

**LETTER OF AMENDMENT #04 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: 30 September 2021**

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*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. The following information does not impact the sample informed consent. Upon receiving final IRB/EC and any other applicable Regulatory Entity (RE) approval(s) for this LoA, sites should 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 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 primary purpose of this LoA is to clarify sample testing for tenofovir alafenamide (TAF) and tenofovir diphosphate (TFV-DP) concentrations as primary endpoints in the protocol. This LoA will add rectal mucosal tissue homogenates to sample testing to measure TAF concentrations and remove rectal mucosal tissue homogenates from testing to measure TFV-DP concentrations.

Unless otherwise noted below, text to be deleted is noted by ~~strike through~~, 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.

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*Detailed Listing of Revisions*

*The following revisions (1-4) were made to add rectal mucosal tissue homogenates to sample testing to measure TAF concentration and remove rectal mucosal tissue homogenates from testing to measure TFV-DP concentration.*

1. In the second to fourth bullet lists of pharmacokinetics in the "Primary Endpoints" subsection of *Protocol Summary*:

**Pharmacokinetics**

- EVG concentrations in:
  - Blood
  - Rectal fluid
  - Rectal mucosal tissue homogenates

- TAF and TFV concentrations in
  - Blood
  - Rectal fluid
  - **Rectal mucosal tissue homogenates**
- TFV-DP concentration in:
  - ~~◦ Rectal mucosal tissue homogenates~~
  - Rectal mucosal tissue cell isolates
- ~~• TFV concentrations in~~
  - ~~◦ Rectal mucosal tissue homogenates~~

2. In the second to fourth bullets of pharmacokinetics in the “Primary Endpoints” subsection of Section 4.2, *Summary of Major Endpoints*:

**Pharmacokinetics**

- EVG concentrations in:
  - Blood
  - Rectal fluid
  - Rectal mucosal tissue homogenates
- TAF and TFV concentrations in
  - Blood
  - Rectal fluid
  - **Rectal mucosal tissue homogenates**
- TFV-DP concentration in:
  - ~~◦ Rectal mucosal tissue homogenates~~
  - Rectal mucosal tissue cell isolates
- ~~• TFV concentrations in~~
  - ~~◦ Rectal mucosal tissue homogenates~~

3. In the second to fourth bullets of pharmacokinetics in the “Primary Endpoints” subsection of Section 10.2, *Study Endpoints*:

**Pharmacokinetics**

- EVG concentrations in:
  - Blood
  - Rectal fluid
  - Rectal mucosal tissue homogenates
- TAF and TFV concentrations in
  - Blood
  - Rectal fluid
  - **Rectal mucosal tissue homogenates**
- TFV-DP concentration in:
  - ~~◦ Rectal mucosal tissue homogenates~~
  - Rectal mucosal tissue cell isolates

- ~~TFV concentrations in~~
- ~~Rectal mucosal tissue homogenates~~

4. In the “Rectal Tissue” column in *Table 16: Specimens to be Collected to Assess Safety, PK and Ex Vivo Antiviral Activity*, of Section 7.10, *Pharmacokinetics (PK) and Pharmacodynamics (PD)*:

Study Visit	Specimens collected for PK, PD and mucosal safety			
	Blood	Rectal Fluid	Rectal Tissue	CVF
Visit 3 & Visit 7 - Samples collected at 1, 2, 4 and 6 hours	<ul style="list-style-type: none"> <li>• Blood for PK</li> </ul>	<p><b>Group 1 at 2-hour</b></p> <ul style="list-style-type: none"> <li>• RF for microbiome</li> <li>• RF for PK</li> <li>• RF for PD</li> </ul> <p><b>Group 1 at 6-hour</b></p> <ul style="list-style-type: none"> <li>• RF for PK</li> </ul> <p><b>Group 2 at 4-hour</b></p> <ul style="list-style-type: none"> <li>• RF for PK</li> </ul>	<p><b>Group 1 only at 2-hour</b></p> <ul style="list-style-type: none"> <li>• 7 samples for biomarkers</li> <li>• 4 samples for PD</li> <li>• 11 samples for PK               <ul style="list-style-type: none"> <li>○ 1 for EVG</li> <li>○ 1 for <b>TAF and TFV and <del>TFV- DP</del></b></li> <li>○ 1 for backup</li> <li>○ 8 for MMC isolation</li> </ul> </li> </ul>	<p><b>Group 1 at 2-hour</b></p> <ul style="list-style-type: none"> <li>• CVF for microflora</li> <li>• CVF for PK</li> <li>• CVF for PD</li> </ul> <p><b>Group 1 at 6-hour</b></p> <ul style="list-style-type: none"> <li>• CVF for PK</li> </ul> <p><b>Group 2 at 4-hour</b></p> <ul style="list-style-type: none"> <li>• CVF for PK</li> </ul>

5. Protocol Signature Page was updated to include Letter of Amendment #04; it is appended to the end of this document.

The above information, as well as the changes from LoA#01, LoA#02 and LoA#03, will be incorporated into the next version of the protocol at a later time if it is amended.

**MTN-039**

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

**INVESTIGATOR SIGNATURE FORM**

**Version 1.0; March 6, 2019**

**Letter of Amendment #01; 20 September 2019**

**Letter of Amendment #02; 23 March 2020**

**Letter of Amendment #03; 24 July 2020**

**Letter of Amendment #04; 30 September 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: 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.

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Name of Investigator of Record (print)

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Signature of Investigator of Record

\_\_\_\_\_  
Date