THE SCIENCE OF IMPROVING LIVES

MTN-003:

Overview of changes

- Increased sample size and length of follow-up
- Upper limit of age expanded
- Incorporated:
  - CMs and LoAs
  - Genital herpes acquisition endpoint
  - Information on results from other studies, including CAPRISA 004 and iPrEx
  - Changes based on updated package inserts and IBs

Overview of changes

- Reduced burden on procedures for seroconverters
- Updated lab QA procedures
- Clinical management guidance
- Statistical Considerations
- Appendix I: Schedule of Study Visits and Evaluation
- Updated Informed Consent Forms

Incorporated CMs and LoAs

Microbicide Trials Network
CLARIFICATION MEMO #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

Date of Clarification Memorandum: 27 May 2009

Section 1: Summary of Clarifications and Rationale

The items clarified in this Clarification Memorandum (CM) have been approved by the NIAID Medical Officer and are to be implemented immediately upon issuance. IRB/EC approval of this CM is not required by the sponsor; however, investigators may submit the CM to the IRB/EC overseeing the study at their site for information. This CM is official MTN-003 documentation and is effective immediately. A copy of this CM must be retained in each study site's Essential Documents file for MTN-003. No change in informed consent is necessitated by or included in this CM.

The primary goal for this CM is to update the Protocol Team Roster. A clarification to Section 8.2, Adverse Events Definitions and Reporting Requirements is also made in this CM.

Section 2: Implementation

With the exception of the modifications to the Protocol Team Roster, text to be deleted is noted by ~~strikethrough~~ and text to be added is noted below in bold.

1. The Protocol Team Roster is 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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Microbicide Trials Network
CLARIFICATION MEMO #02 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

Date of Clarification Memorandum: 25 August 2009

Section 1: Summary of Clarifications and Rationale

The items clarified in this Clarification Memorandum (CM) have been approved by the NIAID Medical Officer and are to be implemented immediately upon issuance. IRB/EC approval of this CM is not required by the sponsor; however, investigators may submit the CM to the IRB/EC overseeing the study at their site for information. This CM is official MTN-003 documentation and is effective immediately. A copy of this CM must be retained in each study site's Essential Documents file for MTN-003. No change in informed consent is necessitated by or included in this CM.

This CM provides clarification on the following items:

- Updates to the Protocol Team Roster
- Anticipated bleeding associated with speculum insertion and specimen collection
- Product hold following positive HIV test results
- Schedule of dipstick urinalysis testing
- Product hold related to hypophosphatemia
- Elimination of discrepancy between Appendix I: Schedule of Study Visits and Evaluations and the protocol

Section 2: Implementation

With the exception of the modifications to the Protocol Team Roster, text to be deleted is noted by ~~strikethrough~~ and text to be added is noted below in bold.

1. The Protocol Team Roster is updated to reflect updates to contact information.

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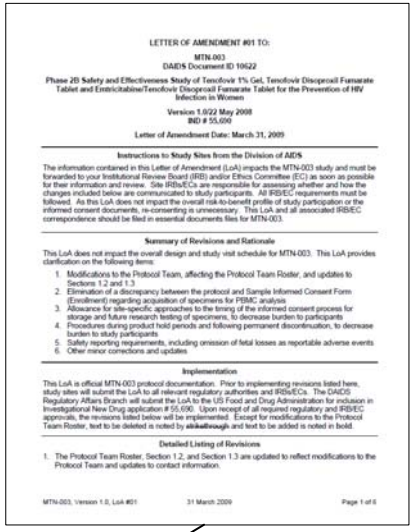

LETTER OF AMENDMENT #01 TO:

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 IRB/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.

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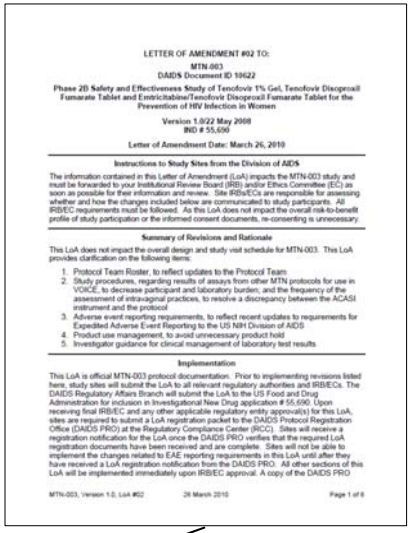

LETTER OF AMENDMENT #02 TO:

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 26, 2010

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.

