SUMMARY OF CHANGES
INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:

MTN-004
DAIDS DOCUMENT ID: 10492

Phase 1 Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel®) Applied Vaginally in Sexually Active Young Women
Version 2.0/15 May 2007

THE AMENDED PROTOCOL IS IDENTIFIED AS:
Version 3.0/30 June 2008

IND # 62,482

Information/Instructions to Study Sites

The information contained in this protocol amendment impacts the MTN-004 study and must be forwarded to your Institutional Review Boards (IRBs) as soon as possible for their information and review. IRB approval is required before implementation of the modifications contained in this amendment. All IRB requirements must be followed.

Please file this Summary of Changes, Version 3.0 of the protocol and all associated IRB correspondence in your essential documents files for MTN-004

Summary of Revisions

This amendment incorporates two previously issued Clarification Memos in addition to the following protocol revisions:

- Correction to grant number to reflect Year 3
- Updates to the Protocol Team Roster
- Updates to the Schema, including change in number of study arms, study products, and modification to the study endpoints
- Inclusion of rationale for study pause
- Updates to Introduction, including pre-clinical and clinical data
- Modifications to Study Products Section
- Modification to Specimen Collection and Processing Section
- Modifications to Statistical Considerations
- Modifications to Appendix I: Schedule of Study Visits and Evaluations
- Modifications to Appendix II: Outcomes, Diagnostics, and Follow-Up Evaluations
- Modifications to Screening, Enrollment, and Storage and Future Testing of Specimens Informed Consent Forms
- Other minor editorial and typographical updates and corrections

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Rationale

The primary rationale for the modifications included in this protocol amendment is to add an extra arm to the study design. The text of the amended protocol (Version 3.0) has been updated to reflect an additional study product resulting from preliminary AE findings from MTN-004. HEC placebo gel has been included in the amended protocol to ascertain whether or not the observed AEs were caused by the active product or if the AEs were a result of the base 3% w/w SPL7013 Gel formulation without the active product. Changes have been made accordingly to the Schema and elsewhere in the amended protocol.

Colposcopic findings will not be graded as Adverse Events. Colposcopic findings, however, will still be included in the study endpoints.

The Statistical Considerations section has been modified to account for the change in the number of study arms stemming from the addition of the HEC placebo gel to the study products, and the resulting increase in the size of the study population.

Implementation

This amendment is now official MTN-004 protocol documentation. Prior to implementing the revisions listed below, MTN-004 study sites will submit this Summary of Changes and protocol Version 3.0 to all relevant regulatory authorities and IRBs. Starpharma Pty Ltd will submit this amendment to the United States Food and Drug Administration for inclusion in Investigational New Drug (IND) application #62,482.

Upon receipt of all regulatory and IRB approvals and completion of protocol registration procedures, the protocol modifications listed below will be implemented. Detailed modifications of the protocol text are indicated by ~~strikethrough~~ (for deletions) and **bold** (for additions).

Detailed Listing of Revisions Included in Clarification Memo #01, dated 28 August 2007

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~~	**Hold Study Gel**	Evaluate for *N.*	**Provide treatment**

Presumed ~~C~~**c**ervicitis (findings on exam such as **mucopurulent cervical** discharge ~~from the cervical os~~)	**(until evaluated)** ~~Continue (at clinician's discretion)~~	*gonorrhoeae* and *C. trachomatis*	**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)**~~l 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~~

Detailed Listing of Revisions included in Clarification Memo #02, dated 03 October 2007

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1. Section 7.6.4, last sentence has been updated to accommodate participants with Enrollment Visits on Thursdays as Study Day 2-3 phone calls fall on the weekend. The window period for phone assessments will therefore be changed to Study Day 2-4.

This contact may be initiated by study staff or the participant on Study Day 2 or ~~3~~ **4** (Target Day 2), as agreed upon prior to the call.

2. Appendix I: Schedule of Study Visits and Evaluations, pg. 83, has been modified accordingly to reflect the window period for phone assessments as Study Day 2-4.

Appendix I: Schedule of Study Visits and Evaluations

	Screen 1	Screen 2	Enroll	Phone Call	1-Week Clinic Visit	2-Week Clinic Visit	3-Week Clinic Visit	Inter./ Safety Visit
Target Day	≤30 Days		Day 0	Day 2	Day 7	Day 14	Day 21	PRN
Window Period	≤36 Days		Day 0	Day 2-~~3~~ **4**	Day 6 – 8	Day 13 – 15	Day 20 – 24	
Study Communications								
Informed Consent	X		X					
Assign Participant ID	X							
Eligibility Assessment	X	X	▲					
Collect Demographics	X							
HIV Pre- & Post-Test Counseling	X							
Screening Results (as available)	X	X	X					
Treatment or Referral	▲	▲	▲		▲	▲	▲	▲
Record/Update Medical and Menstrual History	X	X	X		X	X	X	X
Baseline Behavioral Questionnaire			X					
Record/Update Con. Meds.			X		X	X	X	▲
Record Adverse Events					X	X	X	▲
Vaginal Product History			X					
Acceptability Assessment						X		
Adherence Assessment					X	X		
Male Condom Counseling	X		X		X	X		▲
Record/Update Contacts	X	X	X		X	X	X	X
Schedule Next Visit	X	▲	X		X	X	▲	▲
Obtain Random Assignment			X					
Phone Assessment				X				
Study Burden Questionnaire							X	
Reimbursement	X	X	X		X	X	X	
Laboratory								
Qual. Urine Pregnancy Test	X	X	▲		X	X	X	X
Urinalysis	X		▲		▲	▲	▲	▲
Urine Culture & Sensitivity	▲		▲		▲	▲	▲	▲
CBC, Liver Function Panel, Creatinine Level, Coag. Panel	X		X		X	X	▲	▲
RPR (Syphilis)	X		▲		▲	▲	▲	▲

Confirmatory Tests for Syphilis	▲		▲		▲	▲	▲	▲
HIV Antibody Screen	X							▲
HIV Confirmatory Testing	▲							▲
SPL7013 Level			X			X		
Plasma Archive			X			X		
Vaginal pH	X		X		X	X	X	▲
Quantitative Vaginal Cultures			X		X	X	X	▲
Vaginal Wet Prep Slide	X		X		X	X	X	▲
Gram-Stained Vaginal Smears	X		X		X	X	X	▲
Cervical Swabs for Cytokines and Innate Factors			X		X	X	X	▲
Urine SDA for Gonorrhea & Chlamydia	X		▲					
Genprobe Aptima					▲	▲	▲	▲
Pap Smear of Cervix	X							▲
Herpes Culture	▲				▲	▲	▲	▲
Clinical								
Colposcopy			X		▲	X	▲	▲
Vital Signs	X		X		X	X	X	▲
Abdominal/Pelvic Exam	X		X		X	X	X	▲

3. Section 8.2, Clinical Data Safety Review, fourth (with exception of 1st sentence) and fifth paragraphs have been removed to allow for a format change in the MTN-004 PSRT report format. The MTN-004 PSRT report format has been modified to match the HPTN-059 PSRT report format.

Routine safety review occurs at the start of enrollment, and then daily, weekly, monthly, and every 4 months during the study. ~~Reviews proceed from a standardized set of protocol-specific safety data reports. These reports are produced by the SDMC and are annotated with queries that are sent to the MTN study sites as needed with any additional notes. Events are tracked by the internal reports until resolution. Other reports, containing queries and notes, are distributed to the MTN-004 PSRT.~~

~~The following reports are produced:~~

~~• Clinical quality control~~
~~• Safety review~~
~~• Pre-existing conditions~~
~~• Adverse events (AEs) requiring review~~
~~• Adverse event/concomitant medication~~
~~• Safety summary~~

~~More detailed information regarding the contents and distribution of these reports can be found in the MTN MOP~~.

4. Section 8.2.2, Weekly Review, first sentence, first paragraph, has been modified to be consistent with the changes made to Section 8.2 Clinical Data Safety Review regarding the MTN-004 PSRT report format.

The SDMC Clinical Affairs staff reviews internal reports of all clinical values that fall outside of the ~~standard~~ MTN safety parameters ~~(see MTN MOP)~~.

