Microbicide Trials Network

Clarification Memorandum #01 to:

MTN-004
Phase I Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel™) Applied Vaginally in Sexually Active Young Women, Version #2.0, Dated 15 May 2007

DAIDS PROTOCOL #10492

IND #62,482

Date of Clarification Memorandum: 28 August 2007

Section 1: Summary of Clarifications and Rationale

The procedures clarified in this memorandum have been approved by the NIAID and NICHD Medical Officers and are to be implemented immediately upon issuance. IRB approval of this Clarification Memorandum is not required by the sponsor; however, investigators may submit the clarification memo to the IRB overseeing the study at their site for their information.

This clarification memo is official MTN-004 protocol documentation. It is effective immediately. A copy of this memo must be retained in each study site's Essential Documents file for MTN-004.

No change in the informed consent is necessitated by or included in this Clarification Memo.

The primary goals for this clarification memo are to provide clarification and detail regarding the grading of the severity of Expedited Adverse Events in this study and the criteria for permanent study product discontinuation for an individual participant. In order to make Appendix II: Outcomes, Diagnostics, and Follow-Up Evaluations consistent with Section 9.4.1. Criteria for Permanent Study Product Discontinuation for an Individual Participant, additional guidance is provided for follow up of genital findings. One administrative change to update the protocol team roster is also noted here.

Further detail can be found in the section below.

Section 2: Implementation

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 remove one team member:

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2. Section 8.4.2, second and third paragraphs have been updated to include the applicator as a study agent that must be considered in determining relationships of AEs requiring expedited reporting. This change is consistent with text in Section 9.1 Toxicity Management, which states that study gel use also will be withheld or discontinued in the event of an Expedited Adverse Event (EAE) that is judged by the site principal investigator or designee to be definitely, probably, possibly, or probably not related to the study gel or applicator, and with Appendix II which provides for management of the condition "EAE that is judged by the site investigator or designee to be definitely, probably, possibly, or probably not related to the study gel or applicator".

Study Agents for Expedited Reporting to DAIDS
The study agents that must be considered in determining relationships of AEs requiring expedited reporting to DAIDS are: **study agent delivery applicator,** 3% w/w SPL7013 Gel and Placebo Gel.

Study Agents for Expedited Reporting to Starpharma Pty Ltd
The study agents that must be considered in determining relationships of AEs requiring expedited reporting to Starpharma Pty Ltd are: **study agent delivery applicator,** 3% w/w SPL7013 Gel and Placebo Gel.

3. Section 8.4.2, fourth paragraph has been updated to add a reference to the Female Genital Toxicity Table (Appendix IX).

Grading Severity of Events
The Female Genital Toxicity Table (Appendix IX) will be the primary tool for grading adverse events for this protocol, with the exception of asymptomatic bacterial vaginosis which will not be a reportable AE as noted above. AEs not included in that table will be graded by the DAIDS AE Grading Table Version 1.0,

December 2004. In cases where an AE is covered in both tables, the Female Genital Toxicity Table will be the grading scale utilized.

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December, 2004 ~~must be used and~~ is available on the RCC website at http://rcc.tech-res-intl.com/ . The DAIDS AE Grading Table is also available in the Study Operations Manual.

4. Appendix II: Outcomes, Diagnostics, and Follow-Up Evaluations, page 77, has been modified to require permanent discontinuation of study gel for all cases of trichomoniasis, symptomatic Candida vaginitis, and symptomatic bacterial vaginosis. Additional guidance is provided for follow up of the conditions "Vaginitis" (now clarified here as "Abnormal Vaginal Discharge"), Unexpected Bleeding (now "Unexpected Genital Bleeding), Cervicitis (now Presumed Cervicitis), Petechial Hemorrhage (Genital Petechia(e), and Ecchymosis (Genital Ecchymosis).

   The text following the tables has been deleted, in order to make the guidance in Appendix II consistent with Section 8.3.1 Adverse Events, second paragraph, which states that all participants reporting an AE will be followed clinically, until the AE resolves (returns to baseline) or stabilizes. Deletion of this text is also consistent with Section 9.4.1. Criteria for Permanent Study Product Discontinuation for an Individual Participant, which states that the criteria for permanent discontinuation of further study product use for an individual participant include "signs or symptoms of STI(s)/RTI(s) requiring treatment according to the judgment of the investigator."