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. Protocol Team Roster, to reflect updates to the Protocol Team
2. Study procedures, regarding results of assays from other MTN protocols for use in VOICE, to decrease participant and laboratory burden; and the frequency of the assessment of intravaginal practices, to resolve a discrepancy between the ACASI instrument and the protocol
3. Adverse event reporting requirements, to reflect recent updates to requirements for Expedited Adverse Event Reporting to the US NIH Division of AIDS
4. Product use management, to avoid unnecessary product hold
5. Investigator guidance for clinical management of laboratory test results

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 IRB/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 receiving final IRB/EC and any other applicable regulatory entity approval(s) for this LoA, sites are required to submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Compliance Center (RCC). Sites will receive a registration notification for the LoA once the DAIDS PRO verifies that the required LoA registration documents have been received and are complete. Sites will not be able to implement the changes related to EAE reporting requirements in this LoA until after they have received a LoA registration notification from the DAIDS PRO. All other sections of this LoA will be implemented immediately upon IRB/EC approval. A copy of the DAIDS PRO

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Version 2.0

Increased sample size and length of follow-up

Increased sample size and length of follow-up

Version 1.0	Version 2.0
N = 4,200	N = 5,000
Accrual = 21 Months	Accrual = 24 Months
Product use period: • Minimum = 12 Months • Maximum = 33 Months	Product use period: • Minimum = 12 Months • Maximum = 36 Months
Maximum length of Study Participation = 35 Months	Maximum length of Study Participation = 38 Months

HSV-1 and HSV-2 exploratory objective

- Based on CAPRISA 004 results
- To assess the incidence of genital herpes
- Tested at end of the study on enrollment and PUEV plasma archive specimens
- Participants will receive HSV tests results once these are available

Risks and Benefits

- Risks and benefits modified to reflect updates to package inserts and Investigator Brochures:
  - Phlebotomy may lead to greater than expected bleeding
  - Oral TDF Tablet:
    - depression
    - generalized weakness
    - possible damage to liver
    - bone pain and bone changes

Inclusion and Exclusion Criteria

Version 1.0	Version 2.0
Upper age limit: 40	Upper age limit: 45
(PEP) for HIV infection	(PEP) for HIV exposure
Notes (lab abnormalities):	*Notes (lab abnormalities):*
• Exclusionary dipstick results could not be repeated	• Dipstick retesting allowable if results due to UTI or menses*
• [No provision regarding serum creatinine <LLN]	• Serum creatinine results <LLN will be repeated during the Screening period

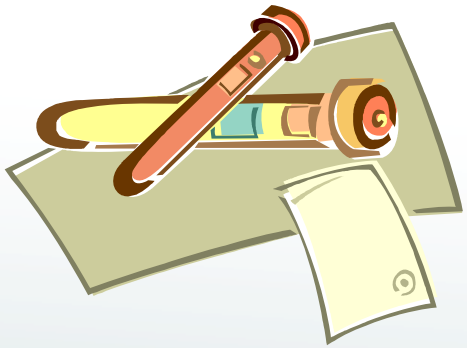
**According to the judgment of the IoR/designee*

Section 6.7: Study Product Adherence

- Clarified that study product counts and self-reported data will not be reconciled

Section 7.4: Enrollment Visit

- Administration of Informed Consent for Enrollment may precede final confirmation of eligibility
  - Allows for single blood draw at enrollment (HIV testing, plasma archive)
  - SOPs must be updated



Section 7.5: Follow-Up Study Procedures

- All pelvic exams, scheduled and unscheduled, should include the following procedures:
  - Vaginal pH
  - Vaginal fluid swab for storage for biomarker analyses
  - Endocervical swab for biomarker analyses
  - Bimanual exam
- BV and candidiasis = only when clinically indicated (symptomatic)
- Clarified behavioral measures omitted when participant not exposed to study product

Section 7.6.1: Reduced Procedures for Seroconverters

Version 1.0	Version 2.0
• HIV serology • Provision of study product, instructions, adherence counseling • Last dose recall	• HIV serology • Provision of study product, instructions, adherence counseling • Last dose recall • ACASI • Gram stain assessment • Following a final test 8 weeks after product hold, the following tests will no longer be completed: – Complete blood count with differential and platelets – Phosphate, creatinine, AST and ALT – Dipstick Urinalysis • Plasma archive at Quarterly and PUEV visits • Scheduled VOICE Termination Visit