Detailed Listing of Revisions New to Version 3.0

1. The grant number on the front page is changed to reflect Year 2: ~~1~~**5**-U01-AI068633-0~~1~~**3**

2. Throughout the amended protocol, the protocol version number and version date are updated to Version 3.0 and 24 June 2008 respectively. The table of contents is updated to reflect current document pagination.

3. The revisions contained in prior Clarification Memo #1 (dated 28 August 2007) and Clarification Memo #2 (dated 03 October 2007) have been incorporated into the amended protocol. Because these revisions have been detailed in previous official protocol documentation, they are not detailed in this Summary of Changes document.

4. In the List of Abbreviations and Acronyms:

ID_{50} intravaginal dose

PBS phosphate-buffered saline

5. The Protocol Team Roster has been updated to reflect the current contact, role, and affiliations of current protocol team members.

6. Throughout the amended protocol, what was referred to as "placebo gel" in MTN-004, Version 2.0, is now referred to as "VivaGel® Placebo".

7. Throughout the amended protocol, 3% w/w SPL7013 Gel has been replaced by VivaGel® where appropriate.

8. In the Schema, Sample Size: Approximately ~~40~~ **61** women, **including 7 participants enrolled under Version 2.0 of the MTN-004 protocol.**

9. In the Schema, Study Design: Phase 1, ~~two~~ **three** arm, two site, randomized, double blind, placebo-controlled trial comparing ~~3% w/w SPL7013 Gel~~ **VivaGel®**, **VivaGel** ~~™~~® placebo, or **HEC placebo gel (HEC gel)** applied vaginally twice daily for 14 days

10. In the Schema, Study Duration: Approximately 21 days per participant, ~~six~~ nine calendar months of accrual and ~~seven~~ **ten** months total planned study duration

11. In the Schema, Study Regimen table:

Arm	Description	N	Frequency
1	~~3% w/w SPL7013 Gel~~ **VivaGel®**	~~20~~ ***18**	Twice daily for fourteen **consecutive** days
2	~~Placebo Gel~~ **VivaGel® placebo**	~~20~~ ***18**	Twice daily for fourteen **consecutive** days
3	**HEC gel**	**18**	**Twice daily for fourteen consecutive days**

***Arms 1 and 2 will each have a final N between 18 and 25.**

12. In the Schema, Primary Endpoints, Second Bullet: Abnormal pelvic exam findings~~, including colposcopic findings,~~**(excluding abnormal findings observed by colposcopy only)** judged by the Investigator to be possibly, probably, or definitely related to product use.

13. In the Schema, Exploratory Objectives: ~~Determine by means of dye-based applicator test the number of applicators returned to the study site that have been exposed to the vagina.~~

14. In the Schema, Exploratory Objectives, third bullet: **To assess the effects of VivaGel® on colposcopic findings.**

15. In the Schema, Exploratory Endpoints: ~~Positive dye-based markers for vaginal exposure of applicators returned to the study site~~

16. In the Schema, Exploratory Endpoints, third bullet: **Assessment of Colposcopic Findings**

17. In the Introduction, First Paragraph: According to UNAIDS, an estimated ~~39.5~~ **33.2** million (~~34.1~~ **30.6** million–~~47.1~~ **36.1** million) people worldwide were living with human immunodeficiency virus (HIV) in ~~2006~~ **2007**. An estimated ~~4.3~~ **2.5** million (~~3.6~~ **1.8** million–~~6.6~~ **4.1** million) became newly infected with HIV and an estimated ~~2.9~~ **2.1** million (~~2.5~~ **1.9** million–~~3.5~~ **2.4** million) lost their lives to acquired immunodeficiency syndrome (AIDS).

18. In Section 2.4, SPL7013, first paragraph, first sentence: SPL7013 is the active pharmaceutical ingredient (API) which, when formulated into a vaginal gel, is known as SPL7013 Gel **or VivaGel®**.

19. In previous Section 2.4.3, Study Product Storage:

~~2.4.3 Study Product Storage~~

~~3% w/w SPL7013 Gel and placebo gel should be stored in the single-use, pre-filled polypropylene applicators at 20-25°C (68-77°F) for up to 12 months, with short-term excursions allowed between 15-30°C (59-86°F) in storage/shipping. SPL7013 Gel has been shown to be stable in the vaginal applicators for up to 9 months at 40°C (104°F). This storage area at study sites should be in a secure limited-access area~~

20. In Section 2.8.1, Cytotoxicity, second paragraph, fifth sentence: This model found shedding of epithelium with intact lamina propria to occur in association with exposure to **5%** SPL7013, without evidence of necrosis on histological analysis.

21. In Section 2.8.2, Genetic Toxicity: Based upon negative findings in Ames test and *in vitro* mammalian chromosome aberration assays (Chinese hamster ovary cells), it was concluded that SPL7013 has no mutagenic potential ~~based on those assays~~. **In an *in vivo* rat micronucleus study, SPL7013 administered intravenously did not increase the incidence of micronucleated polychromatic erythrocytes. SPL7013 was negative in this genetic toxicity assay.**

22. In Section 2.9.1, Oral Administration, first paragraph, fourth and fifth sentences, and second paragraph: **Repeated administration of SPL7013 by once daily oral gavage for 14 days was well tolerated in rats at up to 2000 mg/kg/day. Based on the bioanalytical results, there was very limited systemic exposure to SPL7013 after administration of 500, 1000 or 2000 mg/kg/day. There was some evidence that systemic exposure was greater for 2000 mg/kg/day than for the two lower doses, but there was no clear difference between the two lower doses.**

    Based on these two studies, the no-observed-effect-level (NOEL) was estimated to be greater than 2,000 mg/kg.

23. In Section 2.9.2, Intravenous Administration, second paragraph: **In a study of repeated daily intravenous (bolus) injection of SPL7013 for 7 days in rats, SPL7013 was well-tolerated at levels of 0.4 and 1.7 mg/kg/day with only minor, transient clinical signs (decreased activity and reddened ears) noted at 9 mg/kg/day.**

24. In Section 2.9.3, Vaginal Administration, third paragraph: ~~Mice, rats and dogs have been treated vaginally with placebo, 1, 3, or 5% w/w SPL7013 Gels for up to 90 days. The 90-day data in rats and dogs represent data from an interim sacrifice in 6- and 9-month chronic toxicity studies, respectively, which are ongoing. In all three species, no evidence of systemic toxicity was observed. In addition, no detectable levels of SPL7013 have been measured in the plasma. Minor microscopic changes were noted such as a dose-related increase in the incidence and severity of glandular dilatation of the cervix and uterus, and dose-related vaginal changes (distal, mid, and proximal portions) that included minimal to mild epithelial cell hyperplasia and minimal single cell necrosis in mice, minimal to mild epithelial hyperplasia, minimal cervical vacuolation and minimal to mild luminal exudate in the vagina in rats, and test article-related microscopic observations limited to the cervix and vagina in dogs, including vacuolated macrophages in the submucosa and subacute inflammation. In all three species, the NOEL was determined to be 5% w/w SPL7013 Gel.~~ **Chronic toxicology studies have been conducted in which mice (90 days), rats (6 months) and dogs (9 months) received daily vaginal doses with placebo, 1, 3, or 5%w/w SPL7013 Gels. Additional data were obtained by conducting interim sacrifices after 90-days in both rat and dog chronic studies. In all three species, no evidence of systemic toxicity was observed. In addition, no detectable levels of SPL7013 have been measured in the plasma. Minor microscopic changes were noted such as a dose-related increase in the incidence and severity of glandular dilatation of the cervix and uterus, and dose-related vaginal changes (distal, mid, and proximal portions) that included minimal to mild epithelial cell hyperplasia and minimal single cell necrosis in mice, minimal to mild epithelial hyperplasia, minimal cervical vacuolation and minimal to mild luminal exudate in the vagina in rats, and test article-related microscopic observations limited to the cervix and vagina in dogs, including vacuolated macrophages in the submucosa and subacute inflammation. The pattern of microscopic findings (in terms of number and degree of severity) was the same at the termination of each study (6 months in rats, or 9 months in dogs) as that noted at the 90 day**

interim sacrifice. In all studies, the sub-chronic inflammation observed microscopically did not escalate to show any signs of chronic inflammation or a more pronounced immune response. In the mice and rats, the NOEL was determined to be 5%w/w SPL7013 Gel, while in dogs it was 3%w/w SPL7013 Gel.

