LETTER OF AMENDMENT #01 TO:

MTN-003
DAIDS Document ID 10622

Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women

Version 1.0/22 May 2008
IND # 55,690

Letter of Amendment Date: March 31, 2009

Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the MTN-003 study and must be forwarded to your Institutional Review Board (IRB) and/or Ethics Committee (EC) as soon as possible for their information and review. Site IRBs/ECs are responsible for assessing whether and how the changes included below are communicated to study participants. All IRB/EC requirements must be followed. As this LoA does not impact the overall risk-to-benefit profile of study participation or the informed consent documents, re-consenting is unnecessary. This LoA and all associated IRB/EC correspondence should be filed in essential documents files for MTN-003.

Summary of Revisions and Rationale

This LoA does not impact the overall design and study visit schedule for MTN-003. This LoA provides clarification on the following items:

1. Modifications to the Protocol Team, affecting the Protocol Team Roster, and updates to Sections 1.2 and 1.3
2. Elimination of a discrepancy between the protocol and Sample Informed Consent Form (Enrollment) regarding acquisition of specimens for PBMC analysis
3. Allowance for site-specific approaches to the timing of the informed consent process for storage and future research testing of specimens, to decrease burden to participants
4. Procedures during product hold periods and following permanent discontinuation, to decrease burden to study participants
5. Safety reporting requirements, including omission of fetal losses as reportable adverse events
6. Other minor corrections and updates

Implementation

This LoA is official MTN-003 protocol documentation. Prior to implementing revisions listed here, study sites will submit the LoA to all relevant regulatory authorities and IRBs/ECs. The DAIDS Regulatory Affairs Branch will submit the LoA to the US Food and Drug Administration for inclusion in Investigational New Drug application # 55,690. Upon receipt of all required regulatory and IRB/EC approvals, the revisions listed below will be implemented. Except for modifications to the Protocol Team Roster, text to be deleted is noted by ~~strikethrough~~ and text to be added is noted in **bold**.

Detailed Listing of Revisions

1. The Protocol Team Roster, Section 1.2, and Section 1.3 are updated to reflect modifications to the Protocol Team and updates to contact information.

The following additions are made to the Protocol Team Roster:

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The following listings are deleted from the Protocol Team Roster: Salim Abdool Karim, Nomampondo Barnabas, Muzala Kapina, Corey Kelly, Ayesha Kharsany, and Alain Kouda.

The following listings have updated contact information:

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In Sections 1.2 and 1.3, the following modifications are made:

1.2 Sponsor and Monitor Identification

Sponsor: CONRAD
~~1611 North Kent Street, Suite 806~~**1911 North Fort Myer Drive, Suite 900**
Arlington, VA 22209 USA

1.3 Medical Officer~~s~~

Medical Officer: Jeanna Piper, MD
6700 B Rockledge Drive, Room 5248
Bethesda, MD 20892 USA

~~Medical Officer: Lydia E. Soto-Torres, MD, MPH~~
~~6700 B Rockledge Drive, Room 5138~~
~~Bethesda, MD 20892-7628 USA~~

2. For consistency with the Sample Informed Consent Form (Enrollment), the protocol is modified (PBMC archive is deleted) in Sections 7.5.3, 7.6.1, 7.11, and Appendix I.

   In Section 7.5.3, Laboratory Procedures:

~~• PBMC archive:~~
~~o If indicated (when blood is collected [each sample] for Sample 2 per Appendix III~~
~~o Additionally if required per Section 7.6.1~~

In Section 7.6.1, Participants Who Become Infected with HIV, sixth paragraph:

~~• PBMC archive:~~
~~o Months 1, 3, 6 and every 6 months post-seroconversion~~

Plasma ~~and PBMC~~ collected at the above-listed time points, as well as when blood is collected for confirmatory HIV testing, will be shipped to the MTN NL and utilized for the following:

In Section 7.11, Laboratory Procedures, under Local, Regional, or Network Laboratory:

~~• PBMC archive~~

In Appendix I, SCHEDULE OF STUDY VISITS AND EVALUATIONS, the following deletion is made to the second note under the first table and to procedures in the second table (SCHEDULE OF POST-HIV-1 SEROCONVERSION LABORATORY PROCEDURES):

Note: *If Sample 2 is drawn (per Appendix III), blood is also collected for the following analyses: Plasma archive, CD4+ T-cell count,* ***and*** *HIV-1 RNA PCR~~, and PBMC archive~~.*

SCHEDULE OF POST-HIV-1 SEROCONVERSION LABORATORY PROCEDURES

~~PBMC Archive~~	~~X~~	~~X~~	~~X~~	~~X~~	

3. In Section 7.4.2, a note is added under the first bullet to allow for site-specific approaches to timing the completion of the informed consent for specimen storage and possible future research testing. Appendix I is updated accordingly.

   7.4.2 Administrative, Behavioral, and Regulatory Procedures

   • Informed consent for specimen storage and possible future research testing
   Note: may be deferred (no later than Month 3 follow-up visit) in accordance with site SOPs.

In Appendix I, Schedule of Study Visits and Evaluations, the following note is added under the first table.

NOTE: Informed consent for specimen storage and possible future research testing may be deferred (no later than Month 3 follow-up visit) in accordance with site SOPs

4. In Section 7.6, Follow up Procedures for Participants Who Temporarily Hold or Permanently Discontinue Study Product, the following clarification is made at the end of the first paragraph:

   When a temporary hold or permanent discontinuation of study product occurs, the following assessments will be performed as noted below, and then discontinued until study product use resumes (in the case of a temporary hold):
   - **Adherence assessment will be performed:**
     - **at the next monthly visit (if product hold/discontinuation starts < 7 days prior to the visit)**
     - **at the next quarterly visit (if product hold/discontinuation starts < 4 weeks prior to the visit)**
   - **Last dose recall will be performed at the next quarterly visit**
   - **Study product sharing assessment and assessment of partner's reaction to study product use will be performed at the next annual visit (if product hold/discontinuation starts < 4 weeks prior to the visit)**

5. Fetal losses are omitted as reportable AEs via edits to Section 8.2 and text regarding EAE reporting is updated in Section 8.3.