Section 7.6.1: Changes Relating to MTN-015

For Seroconverters who delay or decline MTN-015:

- Deleted:
  - ~~HBsAb test 6M after vaccine series~~
- Refer to SSP Section 6.10 for guidance
  - HBsAb testing will be performed for these participants, regardless of enrollment in MTN-015, at 1-2 months following vaccine series.
- Enrollment Informed Consent and Appendix I of the protocol updated to incorporate this change

Section 8.2: AE Definitions and Reporting

- Clarified that an AE is considered an untoward medical occurrence from the time of randomization through study termination
- Clarified that genital bleeding clinically assessed to be expected is not an AE
- Lab test abnormalities specified in the DAIDS Toxicity Table, not otherwise associated with a reported clinical AE, are reportable AEs
- SAE/EAE (rather than AE) must be reassessed by study staff 30 days after the participant's study exit

SECTION 9: CLINICAL MANAGEMENT

Grade 3 AE - Related to Product

Not otherwise addressed in section 9

Version 1.0	Version 2.0
No documentation of improvement to ≤ Grade 2 within 2 weeks, permanently discontinue	No documentation of improvement to ≤ Grade 2 within 2 weeks, consult PSRT
Same Grade 3 AE reoccurs, Consult PSRT	Same Grade 3 AE reoccurs deemed related to study product, Consult PSRT

Grade 3 AST and/or ALT Elevations (Oral)

Version 1.0	Version 2.0
• Temporarily hold	• Temporarily hold
• Repeat ALT/AST within 1 week	• Repeat ALT/AST within 1 week
• Follow weekly until Grade ≤1, resume with concurrence from PSRT	• Follow weekly until Grade ≤1, resume with concurrence from PSRT
• If no improvement to Grade ≤1 within 3 weeks, permanently discontinue	• If no improvement to Grade ≤1 within 3 weeks, consult the PSRT

Grade 4 AST and/or ALT Elevations

Version 1.0

- Permanently discontinue
- Consult the PSRT
- Re-test at least weekly until both AST/ALT are grade ≤1

Version 2.0

If RELATED

NOT RELATED:

- Temporarily hold
- Consult the PSRT
- Re-test ALT/AST within 1 week
- Follow weekly until Grade ≤1, resume with concurrence from PSRT

Creatinine (Oral)

Version 1.0	Version 2.0
• Temporarily hold for ≥ 1.5 X BL	• Temporarily hold for ≥ 1.5 X BL
• Re-test as soon as possible to within 1 week	• Re-test as soon as possible to within 1 week
• Resume product when improves to ≤ 1.3 X BL	• Resume product when improves to ≤ 1.3 X BL, in consultation with PSRT
• If product is resumed and creatinine level increases to ≥ 1.5 X BL, permanently discontinue	• If product is resumed and creatinine level increases to ≥ 1.5 X BL, consult PSRT for further guidance on continuing product hold , or progressing to permanent discontinuation

Creatinine Clearance (Oral)

Version 1.0	Version 2.0
• If clearance is < 50mL/min product should be held	• If clearance is < 50mL/min product should be held
• Re-test as soon as possible (at most within 1 week of receipt of results)	• Re-test as soon as possible (at most within 1 week of receipt of results)
• If level of < 50mL/min is confirmed with re-test, permanently discontinued	• If level of < 50mL/min is confirmed with re-test, permanently discontinued, in consultation with PSRT
• If re-test cannot be done within 1 week plus 3 working days, permanently discontinue	• If re-test cannot be done within 1 week plus 3 working days will require PSRT consultation for further product management

Phosphate (Oral)

Version 1.0	Version 2.0
• Management of decreased phosphate was based on grading • Grade 1 and 2 • Grade 3 and 4	• Management of decreased phosphate based on ranges for phosphate results • Phosphate ≥ 2.0 mg/dL • Phosphate 1.4 - 1.9 mg/dL • Phosphate 1.0 – 1.3 mg/dL • Phosphate < 1.0 mg/dL

Version 2.0 Phosphate Guidance (Oral)

- Phosphate ≥ 2.0 mg/dL
  - Continue product, unless other hold requirements apply
  - No recheck needed before the next scheduled phosphate test (e.g. Quarterly Visit)

- Phosphate 1.4 mg/dL-1.9 mg/dL
  - Manage as ≥ 2.0 mg/dL
  - Remind participant to eat a phosphate rich diet

Phosphate (Oral), cont.