25. In Section 2.9.3, Vaginal Administration, seventh paragraph: **Taken together, repeated vaginal administration of SPL7013 Gels (0% to 5%) to multiple species generally produced a low grade response. There was no clear indication from any of the studies of a potential safety concern for humans.**

26. In Section 2.9.7, Pharmacokinetics, first sentence: SPL7013 was not detected in plasma samples drawn from those animals that were dosed vaginally with SPL7013 Gel in the **mouse,** rat, rabbit and dog repeat dose studies and rabbit teratology study that are described above.

27. In Section 2.10, Clinical Studies, first and second paragraphs: ~~Currently there is one completed and fully reported clinical trial of the safety of SPL7013 Gel. This study was a Phase 1, randomized, double blind, placebo-controlled, study of 0.5%, 1% and 3% w/w SPL7013 Gel (Starpharma protocol number SPL7013-001). This study examined the safety, tolerability and pharmacokinetics of SPL7013 Gel at three escalating dose levels when administered vaginally in healthy female volunteers once daily for seven consecutive days. Participants consisted of 37 healthy females aged between 18 and 43 years, all with regular menstrual cycles. A total of 36 participants completed all components of the trial, with one volunteer withdrawn due to a finding present prior to dosing that was deemed unrelated to study procedures or study product.~~ **Clinical experience so far with SPL7013 Gel is comprised of three completed Phase 1, randomized, placebo-controlled studies. The first study investigated the safety and tolerability of a 3.5g dose of different strengths of SPL7013 Gel (0.5%, 1% and 3%w/w SPL7013) when administered once daily into the vagina of healthy, sexually inactive, female volunteers (Study No. SPL7013-001). The second study investigated the safety and tolerability of 2g of 3%w/w SPL7013 Gel when administered once daily to the penile epithelium of healthy male volunteers (Study No. SPL7013-002). The third study investigated the safety and tolerability of 3.5g of 3%w/w SPL7013 Gel when administered vaginally, twice daily for 14 days in healthy, sexually inactive, female volunteers (Study No. SPL7013-004). Data from the three completed safety studies indicate that 3% SPL7013 Gel is safe and well tolerated when administered to the vaginal epithelium once or twice daily for up to 14 consecutive days in sexually abstinent women, and to the penile epithelium once daily for seven consecutive days.**

    Study No. SPL7013-001: Participants consisted of 37 healthy females aged between 18 and 43 years, all with regular menstrual cycles. A total of 36 participants completed all components of the trial, with one volunteer withdrawn due to a finding present prior to dosing that was deemed unrelated to study procedures or study product.

28. In Section 2.10, Clinical Studies, fifth and sixth paragraphs: **Study No. SPL7013-002:** ~~A second Phase 1 safety study to investigate the safety,~~

~~tolerability and systemic absorption of 3.0% w/w SPL7013 Gel when administered to the penile epithelium once daily for 7 days has recently been completed and is in the analysis stage.~~ A total of 37 healthy male subjects aged 18 years or older were enrolled in the study and a total of 36 subjects completed all aspects of the study. ~~Although the data have yet to be unblinded, an ongoing review of the safety data indicates that the product was well tolerated. The most commonly reported AEs with a potential causal relationship to the study product were penile itch (three subjects), penile redness (three subjects) and headache (three subjects) – all of which were mild in intensity. Three AEs were reported of moderate intensity (epistaxis, viral illness and folliculitis on face), but each was considered unlikely to be related to the study product. All other AEs were mild in intensity and only occurred in one subject. No SAEs were reported.~~ **The genital adverse events reported throughout the study were mild (grade 1) and benign in nature and most lasted for less than 24 hours. A total of 12 genital AEs were reported by 33% of study participants in the 3% SPL7013 Gel group (8 of 24 men), compared with 5 genital AEs reported by 33% of study participants in the placebo group (4 of 12 men). There was no difference in the incidence of genital events between the SPL7013 Gel and placebo groups when analyzed either for all genital AEs or for those genital AEs deemed to have a potential causal relationship with study product. The most commonly reported events were genital pruritus (penile itch) (12% participants in SPL7013 Gel group and 8% in placebo) and application site erythema (penile redness) (4% in SPL7013 Gel group and 25% in placebo). No patterns emerged in genital events between the circumcised and uncircumcised strata in either SPL7013 Gel or placebo treatment groups.**

There were no SAEs in any of the subjects during this study, nor any grade 3 or 4 AEs. There was no evidence of systemic toxicity in either treatment group. Of the 32 non-genital AEs reported, 16 were deemed to have a potential causal relationship to study product (6 AEs were reported by 25% participants in the SPL7013 Gel group, and 10 AEs were reported by 33% participants in the placebo group). Three non-genital AEs were considered potentially related to study product and reported as moderate in intensity (grade 2), however all were reported by participants in the placebo treatment group. All other nongenital AEs deemed to be possibly related to study treatment were of mild intensity. The most commonly reported AE was headache with 13% participants reporting in the active group compared with 25% participants in the placebo group. All other non-genital AEs were reported in no more than one participant in each treatment group.

29. In Section 2.10, Clinical Studies, eighth through thirteenth paragraphs: ~~A Phase I safety study of 3.0% w/w SPL7013 Gel in sexually abstinent women is ongoing within the Sexually Transmitted Infections Clinical Trials Group under the IND for HSV-2 prevention. Safety is being measured by clinical symptoms and adverse events, pelvic exam with colposcopy and measurement of innate immunological factors in the genital tract; tolerability is being measured by standardized questionnaire. Data reviewed as part of the ongoing safety assessment indicate that the product is being well tolerated, and no SAEs have been reported to date. This trial is expected to complete enrollment in 2007.~~

Study No. SPL7013-004: A total of 54 healthy women were enrolled in the study with 35 receiving SPL7013 Gel and 19 receiving placebo.

There were no grade 3 or 4 AEs, and no deaths or SAEs reported during the study. The proportion of participants that experienced an AE during the study was not statistically different between the SPL7013 and placebo arms. The most common AEs included vaginal discharge, laboratory abnormalities, metrorrhagia, abdominal symptoms, candidiasis, headache, and vaginal and vulvar pain.

Maintenance of normal vaginal flora, in particular H_2O_2-producing lactobacilli, was common in women throughout the dosing period and overall study, and did not differ by study arm. No laboratory abnormalities were deemed to be clinically significant; these were balanced between the SPL7013 Gel and placebo arms, and none were grade 3 or higher.

There were no study participants that discontinued product use due to any AE indicating that SPL7013 Gel and the placebo were well tolerated.

In keeping with other clinical and non-clinical studies of SPL7013 Gel, no SPL7013 was detected in plasma samples collected during the study.

30. In Section 2.11, VivaGel® Placebo, first sentence: **The VivaGel™ Placebo for this study is the base formulation without SPL7013.**

31. In Section 2.11.3, Clinical Studies, second paragraph, first, second, and third sentences: MTN-004 will utilize as the placebo gel the same Carbopol®-based aqueous gel that was utilized in clinical protocol number SPL7013-001**,** ~~the first clinical study of SPL7013 Gel following vaginal application~~ **SPL7013-002, and SPL7013-004. As previously mentioned, these studies had no deaths or SAEs. In study SPL7013-001,** AEs that were considered to be possibly related to the study treatment were experienced by 3 of 12 participants receiving placebo, including one moderate AE (rash on jaw-line).

