LETTER OF AMENDMENT #01 TO:

MTN-026

A Randomized, Double Blind, Placebo-Controlled, Phase 1 Safety and Pharmacokinetic Study of Dapivirine Gel (0.05%) Administered Rectally to HIV-1 Seronegative Adults

Version 2.0, dated 21 July 2017

DAIDS Protocol #12021
IND #136320

Date of Letter of Amendment: 22 March 2018

Site Instruction

The following information impacts the MTN-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 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-026. 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. This LoA also incorporates protocol changes made in Clarification Memo (CM) #01, changes some time points of required pregnancy testing, specifies in-depth interview (IDI) source data and clarifies IDI source data storage, adds the IND number to the protocol document, adds rationale for timing of the study washout period for female participants, incorporates language to make timing of some sample collection more flexible, and corrects other minor errors.

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-026, Version 2.0, CM #01, dated 13 October 2017:

   - The following revisions were made to Section 2.3.4, *Animal Studies of Universal Placebo Gel,* first sentence of "Local Tolerance" sub-section, and to the Reference List, respectively:

     A 10-day rabbit vaginal irritation study (10 per arm, 2 arms, placebo gel vs. 0.9% saline control) found the HEC-based placebo gel was not irritating to the vaginal mucosa of rabbits when dosed daily for 10 days.[5,~~7~~]

     ~~7. Gilead Sciences. Investigator's Brochure: Tenofovir Gel (GS-1278). Second Edition. 3-31-2005.~~

- The following revisions were made to Section 2.4.1, *Clinical Studies of Dapivirine Gel,* second sentence of first paragraph, and to the Reference List, respectively:

  In addition, one Phase 1 clinical trial has been conducted in 48 male participants to evaluate the safety and tolerability of dapivirine vaginal gel (Gel 4759) following multiple topical penile exposures.[1, 9 ~~10, 11~~]

  ~~11. International Partnership for Microbicides (IPM). Investigator's Brochure: Dapivirine Vaginal Gel (Version 7.0 Final). Version 7.0. 8-28-2013.~~

- Reference numbering for citations #8-10 were revised to citations #7-9 and reference numbering for citations #12-35 were revised to citations #10-33 throughout the protocol text and Reference List.

- The following revisions were made to Section 10.4.1, *Safety Endpoints*, last sentence of fourth paragraph:

  Hence, while comparisons will be made between the drug containing ~~VR~~ arm of the study and the placebo ~~VR~~ arm, the study will only have power to detect very large differences in safety event rates.

- The following revision was made to Appendix I*: Schedule of Study Visits and Evaluations*, fifth row of *Clinical* section:

	Visit 1 SCR	Visit 2 ENR	Visit 3 Dosing Visit	Visit 4, 5, 6 (Sampling Assigned 4, 5, or 6)	Visit 7, 8, 9, 10, 11, 12: Dosing Visits*	Visit 13 (Final Dose)/ Early Term	Visit 14, 15, 16, (Sampling Assigned 14, 15 or 16)	Visit 17 F/U Contact
CLINICAL								
Perform rectal examination	X	X	X	Φ (Visit 4, 5 or 6)	▲ (Visits 7 & 8 only)	X	Φ (Visit 14, 15 or ~~15~~**16**)	

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 LOC, SDMC, LC, NIAID, FDA, OHRP, IRBs/ECs 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, the FDA, OHRP, MTN LOC, IRBs/ECs, 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, the US OHRP, NIH, and/or contractors of the NIH, and other local**,** ~~and~~ US**, or international** regulatory authorities

5. Appendix III, Sample Informed Consent Document, Confidentiality section, second bullet point:

   Other local**,** ~~and~~ US**, or international** regulatory authorities

The following revisions (#6-10) have been made to add required pregnancy testing for female participants to Visit 3, and to change pregnancy testing currently required for Visit 14 to be performed on Visit 13 instead:

6. Section 7.4, Table 9 (Visit 3), in the Urine section:

Urine	• Collect urine – **Qualitative hCG ♀** – Dipstick UA* – Urine culture* – Urine NAAT for GC/CT*