Appendix II: Outcomes, Diagnostics, and Follow-Up Evaluations

CONDITION	PRODUCT USE	EVALUATION	FOLLOW-UP AND TREATMENT ACTION
Deep Epithelial Disruption (Ulceration)	Hold study gel (until evaluated)	Swab for herpes simplex culture. Perform syphilis serology (Herpes serology optional)	Re-evaluate in 48-72 hours and reinstate gel use if resolved. If the ulcer has become worse or not healed in 48-72 hours, follow the lesion per local standard of care. Ask participant to return in 7-10 days for follow up syphilis serology. If there is reoccurrence and there is no other etiology, then consider permanent discontinuation.
Superficial Epithelial Disruption (Abrasion/Peeling)	Continue	Naked eye evaluation and/or colposcopy	Re-evaluate by speculum examination in 48-72 hours. If condition is significantly worse, hold study gel. Otherwise continue gel use.
Localized erythema or edema: area of less than 50% of vulvar surface or combined vaginal and cervical surface	Continue	Naked eye evaluation and/or colposcopy	If asymptomatic, re-evaluate at next regularly scheduled visit. If symptomatic, re-evaluate by speculum examination in 5-7 days. If worsened significantly, hold study gel use, until further evaluation

			is scheduled. Otherwise, continue gel use.
Generalized erythema or severe edema: area of more than 50% of vulvar surface or combined vaginal and cervical surface affected by erythema	Hold Study Gel (until evaluated)	Naked eye evaluation and/or colposcopy	Re-evaluate in 48-72 hours and reinstate gel use if resolved. If there is reoccurrence and there is no other etiology, then consider permanent discontinuation.
~~Vaginitis~~ **Abnormal vaginal discharge**	Hold Study Gel (until evaluated~~, except for asymptomatic Candida vaginitis~~)	Perform wet mount for Candida vaginitis, trichomoniasis, and BV	Provide treatment and ~~re-evaluate in 48-72 hours. If resolved reinstate gel use.~~ **permanently discontinue gel use for all cases of trichomoniasis, symptomatic Candida vaginitis, and symptomatic bacterial vaginosis. Gel use may be continued without treatment in the presence of asymptomatic Candida vaginitis and/or asymptomatic bacterial vaginosis.**

Unexpected **genital** ~~Intermenstrual~~ ~~B~~**b**leeding~~/Spotting~~	**Continue (at clinician's discretion)**~~Hold Study Gel (until evaluated)~~	Naked eye evaluation and/or colposcopy	If determined to be **due to deep epithelial disruption, refer to guidelines in this table. Otherwise** ~~endometrial bleeding with no other source,~~ continue gel use. ~~Reevaluate in 48 - 72 hours if the participant reports bleeding/spotting has not resolved.~~
~~Suspected~~ **Presumed** ~~C~~**c**ervicitis (findings on exam such as **mucopurulent cervical** discharge ~~from the cervical os~~)	**Hold Study Gel (until evaluated)** ~~Continue (at clinician's discretion)~~	Evaluate for *N. gonorrhoeae* and *C. trachomatis*	**Provide treatment and permanently discontinue gel use for all cases of cervicitis.** ~~Re-evaluate in 48 - 72 hours. If condition is worse, hold gel use until further evaluation is scheduled.~~
Genital ~~P~~**p**etechia**(e)**~~I Hemorrhage~~	Continue	Naked eye evaluation and/or colposcopy	**No further evaluation or treatment required.** ~~Re-evaluate by speculum examination in 48 - 72 hours. If condition is significantly worse, hold gel use, until~~

			~~further evaluation is scheduled. Otherwise continue gel use.~~
Genital Ecchymosis	Continue	Naked eye evaluation and/or colposcopy.	**No further evaluation or treatment required.**~~Re-evaluate by speculum examination in 48 - 72 hours. If the condition is significantly worse, hold gel use until further evaluation is scheduled. Otherwise continue gel use.~~
EAE that is judged by the site investigator or designee to be definitely, probably, possibly, or probably not related to the study gel or applicator	For Grades 1, 2, and 3 - Hold Study Gel (until evaluated) For Grade 4 – Permanent Discontinuation	Evaluate as according to current clinical practice at the site Not applicable	Provide treatment as clinically indicated, when resolved reinstate gel use at clinician's discretion Not applicable

- ~~For trichomoniasis or symptomatic BV, treat or refer for treatment. If resolved, restart study gel use. If observed at Two-Week Clinic Visit, treat and follow up to document resolution~~
- ~~For symptomatic candida vaginitis: manage with oral medication and re-evaluate in 3 – 5 days. If resolved, restart study gel use. If observed at Two-Week Clinic Visit, treat and follow up to document resolution~~
- ~~For asymptomatic candida vaginitis:~~
    - ~~If a participant has asymptomatic candida vaginitis she should continue study gel use and be re-evaluated in 7 days~~
    - ~~If at the Two-Week Clinic Visit there are signs and symptoms compatible with vaginitis, treat and follow up to document resolution~~
- ~~For asymptomatic BV:~~
    - ~~Continue study product as scheduled and reevaluate per visit schedule~~