32. In Section 2.11.3, Clinical Studies, third and fourth paragraphs: **In study SPL7013-002, 5 genital AEs were reported by 33% of study participants in the placebo group (4 of 12 men). The most commonly reported events were genital pruritus (penile itch) (8% participants in placebo) and application site erythema (penile redness) (25% in placebo). Three non-genital AEs were considered potentially related to study product and reported as moderate in intensity (grade 2), however all were reported by participants in the placebo treatment group. The most commonly reported AE was headache with 25% participants reporting in the placebo group.**

In study SPL7013-004, signs and symptoms of localised genital irritation potentially associated with administration of the study product were experienced by 47% of participants in the placebo arm. There were no effects of placebo gel on vaginal flora or laboratory parameters in this study.

33. In Section 2.12-Section 2.17 HEC Gel:

2.12 HEC Gel

HEC Gel or the "universal" placebo gel is a vaginal product which contains hydroxyethylcellulose as the gel thickener, purified water, sodium chloride, sorbic acid and sodium hydroxide(17). The gel is isotonic and formulated at a pH of 4.4 to avoid disrupting the normal vaginal pH and has minimal buffering capacity in order to avoid the inactivation of sexually transmitted pathogens. Hydroxyethylcellulose, the gelling agent, is used to approximate the viscosity of other microbicide gel candidates. Each pre-filled applicator will deliver approximately 4 mL of placebo gel. Placebo gel should be stored at 25°C. Excursions are permitted between 15°C and 30°C.

Table 6: HEC Gel Formulation

Ingredient	Function in formulation	Amount (w/w)
Purified Water, USP	Solvent	96.3
Hydroxyethyl Cellulose, NF	Gelling agent	2.7
Sodium Chloride, USP		0.85
Sorbic Acid, NF	Preservative	0.1
Sodium Hydroxide, NF	pH adjusting agent	qs pH 4.4

2.12.1 Strength

There is no active ingredient in the HEC gel. 2.7% w/w HEC gel will be used in this study.

2.13 Anti-HSV Activity

CF-1 mice (n=10 per group) pretreated with medroxyprogesterone acetate were administered 0.02 mL of HEC Gel or phosphate-buffered saline (PBS) vaginally, followed by a 0.01 mL of HSV-2 viral inoculum of 10 ID_{50} 0.3 minutes later. On day 3, vaginal lavage was cultured on human foreskin fibroblasts, and mice were considered infected if a cytopathic effect was observed after 3 days of incubation. Infection rate following pretreatment with HEC Gel (90%) was not significantly different from pretreatment with PBS (80%) or from mice given no treatment (80%). HEC Gel did not enhance susceptibility of mice to HSV-2 when administered 12 hours before vaginal challenge.

2.14 Anti-HIV-1 Activity

***In vitro* analyses of anti-HIV activity were also performed on HEC Gel following a viral binding assay that consisted of a 2-hour incubation of test compound, HIV-1_{IIIB}, and MT-2 cells(17). Cell culture followed by further assessments performed after this incubation period showed no significant antiviral or cytotoxic activity. The HEC Gel had negligible effect on virus-induced cytopathic effect at a 1:5 dilution, the highest concentration tested(18). Additional *in vitro* studies on potential HIV-1 infection of neoplastic T cell lines concluded that the HEC Gel had little or no effect on the infection and replication of HIV in human target cells, or the specific replication steps of virus attachment or cell-to-cell fusion(17).**

The effect of the HEC Gel on vaginal transmission of $SHIV_{162p3}$ (10^3 $TCID_{50}$) to rhesus monkeys (n=5, n=3, respectively) was determined in two separate studies(18). Macaques pretreated with medroxyprogesterone acetate were vaginally administered 1 mL of the HEC Gel formulation 15 minutes prior to challenge with 0.5 mL $SHIV_{162p3}$. Investigators monitored total RNA load in the animal plasma for a total of 8 weeks by means of a standard quantitative RT-PCR. The first study utilized the HEC Gel formulation at pH 6.5; the second study utilized a formulation at pH 4.4. In both studies, all monkeys were infected, as determined by the presence of viral RNA in circulating blood, regardless of the pH of the formulation.

2.15 *In Vitro* Studies

2.15.1 Cytotoxicity

Dilutions of the HEC Gel in culture medium exhibited negligible toxicity to human vaginal epithelial cells (standard MTT assay), even at the lowest dilution tested (1:2)(17). Exposure of human vaginal epithelial cells to the HEC gel resulted in minimal IL-1α induction, even at the lowest dilutions tested (lowest dilution, 1:2)(18).

2.15.2 Spermatozoa Motility

Analyses of pH (HEC Gel mixed with human seminal plasma, 8.03± 0.26) found that the HEC formulation did not show significant buffering capacity and could not acidify the alkaline pH of seminal plasma, a favorable result in a placebo formulation(18). *In vitro* assessments of spermicidal activity utilizing human semen from healthy donors showed that the HEC Gel had no significant deleterious effects on sperm motility, even after a 60-minute incubation.

2.16 Animal Studies

2.16.1 I.V. Administration

Up to 55 intravenous injections of HEC were given to dogs (dose and number not specified) without causing injury other than that typical of the other water-soluble cellulose ethers(18). Only transitory changes in the blood picture and the deposition of the material on the intima of the blood vessels were noted. Groups of rats maintained for two years on diets containing HEC (n not specified, up to 5%) did not exhibit any adverse effects(18). HEC has also been administered to rats in single oral doses as high as 23,000 mg/kg without observed toxic effects (n not specified).

2.16.2 Vaginal Administration

A 10-day rabbit vaginal irritation study (10/arm, 2 arms, HEC Gel vs. 0.9% saline control) found that the HEC Gel was not irritating to the vaginal mucosa of rabbits when dosed daily for 10 days. One animal in the HEC Gel group had an instance of vaginal redness (compared to four animals in the saline group), which did not persist and was not evident at the end of the study. Diarrhea, few feces, and soiling of the anogenital area were noted in that animal. Body weight changes were noted to be normal. In 9 of 10 animals, necropsy results were normal. Anogenital soiling was observed in the animal that exhibited erythema during the

in-life phase of the study. Histopathologic changes observed were similar to those seen in the control group, and likely attributable to those that occur as a result of the repeated insertion of a catheter, rather than due to any effect of the test samples.

2.16.3 Developmental Toxicology

Intraperitoneal administration of unformulated HEC to pregnant mice in a 1% and 4% concentration caused an increase in resorptions, but no detectable increase in birth defects(19). While no epidemiological studies of congenital anomalies in infants born to women exposed to HEC during pregnancy have been reported, the Teratogen Information System (TERIS) considers the magnitude of teratogenic risk to a child born after exposure during gestation to be none(20).

2.16.4 Pharmacokinetics

When swallowed, the cellulose ethers, such as HEC, are not absorbed to any appreciable degree and appear unchanged in the feces.

2.17 Clinical Studies

Unformulated HEC is known to be a non-irritating substance in humans (skin sensitization is unusual), with doses less than 2 gm/kg by ingestion not expected to be toxic(20). No inhalation studies have been conducted, but exposure of humans to the dust in manufacturing operations over many years has not led to any known adverse effects. The HEC Gel formulation was developed and adopted for use in the HPTN 035 microbicide study, the Phase II/IIb Safety and Effectiveness Study of the Vaginal Microbicides Buffer Gel and 0.5% PRO2000/5 Gel (P) for the Prevention of HIV Infection in Women.

A randomized, closed label, Phase I study of daily vaginal HEC Gel exposure was conducted in 2003{Schwartz, 2007 #1}. In this trial, 30 women were randomized to twice-daily vaginal applications of 3.5 mL of HEC gel or polystyrene sulfonate (PSS) vehicle. The primary objective of this study was to assess and compare the effects of the test articles on symptoms and signs of irritation of the external genitalia, cervix, and vagina as seen on naked eye exam after 7 and 14 days of use including disruption of the epithelium and blood vessels as seen on colposcopy after 14 days of use. Secondary objectives included: an assessment and comparison of differences in vaginal health by evaluating the results of wet mounts, pH, and Gram-stained vaginal smears (Nugent score and neutrophil counts) after 7 and 14 days of use and vaginal cultures after 14 days of use; and an assessment of acceptability of the study products after 14 days of use among participants.