7. Section 7.7, Table 12 (Visit 13), in the Urine section:

Urine	• Collect urine – **Qualitative hCG ♀** – Dipstick UA* – Urine culture* – Urine NAAT for GC/CT*

8. Section 7.8, Table 13 (Visits 14-16), in the Urine section:

Urine	• Collect urine ~~– Qualitative hCG ♀∞~~ – Dipstick UA* – Urine culture* – Urine NAAT for GC/CT*

9. Appendix I, Urine section, Qualitative hCG row:

	Visit 1 SCR	Visit 2 ENR	Visit 3 Dosing Visit	Visit 4, 5, 6 (Sampling Assigned 4, 5, or 6)	Visit 7, 8, 9, 10, 11, 12: Dosing Visits*	Visit 13 (Final Dose)/ Early Term	Visit 14, 15, 16, (Sampling Assigned 14, 15 or 16)	Visit 17 F/U Contact
URINE								
Qualitative hCG	♀	♀	♀		▲♀ (Required at Visit 7)	♀	♀ ~~(Visit 14 only)~~	

10. Appendix III:
    - In the Dosing Visit (Visit 3) section and Final Dosing Visit (Visit 13) section, addition of a second bullet under "Study staff will:":
        - o **(For females) Test your urine for pregnancy**
    - In the Final Dosing Visit (Visit 13) section, addition of a fifth bullet under "Study staff will:":
        - o **(For females) Test your urine for pregnancy**
    - In Sampling Visits (Visits 14-16) section, deletion of the fifth bullet from the end of the section:
        ~~(For females) Test your urine for pregnancy (Visit 14)~~

The following revisions (#11-12) have been made to identify IDI source data and clarify source data storage:

11. Section 7.14, Behavioral Assessments, third paragraph:

    These interviews will be triangulated with the behavioral data to understand participants' experiences in greater depth. **The interview notes, recording and transcript from the in-depth interview will be considered as source documentation.**

12. Appendix III, Dosing Visit (Visit 3) and Sampling Visits (Visits 14-16) sections:

    This conversation will be recorded, but your responses will be kept private and confidential~~, and the audio-recording will be destroyed after it has been transcribed and checked~~. You will be asked questions about your thoughts on the study product, what might make the product more appealing to use and your experience with administering the gel in the clinic. **Following the interview or discussion, the audio file should be uploaded onto a password protected hard drive. The IDI source recordings, along with transcripts, notes, and analyses will be kept securely stored by the University of Pennsylvania for entire period of study implementation. [*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 gel is approved for marketing or two years after all developmental research on the gel is stopped**.]

The following revisions (13 - 16) have been made to allow flexibility in timing of sample collection:

13. Section 7.4, Table 9 and Section 7.7, Table 12 - a footnote common to both tables was revised to allow flexibility in timing of sample collection:

    - Participants will be assigned to provide samples at ~~either~~ **approximately** 30-60 or 120 minutes.

14. Section 7.15, Pharmacokinetics, Pharmacodynamics and Mucosal Safety: Table 15 - a footnote was added

    Note: All sampling times are approximate; allowable windows are provided in the MTN-026 SSP manual.

15. Appendix I, Anorectal Samples section – a footnote was added to the table:

    Note: All sampling times are approximate; allowable windows are provided in the MTN-026 SSP manual.

16. Appendix III, in the Enrollment Visit, Dosing Visit (Visit 3) and Final Dosing Visit (Visit 13) sections:

    … either **approximately** between 30-60 minutes later or two hours later**,** …

Other revisions:

17. Page 1 has been revised to add the IND number to the protocol title page.

    IND#: ~~[XXXXX]~~ **136320**

18. The Protocol Roster was revised to add:

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19. Section 7.6, the Note after the first paragraph has been revised to clarify the rationale for the stated timing of the study washout period for female participants.

    The washout period should be timed to coincide with female participants' menses **as menstrual-like bleeding may complicate interpretation of lab assays.**

20. Protocol Signature Page was updated to include Letter of Amendment #01; 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-026

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INVESTIGATOR SIGNATURE FORM

Version 2.0; July 21, 2017
Letter of Amendment #01, March 22, 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

IND Sponsor:
DAIDS (DAIDS Protocol ID: 12021)

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