LETTER OF AMENDMENT #02 TO:

MTN-039

A Phase 1 Open Label Safety and Pharmacokinetic Study of Rectal Administration of a Tenofovir Alafenamide/Elvitegravir Insert at Two Dose Levels

Version 1.0, dated March 6, 2019

DAIDS Protocol #38470
IND #145334

Date of Letter of Amendment: 23 March 2020

Site Instruction

The following information impacts the MTN-039 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-039. The purpose of this LoA is to add an enema as a clinical procedure to the two dosing visits (Visit 3 and Visit 7) so that participants will have an enema prior to rectal administration of the study product at both visits in addition to the enema self-administered at home the evening prior to the two dosing visits.

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 (1-4) were made to add an enema to the two dosing visits and the Sample Informed Consent.

1. After the first sentence of the second paragraph in Section 6.1, *Regimen*:

   Participants will self-administer a saline enema at home the evening prior to a clinic dosing visit. **In addition, another saline enema will be administered in the clinic at each dosing visit prior to administration of the rectal insert(s).**

2. In Table 12 of Section 7.4.1, *Dosing – Visits 3 and 7:*

Clinical	• **Perform rectal enema prior to dosing**

3. In clinical section of Appendix I: *Schedule of Study Visits and Evaluations:*

	Screening Visit 1	**Enrollment** Visit 2 (Day 0)	**Dosing** Visits 3, 7	**24 hours Post-Dosing** Visits 4 and 8	**Other Post-Dosing** Visits 5, 6, 9, and 10	**Final Contact/Early Termination** Visit 11
CLINICAL						
Perform rectal enema prior to dosing			**X**			

4. After the third bullet point in Appendix III, under *Dosing Visits (Visits 3 and 7):*

    - Discuss any health problems you may have had since your last visit (including what medications you are taking)
    - **In preparation for the rectal sample collection, you will have an enema (rectal lavage)**
    - Have study insert(s) administered by study staff

5. Protocol Signature Page was updated to include Letter of Amendment #02; 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-039

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INVESTIGATOR SIGNATURE FORM
Version 1.0; March 6, 2019
Letter of Amendment #01; 20 September 2019
Letter of Amendment #02; 23 March 2020

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: 38470)

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