Results of this trial indicated that both gels appear safe for use twice a day for 14 days in sexually abstinent women. Two out of 14 women (14.3%) randomized to the HEC Gel reported at least one symptom of mild severity of genital irritation, which included genital burning, soreness and pelvic pain. A lower proportion of women in the HEC group experienced any evidence (signs and/or symptoms) of genital irritation. Three out of 14 women (21.4%) had colposcopic findings that included erythema, petechiae and peeling(22). No deep genital disruption was observed in either product group. Minimal changes in wet mounts, pH, Nugent scores, neutrophils, and vaginal flora were observed in both product groups.

A pilot study to optimize trial procedures for a proposed Microbicides Development Programme placebo controlled trial utilized the Universal placebo gel as the study gel. Final analysis of results has not been completed but there were no serious adverse product related events reported(17).

34. In Section 2.18.2, Rationale for Sexually Active Study Population, second paragraph, first sentence: Based upon protocol stipulations and preclinical investigations of the study product to date, neither ~~SPL7013 Gel~~ **VivaGel®** nor ~~the~~ **either type of** ~~P~~**p**lacebo ~~G~~**g**el is expected to be associated with adverse effects or toxicity in male partners of female study participants.

35. In Section 2.18.2, Rationale for Sexually Active Study Population, second paragraph, last sentence: A Phase 1 study of the safety of ~~3% w/w SPL7013 Gel~~ VivaGel® (3% w/w) in male volunteers has ~~completed enrollment and is in the analysis stage; a review of safety data has~~ indicated that the product was **safe and** well-tolerated **after topical administration to the penis, once a daily for 7 days** (Protocol Number SPL7013-002).

36. In Section 2.18.4, Rationale for Change in Study Design: **MTN-004, Version 2.0 was paused in October 2007 because five of the seven women that had enrolled into the study had experienced some signs and symptoms of genital irritation which were considered to be likely related to their use of the study products. These signs and symptoms were all mild and included vaginal dryness, vulvovaginitis, erythema, pelvic pain, cervical peeling, metrorrhagia, vaginal laceration and vaginal burning sensation, and lasted between 0-16 days (mean 5 days). An interim review of all available data at the time, including laboratory and clinical information, on the seven women who had been enrolled was then conducted. The review was blinded. This assessment confirmed that these signs and symptoms were minor in nature and typical for a Phase I microbicide study. They all resolved completely and rapidly during follow-up. A third study arm is being added and enrollment increased to provide more comprehensive data about the safety of these products that will strengthen the study conclusions. The third study arm will receive HEC gel as an inert placebo to assess the safety and tolerability of VivaGel® and the VivaGel® placebo, or "vehicle gel."**

37. In Section 3.3, Exploratory Objectives: ~~Determine by means of dye-based applicator test the number of applicators returned to the study site that have been exposed to the vagina.~~

38. In Section 3.3, Exploratory Objectives, third bullet: **To assess the effects of VivaGel® on colposcopic findings**

39. In Section 4.1, Identification of Study Design: MTN-004 is a two site, Phase I, double blind, randomized, controlled comparison with 14 days of twice daily exposure to ~~3% w/w SPL7013 Gel~~ **VivaGel®** , ~~placebo gel~~ **VivaGel® placebo**, or

HEC gel, and follow-up among HIV-uninfected sexually active women. Participants in ~~both~~ **all three** arms will receive male condom counseling and free male condoms on an ongoing basis.

40. In Table 7, Study Design:

Arm	Description	N	Frequency
1	~~3% w/w SPL7013 Gel~~ **VivaGel®** daily use	~~20 *~~**18**	Twice daily for fourteen **consecutive** days
2	~~Placebo Gel~~ **VivaGel® placebo daily use**	~~20~~ ***18**	Twice daily for fourteen **consecutive** days
3	**HEC gel daily use**	**18**	**Twice daily for fourteen consecutive days**

***Arms 1 and 2 will each have a final N between 18 and 25.**

41. In Section 4.2, Summary of Major Endpoints, Primary Endpoints, second bullet: Abnormal pelvic exam findings~~, including colposcopic findings,~~**(excluding findings by colposcopy only)** judged by the Investigator to be possibly, probably, or definitely related to product use

42. In Section 4.2, Summary of Major Endpoints, Exploratory Endpoints: ~~Positive dye-based markers for vaginal exposure of applicators returned to the study site;~~

43. In Section 4.2, Summary of Major Endpoints, Exploratory Endpoints, third bullet: **Assessment of colposcopic findings**

44. In Section 4.4, Time to Complete Enrollment: The approximate time to complete study enrollment is expected to be ~~six~~ **nine** months.

45. In Section 4.5, Study Groups: ~~Two~~ **Three** study **including a total of 61 women** arms are planned. **Of these 61 women seven were randomized at a 1:1 ratio to VivaGel® or VivaGel® placebo, and a** total of approximately ~~40~~ **54** women will be randomized at a **1:**1:1 ratio stratified by site to ~~3% w/w SPL7013 Gel~~**VivaGel®**, **VivaGel I® placebo,** or ~~base~~ **HEC** ~~placebo~~ gel, with ~~both~~ **all three** groups applying the product vaginally twice daily (approximately every 12 hours) for 14 days. Additional participants ~~will~~ **may** be enrolled to ensure that a total of ~~40~~ **approximately 61** evaluable participants complete the ~~two~~ **three**-week study.

46. In Section 4.6, Sequence and Duration of Trial Periods, Table 9: Projected Sequence and Duration of Trial Periods for MTN-004, Version 3.0:

Table 9: Projected Sequence and Duration of Trial Periods for ~~Entire Trial~~ **MTN-004, Version 3.0**

Enrollment Period	Follow-Up Period	Total Duration
~~6~~**9** months	1 month	~~7~~**10** months

47. In Section 5.1, Selection of Study Population, first paragraph, first sentence: A total of ~~40~~ **61** healthy, non-pregnant, sexually active, HIV-negative women of the

ages 18 through 24 years inclusive with a normal genital tract who are using adequate contraception will be enrolled in this study.

48. In Section 5.1, Selection of Study Population, second paragraph, third sentence: Each site will enroll approximately ~~20~~ **30** participants.

49. In Section 5.2, Inclusion criteria, tenth bullet, second sentence: Effective method of contraception is defined as either hormonal method (except vaginal ring); IUD inserted at least 30 days prior to enrollment; sterilization; or sexual activity with documented vasectomized partner**(s).**

50. In Section 5.2, Inclusion Criteria, Twelfth Bullet: Willing to use 3% w/w SPL7013 Gel **VivaGel®**, ~~placebo gel,~~ **VivaGel® placebo**, or **HEC gel** as required by protocol.

51. In Section 5.3, Exclusion Criteria, seventh bullet: Any abnormal finding on physical or pelvic examination, which, in the opinion of the investigator, precludes participation in the trial (including anatomical abnormalities, non-iatrogenic colposcopic findings involving deep disruption of the epithelium**, and inflammation of the vulva, vagina, or cervix**); women with HPV warts exterior to labia minora requiring treatment will be excluded.

52. In Section 6.1, Regimen, Table 10, Study Product Regimen:

Table 10: Study Product Regimen

Arm	Description	N	Dose, Route, and Frequency
1	~~3% w/w SPL7013 Gel~~ **VivaGel® daily use**	~~20~~ ***18**	One 3.5 g applicator per vagina twice daily for fourteen **consecutive** days
2	~~Placebo Gel~~ **VivaGel® placebo daily use**	~~20 *~~**18**	One 3.5 g applicator per vagina twice daily for fourteen **consecutive** days
3	**HEC gel daily use**	**18**	**One 3.5 g applicator per vagina twice daily for fourteen consecutive days**

***Arms 1 and 2 will each have a final N between 18 and 25.**

53. In Section 6.1, Study Regimen, second paragraph, second sentence: Beginning on Day 0, participants in ~~both~~ **all three** arms of the study will utilize one single-dose, pre-filled applicator containing 3.5 g of study product (~~3% w/w SPL7013 Gel~~ **VivaGel®**, **VivaGel** placebo ~~gel~~, or **HEC gel**) twice daily, for fourteen consecutive days.

