LETTER OF AMENDMENT #1 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: 2 April 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 primary purpose of this LoA is to include language allowing international regulatory authority review of study records in both the protocol and informed consent. Other changes include incorporating protocol changes made in Clarification Memo #01, clarifying data management and documentation storage information for the in-depth interview (IDI) source data, specifying that product adherence assessments will exclude ring removals initiated by the clinician for purpose of clinical examination, a clarification to study eligibility to indicate that only symptomatic reproductive tract infections and urinary tract infections are exclusionary, adding time windows around blood collection for pharmacokinetic analyses, 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

1. The following items were previously noted in MTN-036/IPM 047, Version 1.0, CM #01, dated 14 September 2017:

   - Inclusion criterion 9d was updated:

     d) having sex exclusively with ~~cis-women~~ **individuals assigned female sex at birth**

   - The version of the DAIDS Table for Grading Adult and Pediatric Adverse Events to be used in this study was updated throughout the protocol document:

     Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, **Corrected** Version 2.1, ~~March~~ **July** 2017

The following revisions (#2-5) have been made to allow international regulatory authority review of study records:

2. Section 12, Clinical Site Monitoring, last paragraph, second sentence:

   The IoR/designee also will allow inspection of all study-related documentation by authorized representatives of the MTN Coordinating LOC, SDMC, LC, IPM, NIAID, FDA, OHRP, IRBs and **other** local**,** ~~and~~ US**, or international** regulatory authorities.

3. Section 13, Human Subjects Protections, first paragraph, last sentence:

   The IoR/designee will permit audits by the NIH, IPM, the FDA, OHRP, MTN LOC, IRBs, SDMC, and other local**,** ~~and~~ US**, or international** regulatory authorities or any of their appointed agents.

4. Section 13.6, Participant Confidentiality, first bullet point:

   Representatives of the US Federal Government, including the US FDA, OHRP, NIH, and/or contractors of the NIH**, and other local, US, or international regulatory authorities**

5. Appendix III, Sample Informed Consent Form, Confidentiality, first bullet point:

   Representatives of the US Federal Government, including the US FDA, US OHRP, NIH, contractors of NIH, and other local**,** ~~and~~ US **or international** regulatory authorities.

The following revisions (#6-8) have been made to clarify data management and documentation storage for the IDI source data, including audio recordings:

6. Section 7.9, In-depth Interview has been revised to specify IDI interview notes, recordings and transcripts as data source documentation:

   The audio from the IDI will be recorded and transcribed for analysis. **The interview notes, recording and transcript will be considered as source documentation.**

7. Section 11.1, Data Management Responsibilities, second paragraph, first sentence, has been revised to be more clear about storage of different interview file types:

   Transcriptions of interviews will be generated **by an external transcription service using the audio files recorded at RTI. Both the audio files and the transcripts will be** ~~in the field and~~ electronically transferred **to RTI** using a secure File Transfer Protocol site, where they will be uploaded and managed using a qualitative software package. **Interview notes will be kept at RTI in the participant files.**

8. Appendix III, Sample Informed Consent Form, In-depth Interview Subset section has been revised to add information regarding the destruction of audio recordings to the end of the paragraph:

   [*Sites to modify with their site-specific source documentation storage duration requirements if required by their IRBs:* The audio recordings, notes, and transcripts from these materials will be kept for at least two years after the vaginal ring is approved for marketing or two years after all developmental research on the vaginal ring is stopped.]

The following revisions (#9-10) have been made to specify that product adherence assessments will exclude ring removals initiated by the clinician for purpose of clinical examination:

9. Section 7.9, the Product Adherence Assessment section:

   The questions will assess study VR use, report of frequency of study VR removal/expulsions (voluntary and involuntary) and duration without VR inserted in the vagina. **(Clinician-initiated VR removals for the purpose of clinical examination are to be excluded from consideration during product adherence assessment.)**

10. Section 10.7.3, Adherence Analysis section:

    To assess adherence of participants to the assigned VR, the proportion of participants who kept the study VR inserted at all times during the 91 days will be calculated along with a 95% confidence interval. **(Clinician-initiated VR removals for the purpose of clinical examination will be excluded from consideration.)**

Other revisions:

11. Protocol Team Roster

    - Removals: Colin O'Rourke, Josephine Ayankoya
    - Additions:

    Holly Gundacker, MS
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12. Section 5.3, exclusion criterion 2 was clarified to indicate that only symptomatic disease is exclusionary.

    Diagnosed with a **symptomatic** UTI or reproductive tract infection (RTI) at Screening or Enrollment

13. Section 7.8, Pharmacokinetics, Table 15, footnote ▲ (regarding blood samples to be collected at the Enrollment visit):

    ▲ To be collected at 1 hour **+/- 15 minutes**, 2 hours **+/- 15 minutes**, and 4 hours **+/- 15 minutes** following ring insertion

14. Appendix III, first paragraph, second sentence: as the study IND is held by IPM, the following statement was updated:

    This study is sponsored by **International Partnership for Microbicides (IPM)** ~~the US National Institutes of Health (NIH)~~ and conducted by the Microbicide Trials Network (MTN).

15. Protocol Signature Page was updated to include Letter of Amendment #1; it is appended to the end of this document.

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

MTN-036/IPM 047

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INVESTIGATOR SIGNATURE FORM
Version 1.0; June 28, 2017
Letter of Amendment #1, April 2, 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