- Phosphate 1.0 - 1.3 mg/dL
  - Continue product, unless other hold requirements apply
  - Remind participant to eat a phosphate rich diet
  - May offer two week course of phosphate supplements*
  - Retest phosphate at the next study visit. If on recheck:
    - ≥ 2.0 mg/dL: follow ≥ 2.0 mg/dL guidance
    - 1.0 - 1.9 mg/dL: remind participant to eat a phosphate rich diet; may offer two week course of phosphate supplements.* Phosphate level should be rechecked at the next study visit.
    - < 1.0 mg/dL: follow guidance on Phosphate level < 1.0 mg/dL

**According to the judgment of the IoR/designee*

Phosphate (Oral), cont.

- Phosphate < 1.0 mg/dL
  - Temporary product hold
  - Advise participant to eat a phosphate rich diet
  - May offer two week course of phosphate supplements*
  - Retest within 2 weeks of the receipt of the results
    - If improvement to ≥ 1.0 mg/dL is documented within two weeks, product may be resumed and guidance related to ≥ 1.0 mg/dL followed, depending on the phosphate level result
      - If not, continue hold and consult PSRT

**According to the judgment of the IoR/designee*

Proteinuria (General)

Version 1.0	Version 2.0
• **1+** finding, confirm with a second urine dipstick no earlier than 1 week but no later than 2 weeks from detection • **2+ or greater** does not need to be confirmed at a separate visit	• **Greater than trace** finding, should prompt serum creatinine and phosphate testing on day of detection • **1+** requires a repeat dipstick 1-2 weeks after initial detection • **2+ or greater** does not need to be confirmed at a separate visit

Proteinuria (Oral)

Detection of 1+

Version 1.0	Version 2.0
• Hold product if detection of 1+ confirmed on two separate visits • Product should only be held if creatinine or phosphorus results obtained at time of detection meet hold criteria	• Product held only if creatinine or phosphorus results obtained at time of detection meet hold criteria • Detection of 1+ alone should not lead to product hold

Proteinuria (Oral)

Detection of 2+

Version 1.0	Version 2.0
• Hold product until serum creatinine or phosphorus results obtained at time of detection are available • Continue product hold if hold criteria outlined for creatinine and/or phosphate are met • If neither value meet hold criteria, study product should be resumed	• Hold product until serum creatinine or phosphorus results obtained at time of detection are available • Continue product hold if hold criteria outlined for creatinine and/or phosphate are met • If neither value meet hold criteria, study product should be resumed

Proteinuria (Oral)

Detection of 3+ or greater

Version 1.0	Version 2.0
• Hold product regardless of serum creatinine or phosphorus result obtained at time of detection • Urine dipstick, creatinine and phosphate testing should be performed monthly for at least 3 months	• Hold product and consult PSRT regarding further testing and product management

Proteinuria (Oral)

Resuming product following a hold

Version 1.0	Version 2.0
• Product use may be resumed following resolution of proteinuria no earlier than 3 months after product cessation • If product resumed and protienuria increases to 2+ or greater, product us must be permanently discontinued	• Product use may be resumed following the resolution to < 2+, and approved by PSRT • If product resumed (in the setting of 3+ or greater), and proteinuria increases to 2+ or greater, product use must be held, and PSRT consulted

Glycosuria (Oral)

Version 1.0

- Clinical management based on:
  - Detection of 1+
  - Detection of 2+
  - Detection of 3+ or greater

Version 2.0

- 1+ → confirmed ≥ 1+: temporarily hold product and test serum creatinine and phosphorus
- ≥ 2+ → Temporarily hold product and test serum creatinine and phosphorus
- PSRT must be consulted for further guidance regarding product management

Updated Informed Consent Forms

- Increased sample size
- Increased study duration
- Increased age limit (site specific)
- Added CAPRISA 004 and iPrEx results
- Updated risks
- Added HSV testing
- Clarified HIV resistance, and Hepatitis B testing
- Enrollment IC may precede final confirmation of eligibility to reduce number of blood draws

Other Updates

- Appendix III: Follow-up HIV Testing Algorithm was updated to include guidance to consult NL for participants whose Sample 1 WB are indeterminate or negative.
- Appendix IV: Algorithm for Hep B Management was modified to include that vaccination may also follow local guidelines.

Thank you!

What are your questions?