54. In Section 6.1, Study Regimen, second paragraph, last sentence: If the next dosing time is in 2 or less hours, then the missed dose should not be made up; rather, the participant should wait until ~~this~~ **the** next dosing time to insert the study gel.

55. In Section 6.1, Study Regimen, third paragraph, third sentence: Participants will be informed that **tampons, sanitary pads,** swimming, bathing, and sauna use are permitted.

56. In Section 6.2.1 Study Product Supply, first, second, and third paragraphs: ~~The drug substance is, SPL7013 Gel~~ **VivaGel**™® and VivaGel™® ~~P~~**p**lacebo ~~G~~**g**el are ~~manufactured in Wellington, New Zealand and sent to CPST. CPST,Coldstream Laboratories, Inc (Lexington, University of Kentucky) will to formulate the gel, label,~~ package**d** in single-use applicators and analyze**d**/release**d** ~~3% w/w SPL7013 Gel VivaGel™ and VivaGelplacebo gel~~ under current good manufacturing practices (cGMP). ~~Study site pharmacists will obtain study products directly from CPST.~~

    HEC gel will be manufactured, analyzed/released, and packaged in single-use applicators under current good manufacturing practices (cGMP).

57. In Section 6.2.1. Study Product Supply, third paragraph:

~~SPL7013 Gel~~ **VivaGel**®, **VivaGel** Placebo ~~Gel~~, **HEC Gel** Applicators

This study will utilize test article packaged in identical, pre-filled, opaque white, single-use plastic applicators containing 3.5g of the study products (~~3% w/w SPL7013 Gel~~ **VivaGel®, VivaGel® placebo or** ~~Placebo~~ **HEC** ~~G~~**g**el). ~~provided by CPST, University of Kentucky.~~ Both active and placebo gels are clear and are of similar viscosity. ~~All single-use gel applicators will be packaged in sealed opaque tamper-proof plastic overwraps, and then packaged again in sealed outer containers. Labels for the individual applicators will include the protocol name and product, i.e., "MTN-004 Study Gel", a blinded code/number provided by the SDMC, storage requirements, the manufacturer's name, the retest date (the date 12 months from manufacture)and the warnings, "For Vaginal Use Only", "Keep Out of Reach of Children", and "Caution: New Drug - Limited by Federal (or United States) Law to Investigational Use."~~ Each product (~~3% w/w SPL7013 Gel~~ **VivaGel®** ~~and~~, **VivaGel®** placebo **and HEC** gel) will be packaged in cartons containing 10 pre-filled, single use applicators per carton. ~~Each carton of applicators will be labeled with the protocol name and number, a blinded code/number provided by the SDMC, storage requirements, the manufacturer's name, and the warnings, "For Vaginal Use Only", "Keep Out of Reach of Children", and "Caution: New Drug - Limited by Federal (or United States) Law to Investigational Use."~~

58. In Section 6.2.2, Study Product Receipt, First Sentence: Site pharmacists will be required to maintain complete study records of all study product supplies received ~~from the CPST~~.

59. In Section 6.2.3, Storage, First Paragraph: In accordance with documented 12-month stability data, ~~3% w/w SPL7013 Gel~~ **VivaGel**™® and **VivaGe**l™® placebo gel should be stored in the single-use, pre-filled polypropylene applicators at 20-25°C (68-77°F) for up to 12 months, with short-term excursions allowed between 15-30°C (59-86°F) in storage/shipping. ~~After 12 months from manufacture as recorded on the Certificate of Analysis (CoA)(this date is recorded on the label as the "retest date"), the product should be returned to the MTN CORE in Pittsburgh, unless study sites receive notification from the MTN confirming that stability data indicate a longer period of allowable storage under the conditions described in this section. SPL7013 Gel~~VivaGel™® has been shown to be stable in the vaginal applicators for up to 9 months at 40°C (104°F). **The HEC gel should be stored at room temperature (15-30°C).**

60. In Section 6.2.1, Study Product Supply, first paragraph: VivaGel®, and VivaGel® placebo are manufactured and packaged in single-use applicators and analyzed/released under current good manufacturing practices (cGMP).

61. In Section 6.2.1, Study Product Supply, third paragraph, heading: VivaGel®, VivaGel® Placebo, and HEC Gel Applicators

62. In Section 6.2.4, Dispensing, second paragraph, third sentence: Participants will also receive four transparent one-quart resealable plastic storage bags to be used to collect and store unused and used applicators prior to them being returned to the clinic at the Weeks 1 and 2 Clinic Visits.

63. In Section 6.2.4, Dispensing, third paragraph, last sentence: **The pharmacist will record the dispensing of any additional study product on the documents maintained by the Pharmacist of Record or designee.**

64. In Section 6.2.5, Accountability, second sentence: The study pharmacist must maintain complete records of study gel received from CPST as well as study gel re-supply, transfers, chain of custody (e.g., record if dispensed directly to patient or other study staff), returns, destruction (if applicable), and other related issues as outlined in the Pharmacy Instructions Manual for the MTN Clinical Trials.

65. In Section 6.3 Assessment of Participant Adherence, first paragraph, first sentence: Used applicators should be placed into the resealable plastic bags provided and returned to the clinic.

66. Previous Section 6.4, Assessment of Applicators: Assessment of Applicators Applicators will be tested in the MTN Network Laboratory using the Population Council dye-based applicator test noted in Section 7.4.3.

67. In Section 6.4.4, Required Medications and Procedures, Panty Liners and Pads, third sentence: It is hoped that women enrolled on **in** the study will not be menstruating during the two weeks of study drug administration.

68. In Section 7.2.1, Baseline Behavioral Questionnaire, second sentence: Next, the staff member will enter the participant's ID and date, select language choice (either Spanish or English) and let the participant complete the rest of the questionnaire.

69. In Section 7.2.2, Acceptability and Adherence Questionnaire, first sentence: At the Three **Two**-Week Clinic Visit, the participant will once again fill in a Web-based survey.

70. In Section 7.2.3, Study Burden Questionnaire, first paragraph: At the 3 **Three**-Week Clinic Visit, the participant will complete the final Web-based survey, the Study Burden Questionnaire that will explore through close-ended questions the participant's overall experiences during the trial, and her likes and dislikes.

71. In Section 7.3, Laboratory Evaluations, second to last bullet: ~~Dye-based applicator testing~~

72. In Section 7.4.3, Network Laboratory Specimens, last sub-section:

~~Applicators~~
~~Applicators returned to the study sites will be shipped to the MTN CORE in Pittsburgh. Applicators with visible remaining product will be emptied of product by the MTN Senior Pharmacist or their delegate before they are transferred to the MTN NL for dye-based testing similar to that described by Wallace et al.~~

73. In Section 7.4.3.1, Quality Control and Quality Assurance Procedures: Network Laboratory staff will conduct visits ~~periodic~~ **as needed** to both sites to assess the implementation of on-site laboratory quality control procedures, including the proper maintenance of laboratory testing equipment, etc.

74. In Section 7.6.1, Screening 1 Visit, first paragraph: The Screening 1 Visit may occur up to Day-36 **of enrollment**. Written informed consent will be obtained prior to the onset of any study procedures, in concordance with Good Clinical Practices, and after a thorough discussion of risks, benefits and alternatives. Further information on the informed consent process ~~will be available~~ **is** in the MTN Manual of Procedures.

75. In Section 7.6.2, Screening 2 Visit, second sentence: The Screening 2 Visit will be scheduled to occur within 36 days of enrollment **and can also occur on the same day as the Enrollment Visit**.