In Section 8.2, Adverse Events Definitions and Reporting Requirements, third paragraph, text is added:

Study site staff will document in source documents all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. Study staff also will report on CRFs the following subset of AEs reported by or observed in enrolled participants:

- All genital, genitourinary, and reproductive system AEs**, except fetal losses**
  - **Fetal losses (e.g., spontaneous abortions, spontaneous fetal deaths, stillbirths) will not be reported as AEs. However, untoward maternal conditions that either result in or result from fetal losses will be reported as reproductive system AEs**
- All fractures
- All AEs of severity Grade 2 or higher in the following categories: dizziness, headache, nausea, vomiting, diarrhea, abdominal pain, rash
- All AEs of severity Grade 3 or higher
- All serious AEs, as defined by the International Conference on Harmonization Consolidated Guidance for Good Clinical Practice
- All AEs that result in permanent discontinuation of study product use
- All laboratory test abnormalities not otherwise associated with a reported clinical AE
- AEs that do not meet the above-listed criteria but do meet expedited reporting requirements per Section 8.3 below**; this includes all congenital anomalies identified in the fetuses and/or infants of study participants**.

In Section 8.2, fourth paragraph, the last sentence is deleted:

~~After the Termination Visit, only pregnancy outcomes that meet criteria for expedited adverse event (EAE) reporting (see Section 8.3 below) occurring among participants known to be pregnant at the Termination Visit will be reported.~~

In Section 8.2, fifth paragraph, first bullet, text is added, and grading criteria are modified:

- AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 and the Female Genital Grading Table for Use in Microbicide Studies (~~Appendix~~ **Addendum** 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004), except that asymptomatic BV will not be a reportable AE and **bleeding during pregnancy prior to the onset of labor (regardless of trimester) will be graded per the table below.** AEs not included in the Female Genital Grading Table will be graded by the DAIDS AE Grading Table Version 1.0, December 2004. In cases where a genital AE is covered in both tables, the Female Genital Grading Table for Use in Microbicide Studies will be the grading scale utilized.

PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
COMPLICATIONS OF PREGNANCY					
Bleeding during pregnancy prior to the onset of labor	None	Spotting or bleeding less than menses	Bleeding like menses or heavier, no intervention indicated	Profuse bleeding with dizziness or orthostatic hypotension, transfusion indicated	Potentially life-threatening profuse bleeding and/or shock

In Section 8.3, Expedited Adverse Event Reporting Requirements, two updates are made:

The EAE reporting requirements and definitions for this study and the methods for expedited reporting of AEs to the DAIDS Regulatory Compliance Center (RCC) Safety Office are defined in the DAIDS EAE Manual, available on the RCC website: http://rcc.tech-res-intl.com/. **Sites using the DAERS internet-based reporting system for submission of EAEs to DAIDS will follow the DAERS processes as outlined in the DAERS training information. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov or from within the DAERS application itself. If the site cannot use DAERS to report an AE on an expedited basis, the** EAEs must be documented on the DAIDS EAE Reporting Form available on the RCC website: http://rcc.tech-res-intl.com. DAIDS EAE forms should be submitted to DAIDS through the RCC Safety Office (rccsafetyoffice@tech-res.com) or call 1-800-537-9979 or 301-897-1709 or fax 1-800-275-7619 or 301-897-1710.

EAE Reporting Requirements for this Study
EAE Reporting Level
This study uses the Standard Level of expedited AE reporting as defined in the DAIDS EAE Manual**, except that fetal losses will not be reported as EAEs**. **Although not reported as EAEs, all fetal losses will be documented on case report forms and routinely reviewed by the PSRT and DSMB, as described in Section 8.1. After the Termination Visit, only pregnancy outcomes that meet criteria for EAE reporting (e.g., congenital anomalies) occurring among participants known to be pregnant at the Termination Visit will be reported.**

6. Minor clarifications and updates are made to Sections 5.2 and 9.5.6.

In Section 5.2, Inclusion Criteria, text is edited as follows:

4) HIV-uninfected based on testing performed by study staff at screening and enrollment (per applicable algorithm~~s~~ in Appendi**x**~~ces~~ II ~~and III~~)

In Section 9.5.6, Hypophosphatemia, the following edits are made:

ORAL STUDY PRODUCT
Grades 1 and 2
The phosphate test should be repeated within 2 weeks of the receipt of the results. **Intake of** ~~Supplemental phosphate should be given with~~ phosphate-rich food or fluid ~~with or without neutral phosphate solution~~ **should be advised**. **Oral phosphate supplementation may be implemented at the discretion of the site investigator. Other causes of low phosphate should be investigated.** Unless other temporary product hold requirements apply, study product need not be held.

Grades 3 and 4
The phosphate test should be repeated within 1 week of the receipt of the results. **Intake of** ~~Supplemental phosphate should be given with~~ phosphate-rich food or fluid ~~with or without neutral phosphate solution~~ **should be advised. Oral phosphate supplementation may be implemented at the discretion of the site investigator.** Other causes of low phosphate should be investigated. During the time that supplemental phosphate is provided to the participant and the time that testing is repeated, sites should follow temporary product hold/permanent discontinuation guidelines described in Section 9.4. If improvement to ≤ Grade 2 can not be documented within one week **of the receipt of the Grade 3 or 4 result**, study product must be permanently discontinued.