LETTER OF AMENDMENT #01 TO:

MTN-012/IPM 010
DAIDS Document ID: 11771

Male Tolerance Study of Dapivirine Gel Following Multiple Topical Penile Exposures

Version 1.0 / 29 November 2010

IND# 69,022

Letter of Amendment Date: February 11, 2011

Instructions to Study Sites from the Division of AIDS

The following information impacts the MTN-012/IPM 010 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 will also impact the sample informed consent. Your IRB/EC will be responsible for determining the process of informing subjects of the contents of this letter of amendment.

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 an 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. An 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 and Rationale

This LoA does not impact the overall design and study visit schedule for MTN-012/IPM 010. This LoA includes changes to the following items:

1. Updates to Section 5.3, *Exclusion Criteria*, to reflect the Cockcroft-Gault formula for males.
2. Updates to Section 6.7, *Study Product Adherence*; Section 7.2, *Enrollment*; Section 7.9, *Behavioral Assessments*; Appendix I and the *Enrollment Sample Informed Consents*; to indicate that the Phone Reporting System will not be used to collect adherence data during the study.
3. Section 7.6, *Interim Visit*, Table 11: *Interim Visit* updated to indicate that participants will be counseled regarding product use instructions, if indicated.
4. Updates to the Protocol Team Roster.
5. List of Abbreviations and Acronyms has been updated.

Implementation

This LoA is official MTN-012/IPM 010 protocol documentation. Prior to implementing the revisions listed below, the MTN-012/IPM 010 study sites will submit this LoA to all relevant regulatory authorities and the IRB/EC. Upon receipt of all required regulatory and IRB/EC approvals, the protocol revisions listed below will be implemented. With the exception of protocol roster changes, 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 update was made to Section 5.3, *Exclusion Criteria*, j., vi., to reflect the Cockcroft-Gault formula for males.

   Calculated creatinine clearance less than 80 mL/min by the Cockcroft-Gault formula ~~where creatinine clearance in mL/min= (140-age in years) X (weight in kg) x 0.85/72 x serum creatinine in mg/dL.~~ **for males."**

2. The following changes are made to Section 6.7, *Study Product Adherence*; Section 7.2, *Enrollment*; Section 7.9, *Behavioral Assessments*; Appendix I: *Schedule of Study Visits and Evaluations* and Appendix IV: *Enrollment Sample Informed Consents*; to indicate that the Phone Reporting System will not be used to collect adherence data during the study.

   Section 6.7, Study Product Adherence Counseling and Assessment, second paragraph:

   Participants will be instructed to apply the product daily before bedtime, usually in the evening or before longest period of rest, which is expected to result in better adherence. To monitor adherence, participants will be asked to ~~use a phone reporting system (PRS) immediately after each episode of gel use. To access the PRS, participants call a toll-free number, identify themselves to the system using a unique ID number (corresponding to the participant identification number or PTID), and then~~ respond to ~~pre-recorded~~ questions on product use ~~since last call~~ and adherence to protocol guidelines on product use **at the Final Clinic/Termination Visit**. ~~Responses to the PRS can be entered by either pressing keys (i.e., 1 for yes, 2 for no) or by voice response that is understood and registered by the system. Participants receive a small monetary incentive for each call regardless of their report of product use or lack of use; furthermore, a bonus at the end of the seven days is accrued by those who have not missed any day in calling the system. When participants do not call the system within 48 hours, an alert is automatically generated and sent by email to a staff member at Columbia University. The staff member at Columbia University will then contact the study coordinator at the study site who will then contact the participant to inquire about missed calls (e.g., if the participant forgot to call) and adherence to the study product regimen. Thus, this system allows monitoring of the reporting on adherence to the PRS on a time-stamped basis. Given that participants are instructed to use the product prior to their longest period of rest and to call the system immediately after applying the product, the calls are a proxy for compliance with time of application. There will be a recall question on adherence (How many times did you apply the gel on your penis during the days of the trial?) at the Final Clinic/Termination Visit. However, the answer to this question will only be used to replace PRS reporting in the case that PRS data is completely missing.~~ In addition, participants will be asked to return both used and unused applicators and these applicators will be documented by study staff.

   Section 7.2, Enrollment (Day 0), Table 8, Behavioral Component:

   Table 8: Enrollment Visit (Day 0)

Visit 2: Enrollment Visit	
Component	Procedures
Behavioral	• ~~Provide instructions on use of Phone Reporting System (PRS) to participants~~

   Section 7.9, Behavioral Assessments, first sentence:

   There will be ~~three~~**two** sets of behavioral measures used in this protocol:

   Section 7.9, Behavioral Assessments, Adherence Questionnaire and Product Acceptability Questionnaire Sections:

   ~~Adherence Questionnaire~~
   ~~Adherence will be assessed with the PRS which participants will be asked to call daily. Responses to specific questions on product use since the prior call (e.g., "Did you use the product? Y/N) will constitute~~

~~one measure of adherence. In addition, at the Final Visit, participants will be asked to report on study product use during the trial via the self-interview.~~

Product Acceptability **and Adherence** Questionnaire
This self-interview will be completed by participants at the Final Clinic Visit. This tool includes structured and semi-structured questions about experiences the participant had using the gel, likes and dislikes concerning the gel, any changes he may have introduced or may wish to introduce in the product used, any problems he may have had or product side-effects (and how much the participant was bothered by them), and likelihood of using a microbicide in the future. **Adherence will be measured by a recall question on adherence (How many times did you apply the gel on your penis during the days of the trial?) and questions related to missed doses at the Final Clinic/Termination Visit.** It is anticipated that the Product Acceptability **and Adherence** Questionnaire will include a few questions similar to those asked on the Baseline Behavioral Assessment so that responses may be compared (i.e. anticipated likelihood of product use).

Appendix I: Schedule of Study Visits and Evaluations, Behavioral Assessments section:

~~Instructions on use of Phone Reporting System~~		~~X~~			

Appendix IV: Sample Informed Consent, Enrollment, What do I have to do if I am in this study?

- ~~Receive instructions about how to call an automated phone system each time you use the gel at home. When you call, you will be asked a brief set of questions. You will learn how the phone system works, and about the compensation you will receive for the calls. You will also have the opportunity to try the phone system out and ask any questions you may have.~~

Appendix IV: Sample Informed Consent, Enrollment, Will I receive any payment?

WILL I RECEIVE ANY PAYMENT?
You will be compensated for your time and effort for your scheduled study visits ~~and phone calls~~. You will receive [SITE TO INSERT – SPECIFIC AMOUNT OF MONEY] for each visit. ~~You will receive [SITE TO INSERT – SPECIFIC AMOUNT OF MONEY] for each phone call~~. You will also be paid for other costs to you for coming to your scheduled visits [SUCH AS CHILD CARE, TRAVEL, AND LOSS OF WORK TIME – SITES TO COMPLETE].

3. Section 7.6*, Interim Visit*, Table 11: *Interim Visit* has been updated to eliminate the redundancy in the Clinical Component section of the Interim Visit. This update still allows participants to be counseled at the Interim Visit regarding product use instructions, if indicated:

Interim Visit	
Component	Procedures
Clinical	• ~~Product use instructions*~~

4. The following updates are made to the Protocol Team Roster:

Added:

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Added (continued):

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Removed:

Rebecca Giguere, MPH
Joseph Romano, PhD

5. The List of Abbreviations and Acronyms is updated:

~~PRS Phone Reporting System~~

The above information will be incorporated into the next version of the protocol at a later time if it is amended.