

LETTER OF AMENDMENT #2 TO:

MTN-036/IPM 047

A Phase 1, Randomized Pharmacokinetics and Safety Study of Extended Duration
Dapivirine Vaginal Rings

Version 1.0, dated 28 June 2017

DAIDS Protocol #30009
IND #108,743

Date of Letter of Amendment: 21 August 2018

Site Instruction

The following information impacts the MTN-036/IPM 047 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 impacts the sample informed consent. Your IRB/EC will be responsible for determining the process of informing participants 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-036/IPM 047. The purpose of this LoA is to include provision of the clinical trials insurance for study participants by the International Partnership for Microbicides (IPM) in both the protocol and the Sample Informed Consent, and to clarify that participants who have undergone supracervical hysterectomy or bilateral oophorectomy verified by medical records are not required to undergo pregnancy testing and contraceptive counselling. Other changes included in this LoA: updating co-enrollment guidelines to include studies involving rectal products in the list of prohibited research studies for participants while on study, adding the word "approximately" before timepoints in footnotes in order to add flexibility in sample collection following ring insertion and after ring removal, modifying HIV-1 to HIV-1/2 in several sections of the protocol to indicate HIV testing detection of both HIV-1 and HIV-2, correction of a weblink, and protocol roster changes.

Unless otherwise noted, text to be deleted is noted by ~~strikethrough~~ and text to be added is noted below in **bold**.

Detailed Listing of Revisions

The following revisions (1-2) were made to accommodate the provision of clinical trials insurance by IPM for study participants:

1. In Section 13.8, *Compensation*, after the first paragraph:

If a participant becomes ill or injured as a result of participation in this trial, medical treatment for the adverse reaction or injury will be provided appropriately. The site staff will refer the participant for ongoing treatment for the injury, if needed. IPM will be responsible for compensation for appropriate medical expenses for treatment of any such illness or injury. An HIV infection that occurs during the course of the trial will not be considered an injury or illness caused by trial participation.

2. The following revisions were made to Appendix III, Sample Informed Consent Form, in the "RESEARCH-RELATED INJURY" section:

[SITE TO SPECIFY INSTITUTIONAL POLICY]: It is unlikely that you will be injured as a result of study participation. If you are injured, the ~~[INSTITUTION]~~ will give you immediate necessary treatment for your injuries. You ~~[WILL/WILL NOT]~~ have to pay for this treatment. You will be told where you can receive additional treatment for your injuries. The U.S. NIH does not have a mechanism to pay money or give other forms of compensation for research related injuries. You do not give up any legal rights by signing this consent form. **If you become ill or injured as a result of participation in this study, medical treatment for the adverse reaction or injury will be provided appropriately. The site staff will refer you for ongoing treatment for the injury, if needed. IPM will be responsible for compensation for appropriate medical expenses for treatment of any such illness or injury. An HIV infection that occurs during the course of the trial will not be considered an injury or illness caused by trial participation. The research site or sponsor is not responsible for any loss, injuries and/or damages that are caused by any of the following things:**

- Any injury that happens because you used other medicine during the study that you did not tell us about
- Any injury that happens because you did not follow instructions given by the study doctor or nurse
- Any injury that happens because of negligence on your part

The following revisions (3-6) identify a subset of participants – those who have undergone supracervical hysterectomy or bilateral oophorectomy verified by medical records – as not subject to the protocol requirements of pregnancy testing and contraception counselling:

3. Section 7, Visit Tables 8-9, 11-13 and Appendix I – The π symbol and a footnote was added to the Laboratory row “Pregnancy test” to indicate that participants who have undergone supracervical hysterectomy or bilateral oophorectomy verified by medical records are not required to do pregnancy test.

Urine	• Pregnancy test π
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π Not required for participants who have undergone supracervical hysterectomy or bilateral oophorectomy verified by medical records

LABORATORY								
URINE	Pregnancy test	X π	X π	*	X π	X π	X π	*

π Not required for participants who have undergone supracervical hysterectomy or bilateral oophorectomy verified by medical records

4. Section 7.7, after the second sentence:

Persons who have undergone supracervical hysterectomy or bilateral oophorectomy verified by medical records are not required to receive contraceptive counseling.