76. In Section 7.6.3, Enrollment Visit, second sentence: **The Screening 2 Visit and the Enrollment Visit can also occur on the same day.**

77. In Section 7.6.3 Enrollment Visit, Table 13: Enrollment Visit, Study Communications:

Study Communications	• Explain study requirements
	• Informed consent document
	• Administer informed consent comprehension test
	• **Record concomitant medications**
	• If Enrollment does not take place on the same day as the Screening 2 Visit:
	  o Update contact information
	  o Re-assess eligibility**
	  o Update medical and menstrual history
	• Provide test results as available, with associated counseling
	• *Treat or refer for treatment and/or further counseling (including STI treatment and/or counseling)
	• Provide study product usage instructions
	• Schedule 1-Week Clinic Visit
	• Provide reimbursement for study visit

78. In Section 7.6.3, Enrollment Visit, second paragraph, fourth bullet: Re-confirmation that the participant has not used ~~oral and/or vaginal preparations~~ prohibited products as outlined in Section 6.4.2 in the last 30 days

79. In Section 7.6.5, One-Week Clinic Visit, Table 14: One-Week Clinic Visit, Behavioral Measures:

Behavioral Measures	• **Administer adherence assessment**

80. In Section 7.6.5, One-Week Clinic Visit, Table 14: One-Week Clinic Visit, Study Supplies:

Study Supplies	• Count returned ~~used and~~ unused applicators • Dispense one carton (ten applicators) of study gel • Dispense more male condoms~~, resealable plastic bags,~~ and panty liners and/or pads if needed

81. In Section 7.6.6, Two-Week Clinic Visit, Table 15: Two-Week Visit, Study Supplies:

Study supplies	• Count returned ~~used and~~ unused applicators

82. In Section 7.6.7, Three-Week Clinic/Early Termination Visit, Table 16: Three-Week Clinic/Early Termination Visit, Study Supplies:

Study supplies	• Count returned ~~used and~~ unused applicators (if not already returned at previous visit)

83. In Section 7.7, Colposcopy, second sentence: In addition, an MTN ~~Study~~ **Safety** Physician will provide specialized training in colposcopy for the evaluation of vaginal products.

84. In Section 7.8, Colposcopic Images: Records of digital colposcopic images are ~~not~~ required for enrollment and **for any findings at** follow up visit examinations. The colposcopist will document findings in the participant's chart notes and on the study case report forms. When ~~clinically appropriate~~ **there are findings on follow-up visits**, the clinician ~~may choose to~~ **should** retain digital video images in order to complement documentation of baseline findings, abnormal findings or injury.

85. In Section 8.1, Safety Monitoring, first sentence: A sub-group of the Protocol Team, including the ~~MTN Safety Physicians,~~ the MTN PI, MTN-004 Protocol Chair, MTN Protocol Specialist, Statistical Data Management Center (SDMC) Clinical Affairs Research Nurse, SDMC Project Manager, MTN Protocol Safety Physicians, both Site PIs, FHI Protocol Coordinator, DAIDS and NICHD Medical Officers, **and** DAIDS Clinical Operations Study Coordinator~~, and Protocol Statistician,~~ will serve as the Protocol Safety Review Team (PSRT).

86. In Section 8.2, Clinical Data Safety Review, first and second paragraphs: A multi-tiered safety review process will be followed for the duration of this study. ~~The review process, which is both timely and extensive in scope, includes review of medical history information, clinical and laboratory AEs and concomitant medications.~~ The study site investigators are the first layer of this tiered system and are responsible for the initial evaluation and reporting of safety information at the participant level, and for alerting the PSRT if unexpected concerns arise. **Participant safety is also monitored at the Network level through a series of routine reviews conducted by the SDMC Clinical Affairs staff, the PSRT, and study sponsors.** Additional special reviews may also be conducted as dictated by the occurrence of certain events.

    ~~The SDMC Clinical Affairs Research Nurse represents the second tier. This research nurse will review incoming safety data on an ongoing basis. Values identified during review that are considered questionable, inconsistent, or unexplained will be queried for verification.~~

    All EAE reports submitted to the DAIDS Safety Office will be synchronously sent by the sites to the DAIDS Medical Officer, NICHD Medical Officer, SDMC Clinical Affairs Research Nurse, and the Protocol Chair for review. ~~Values identified during the review that are considered questionable, inconsistent, or unexplained are referred to the MTN Site Clinicians.~~ **The SDMC Clinical Affairs staff review AEs, events requiring expedited reporting to DAIDS, and events that meet safety pause criteria.**

87. In Section 8.2, Clinical Data Safety Review, third paragraph, first sentence: ~~Routine safety review occurs at the start of enrollment, and then daily, weekly, monthly, and every 4 months during the study.~~

88. In Section 8.2, Clinical Data Safety Review, fourth paragraph: ~~More detailed information regarding the contents and distribution of these reports can be found in the MTN MOP.~~

89. In previous Section 8.2.1, Daily Review:

~~8.2.1 Daily review~~
~~Blinded daily safety reviews are routinely conducted by the SDMC Clinical Affairs staff for AEs, events requiring expedited reporting to DAIDS, lab values that fall outside of the sites' normal ranges and events that meet safety pause criteria.~~

90. In Section 8.2, Clinical Data Safety Review, sixth paragraph (previously, Section 8.2.2, Weekly Review, fifth paragraph): Accrual and overall study product use for all participants will be suspended for a data safety review by the PSRT if any two

women enrolled in the study experience **the same** safety ~~and~~ or toxicity endpoint, defined as:

91. In Section 8.2, Clinical Data Safety Review, sixth paragraph, second bullet (previously Section 8.2.2, Weekly Review, fifth paragraph, second bullet): Having at least one Grade 3 or higher macroscopic finding or other clinical evidence (**excluding findings observed by colposcopy only)** of damage during follow up (judged not to be due to pathogen or iatrogenic trauma) to the vulvar and/or vaginal deep epithelium and/or cervical mucosa including ulceration and other lesions, severe global erythema, and/or severe global edema judged definitely, probably, or possibly related to the study gel or applicator.

92. In Section 8.2, Clinical Data Safety Review, seventh paragraph, first sentence (previously Section 8.2.2, Weekly Review, sixth paragraph): **Any additional two women with the same safety or toxicity event will be referred to the PSRT for discussion. The PSRT may decide to invoke an additional pause.**

93. In Section 8.2, Clinical Data Safety Review, last paragraph, third sentence (previously Section 8.2.2, Weekly Review, last paragraph, third sentence): If at any time, a decision is made to discontinue study gel in all participants, Starpharma Pty Ltd after consultation with the D~~ivision of~~ AIDS and the protocol team will inform the US FDA.

94. In Section 8.3.1., Adverse Events, First Paragraph, Last Sentence: The term "investigational product" for this study refers to the ~~3% w/w SPL7013 gel~~ **VivaGel®** ~~and~~ **VivaGel®** placebo ~~gel~~, **and HEC gel** as well as the study gel delivery applicators.

95. In Section 8.3.1, Adverse Events, Fourth Paragraph, first sentence: Participants who develop any pelvic exam abnormality, **excluding findings observed by colposcopy only** will be followed until the AE resolves or stabilizes.

96. In Section 8.3.1, Adverse Events, fourth paragraph, third and fourth sentences: **The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004, Addendum 1 (The Female Genital** ~~Toxicity~~ **Grading** Table ~~(Appendix IX)~~ **for Use in Microbicide Studies)** 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. Adverse events not included in that table will be graded by the DAIDS AE Grading Table Version 1.0, Dec 2004. In cases where an AE is covered in both tables, the Female Genital ~~Toxicity~~ **Grading** Table **for Use in Microbicide Studies** will be the grading scale utilized. **These tables are available at: http://rcc.tech-res.com/eae.htm.**

97. In Section 8.3.2, AE Severity/Intensity: The severity (intensity) grades that will be used for this study are defined in the DAIDS AE Grading Table Version 1.0, Dec 2004 ~~(Appendix IV)~~ and ~~the Female Genital Toxicity~~ **Addendum 1 to the** ~~T~~table ~~(Appendix IX).~~ **These tables are available at: http://rcc.tech-res.com/eae.htm.**

98. In Section 8.4.2, EAE Reporting Requirements for this Study, 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~~ **VivaGel®**, ~~and~~ **VivaGel®** ~~P~~**p**lacebo**, and HEC placebo** ~~G~~**g**el.

99. In Section 8.4.2, EAE Reporting Requirements for this Study, 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~~ **VivaGel®**, ~~and~~ **VivaGel®** ~~P~~**p**lacebo**, and HEC** ~~G~~**g**el.

