7, 14, 21	VISIT DAY 28	VISIT DAYS 29, 30	VISIT DAYS 31, 35, 42	DAY 52 Final Clinic/ Term.	Interim
<b>LABORATORY</b>									
<b>Pelvic</b>	Vaginal swab for vaginal biomarkers (PD testing to be performed at Enrollment, Day 28, and Day 31); <b>an additional swab will be collected on Day 3 and Day 28 for validation testing.</b>		X	♦	X		■	X	

X required; \*if indicated; ♦ on Day 3 only; ☼ Day 7, Day 14 and Day 21 visits only; ◇ Day 7 only; ☹ Required at Day 14; ☼ to be completed on randomization Day 31, Day 35, or 42 only; ■ Day 31 only; ▲ if early termination visit and not previously collected

5. Section 7.6, *Pharmacokinetics*, first sentence has been updated:

- ~~All enrolled~~ Participants will undergo PK specimen collection procedures

6. As with any vaginally retained product the potential risk for toxic shock syndrome exists, the protocol has been revised to include this information, see modifications to Section 13.4.1, Risks and Appendix IV.

- Section 13.4.1, *Risks*, third paragraph, second sentence added:

Use of the study VR may lead to vaginal symptoms, including irritation, increased discharge, and discomfort (including with vaginal intercourse). **As with any vaginally retained product, the possibility of toxic shock syndrome, although rare, exists.**

- Appendix IV, *Sample Informed Consent Document (Enrollment), Risks and/or Discomforts* section a new paragraph has been added:

**As with any product that is placed into the vagina, the possibility of toxic shock syndrome exists. Toxic shock syndrome is a serious but uncommon infection caused by bacteria. While it is unlikely that you should experience toxic shock syndrome as a result of using the vaginal ring, it is important that you alert the study staff if you experience any symptoms associated with toxic shock syndrome, i.e., sudden high fever, a faint feeling, diarrhea, headache, a rash, and muscle aches.**

The above information will be incorporated into the next version of the protocol at a later time if it is amended.