5. Section 9.8, after the first sentence:

Pregnancy testing is not required for participants who have undergone supracervical hysterectomy or bilateral oophorectomy verified by medical records.

6. Sample Informed Consent, in Screening Visit Procedures and Enrollment and Follow-up Visit Procedures sections, under “Test your urine for pregnancy” bullet:

- **If your medical records confirm that you have had your uterus removed above the cervix or have had both ovaries removed, you will not have to have pregnancy testing performed.**

Other revisions:

7. In Section 5.4, the co-enrollment guidelines were updated to include studies involving rectal products in the list of prohibited research studies for participants while on study.

As indicated in Sections 5.2 and 5.3, participants must not take part in other research studies involving drugs, medical devices, vaginal or rectal products, or vaccines after the Screening Visit and while taking part in MTN-036/IPM 047 unless approved by the Protocol Safety Review Team (PSRT) and Protocol Chair.

8. In Section 7, Visit Tables 9, 13, 15 and Appendix I, footnotes were modified to add “approximately” before timepoints to add flexibility for sample collection following ring insertion and after ring removal.

Table 9:

- ▲ Samples to be taken **approximately** 1, 2, and 4 hours following ring insertion
- △ Sample to be taken **approximately** 4 hours following ring insertion

Table 13:

- ∞ Samples to be taken immediately prior to ring removal, as well as **approximately** 1, 2, and 4 hours following ring removal

Table 15:

- ▲ To be collected at **approximately** 1 hour, 2 hours, and 4 hours following ring insertion
- △ To be collected **approximately** 4 hours following ring insertion
- ∞ To be collected immediately prior to ring removal, as well as **approximately** 1 hour, 2 hours, and 4 hours following ring removal

Appendix I:

- ▲ Samples to be taken **approximately** 1, 2, and 4 hours following ring insertion
- △ Sample to be taken **approximately** 4 hours following ring insertion
- ∞ Samples to be taken immediately prior to ring removal, as well as **approximately** 1, 2, and 4 hours following ring removal

9. In Section 7, Visit Tables 8-13, Sections 7.11, 9.3, 9.7, 13.9, 13.10, and Appendix I, HIV-1 were modified to HIV-1/2 to clarify that the HIV testing detects both HIV-1 and HIV-2.
10. In Section 7, Visit Tables 8-11, and Appendix I, the asterisk footnote was added to the Study Product row “Offer condoms” to indicate that condoms should be offered “If indicated and/or per local standard of care.”

Study Product Supply	• Offer male condoms*
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* If indicated and/or per local standard of care

Offer male condoms	X*	X*	X*	X*	X*	X*	X*
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* If indicated and/or per local standard of care

11. In Section 7.12, *Specimen Management*, a weblink was corrected:

<http://www.mtnstopshiv.org/studies>

12. Protocol Team Roster

- Removals: Charlene Dezzutti, Lorna Rabe
- Additions:

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

**A Phase 1, Randomized Pharmacokinetics and Safety Study of Extended Duration
Dapivirine Vaginal Rings**

INVESTIGATOR SIGNATURE FORM

Version 1.0; June 28, 2017

Letter of Amendment #1, April 2, 2018

Letter of Amendment #2, August 21, 2018

A Study of the Microbicide Trials Network

Funded by:

Division of AIDS (DAIDS), US National Institute of Allergy and Infectious Diseases
US *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
US National Institute of Mental Health
US National Institutes of Health (NIH)

IND Holder:

International Partnership for Microbicides (IPM) (DAIDS Protocol ID: 30009)

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference for Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., NIH, DAIDS) and institutional policies.

I agree to maintain all study documentation for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. DAIDS will inform the investigator/institution as to when these documents no longer need to be retained.

I have read and understand the information in the Investigator's Brochure(s), including the potential risks and side effects of the products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Name of Investigator of Record (print)

Signature of Investigator of Record Date