LETTER OF AMENDMENT #01 TO:

MTN-042

Phase 3b, Randomized, Open Label Safety Trial of Dapivirine Vaginal Ring and Oral TRUVADA® Use in Pregnancy

Version 2.0, dated May 20, 2021

DAIDS Protocol #38544
IND #139598

Date of Letter of Amendment: 1 October 2021

Site Instruction

The following information impacts the MTN-042 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-042. The purpose of this LoA is to change one of the Protocol Chairs for the study due to the unexpected and untimely passing of our esteemed colleague Dr. Bonus Makanani. This LoA also modifies consent form language regarding the regulatory status of the Dapivirine Vaginal Ring-004 (25 mg) (DPV VR), removes the prohibition of vaginal medication use to treat candidiasis, clarifies that completion of 6-week Post Pregnancy Outcome (PPO) Visit/Study Exit Visit (SEV)/Early SEV procedures should be attempted as a phone contact if necessary, and updates the Protocol Team roster.

Unless otherwise noted below, text to be deleted is noted by ~~strikethrough~~, text to be added is noted in **bold**, and text in ***bold italics*** is not to be added, but to serve as a clarification of the implementation item in question.

Detailed Listing of Revisions

The following revisions (1-2) were made to change one of the Protocol Chairs for the study due to the unexpected and untimely passing of our esteemed colleague Dr. Bonus Makanani:

1. Protocol Cover Page, Protocol Chairs:

   Katherine Bunge, MD, MPH

~~Bonus Makanani, MBBS, FCOG(SA)~~ **Felix Mhlanga, MBChB, MMed**

2. Protocol Summary, Protocol Chairs:

   Protocol Chair**s**: Katherine Bunge, MD, MPH
   ~~Bonus Makanani, MBBS, FCOG(SA)~~ **Felix Mhlanga, MBChB, MMed**

The following revision was made to update language in the sample informed consent (SIC) forms regarding the DPV VR's regulatory status as countries continue to consider and start approving its use for HIV prevention:

3. Last sentence of first paragraph of "Study Details – Study Products" section in Appendices VI-VII, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage and Off-Site Visit), MOTHER – COHORTS 2-3* and Appendix VIII, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage, Off-Site Visit, and Photography), INFANT*:

   It remains under review by **regulatory authorities in the United States and several African countries. Study staff can keep you informed on progress being made towards approvals.** ~~the US Food and Drug Administration (FDA) and has yet to be approved for HIV prevention in any country.~~

The following revisions (4-5) were made to remove the prohibition of vaginal medication use to treat candidiasis:

4. First sentence of second paragraph of Section 6.6, *Concomitant Medications and Practices*:

   The use of vaginal products, including, spermicides, lubricants, contraceptive VRs, douches, vaginal medications, etc., is prohibited**, with exceptions for vaginal treatment of candidiasis**.

5. First sentence after "Activity" table in "What procedures will be done for this study?" section of Appendices VI-VII, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage and Off-Site Visit), MOTHER – COHORTS 2-3*:

   Using vaginal products like spermicides, lubricants, contraceptive vaginal rings, douches, vaginal medications **(with exceptions)**, etc., is not allowed at any time during this study.

The following revisions (6-9) were made to clarify that completion of some 6-week PPO Visit/SEV/Early SEV procedures should be attempted as a phone contact if participants will be unable to return to the clinic to complete those procedures within the visit window:

6. Third sentence of Section 7.5.3, *6-week PPO/Study Exit Visit (SEV)/Early SEV*:

   This will be the Study Exit Visit (SEV) for all participant mothers.*****

**** If participant mothers will be unable to return to the clinic to complete their SEV within the visit window, study staff should attempt to complete as many of the visit procedures as possible through a phone contact.***

7. Added bullet point to list in Section 7.7.5, *Interim Visits*:

   - **To capture safety outcomes of participant mothers at study end (e.g., if a participant misses her 6-week PPO Visit/SEV/Early SEV).**

8. Added sentence to fourth paragraph of "Why You May Stop Taking the Study Drug Early or Be Asked to Leave the Study" section in Appendices VI-VII, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage and Off-Site Visit), MOTHER – COHORTS 2-3*:

   If you are unable to come back for one final clinic visit, staff members will contact you by phone to complete some of the procedures we talked about earlier.

9. Added sentence to second paragraph of "Why Your Baby May Be Asked to Leave the Study" section in Appendix VIII, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage, Off-Site Visit, and Photography), INFANT*:

   If you are unable to come back for one final clinic visit, staff members will contact you by phone to complete some of the procedures we talked about earlier.

10. Protocol Team Roster – Deletion: Bonus Makanani.

11. Protocol Team Roster – Additions:

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12. 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-042

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INVESTIGATOR SIGNATURE FORM
Version 2.0; May 20, 2021
Letter of Amendment #01; October 1, 2021

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:
DAIDS (DAIDS Protocol ID: 38544)

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