100. In Section 10.1, Overview and General Design: This is a two site, Phase I, double blind, randomized, controlled comparison with 14 days of twice daily exposure to ~~3% w/w SPL7013 Gel~~ **VivaGel®**, ~~and~~ **VivaGel®** ~~P~~**p**lacebo**, or HEC** ~~G~~**g**el, and follow-up among HIV-uninfected sexually active women.

101. In Section 10.2.1, Primary Endpoint, second bullet: Abnormal pelvic exam findings ~~including colposcopic,~~ **(excluding** findings **observed by colposcopy only)** judged by the Investigator to be possibly, probably, or definitely related to product use;

102. In Section 10.2.3, Exploratory Endpoints: ~~Positive dye based markers for vaginal exposure of applicators returned to the study site~~

103. In Section 10.2.3, Exploratory Endpoints, third bullet: **To assess the effects of VivaGel® on colposcopic findings**

104. In Section 10.4, Sample Size, first paragraph: The primary aim of the study is to assess the local and systemic safety of vaginal application of ~~3% w/w SPL7013 Gel~~ VivaGel® versus placebo gel among HIV uninfected women. The proposed total sample size is approximately n**=61**evaluable participants with approximately ~~40~~ **36 included in comparisons between** ~~divided into 2 arms (3% w/w SPL7013 Gel~~ **VivaGel®** ~~or placebo~~ and the **HEC gel (18 participants in each of the 2 arms), and approximately 43 included in comparisons between VivaGel® and VivaGel® placebo (18 participants in each of the 2 arms plus 7 previously enrolled)**~~., assigned at a 1:1 ratio) each with 14 days of exposure to study product~~. This sample size is based upon the size of similar Phase ~~I~~ 1 studies of topical microbicide products. Additional participants may enroll in the study, at the discretion of the protocol team, to replace currently enrolled participants who are non-adherent to the study product and/or the study visit schedule. ~~Thus, in the event that participants are replaced for this purpose, the total sample size at the end of the study may slightly exceed 40 participants. In addition~~ **Finally,** if for some reason a site experiences difficulty reaching its accrual target, consideration will be given to shifting enrollment “slots” to the other site, with prior approval of the Protocol Chair.

105. In Section 10.4, Sample Size, second paragraph: As a means to characterize the statistical properties of this study, the following table presents the probability of observing zero, at least one, and two or more safety endpoints among the ~~group~~ **minimum sample size** of ~~20~~ **18** women using ~~the SPL7013 Gel~~ **VivaGel®** for various “true” event rates:

106. In Section 10.4, Sample Size, Table 17: Analysis of Adverse Event Frequency with n=18:

Table 17: Analysis of Adverse Event Frequency **with n = 18**

Event Rate	P (0 events | n=~~20~~**18**)	P (≥1 event | n=~~20~~**18**)	P (≥2 events | n=~~20~~**18**)
1%	0.**8**~~2~~**3**	0.1~~8~~**7**	0.0~~2~~**1**
5%	0.~~36~~**40**	0.64**0**	0.2~~6~~**3**
10%	0.1~~2~~**5**	0.8~~8~~**5**	0.~~61~~**55**
15%	0.04**5**	0.9~~6~~**5**	0.**7**8~~2~~
25%	<0.01	>0.99	0.9**6**
35%	<0.01	>0.99	>0.99
45%	<0.01	>0.99	>0.99

107. In Section 10.4, Sample Size, third paragraph: For example, if the true rate of a given endpoint is five percent, the probability that the endpoint will be observed in at least one of the **(minimum of)** ~~20~~ **18** women exposed to ~~SPL7013 Gel~~ **VivaGel®** is 0.64**0**.

108. In Section 10.4, Sample Size, fourth paragraph and Table 18: Analysis of Adverse Event Frequency with n=21:

The actual number of women using VivaGel® who will be available for analysis is unknown, but is likely to be approximately 21. Given this, the table below presents the probability of observing zero, at least one, and two or more safety endpoints assuming 21 women were randomized to VivaGel® for various "true" event rates:

Table 18: Analysis of Adverse Event Frequency with n = 21

Event Rate	P (0 events | n=21)	P (≥1 event | n=21)	P (≥2 events | n=21)
1%	**0.81**	**0.19**	**0.02**
5%	**0.34**	**0.66**	**0.28**
10%	**0.11**	**0.89**	**0.64**
15%	**0.03**	**0.97**	**0.84**
25%	**<0.01**	**>0.99**	**0.98**
35%	**<0.01**	**>0.99**	**>0.99**
45%	**<0.01**	**>0.99**	**>0.99**

109. In Section 10.5, Randomization Procedures, first paragraph, first sentence: Women will be randomized at a 1:1**:1** ratio to one of the t~~wo~~hree arms. Randomization will be stratified by site to ensure balanced assignment to each product (~~3% w/w SPL7013 Gel,~~ VivaGel®, VivaGel® placebo**, or HEC gel**) within each site.

110. In Section 10.5, Randomization Procedures, first paragraph, last sentence: Additional envelopes will be provided to each site for the purpose of enrolling

>~~20~~ **18** participants per site if non-adherent participants need to be replaced or if enrollment "slots" need to be shifted from one site to another.

111. In Section 10.5, Randomization Procedures, second paragraph, second sentence: Clinic staff will prepare a written prescription contained within the envelope that, among other things, documents the randomization envelope number and randomization code indicating the product (~~3% w/w SPL7013 Gel~~ **VivaGel®**, VivaGel® ~~Gel, or~~ placebo **or HEC gel**) to which the participant was assigned.

112. In Section 10.6, Justification for Placebo Gels: Inclusion of placebo gel**s** in this safety trial will enable investigators to examine the incidence of adverse events in the presence of the study product containing SPL7013 in comparison to those occurring in the presence of the **two different** placebo gel**s (one of which is the same formulation as VivaGel®, but containing no SPL7013, and one of which is a placebo gel that has been used in several placebo controlled microbicide trials)** ~~which~~ **that** has**ve** been shown to have ~~a~~ good safety profile**s** and ~~a~~ low likelihood**s** ~~to~~ **of** induc**eing** mucosal damage.

113. In Section 10.7, Blinding, second sentence: ~~Both~~ **All** study gels will be supplied in identical, single-use applicators packaged in individual wrappers.

114. In Section 10.9, Participant Accrual and Follow-Up, first sentence: **Based on previous studies of vaginal products with similar eligibility requirements, the accrual of** ~~40~~ eligible participants with normal reproductive tracts is expected to require the screening of approximately 1~~2~~**6**0 volunteers.

115. In Section 10.9, Participant Accrual and Follow-Up, third, fourth, and fifth sentences: The target for retention will be 95% of enrolled participants over the 21-day follow-up period. Therefore, it is anticipated that approximately ~~42~~ **64** women will be enrolled in the study. Accrual is anticipated to take approximately ~~6~~ **9** months. Monthly accrual targets ~~are in the table below~~ **will be available in the SSP**.

116. In Section 10.9, Participant Accrual and Follow-Up: The table reflecting monthly accrual targets for MTN-004 is deleted and will be available in the SSP.

117. **In Section 10.10.2, Data Analysis, first paragraph: For analyses comparing VivaGel® to the VivaGel® placebo, data from approximately 43 women will be included (18 participants in each of the 2 arms plus 7 previously enrolled) whereas for analyses comparing VivaGel® to the HEC gel, data from approximately 36 women will be included (18 participants per arm). All references to "control gel" below apply to 1) the VivaGel® placebo in analyses comparing VivaGel® to the VivaGel® placebo and, 2) the HEC gel in analyses comparing VivaGel® to the HEC gel.**

118. In Section 10.10.2, Data Analysis, second paragraph, last sentence: When use of formal testing to assess differences between **users of** the control gel and ~~SPL7013 Gel arms~~ **users of VivaGel®** is required, the following methods will

be used: for binomial response variables, chi-square tests and logistic regression; for continuous variables, t-tests and linear regression or nonparametric methods if data are non-Normal.

119. In Section 13.6, Special Populations, Prisoners (former Section 13.6.3): Prisoners.

~~13.6.3 Prisoners~~

~~MTN-004 does not meet the criteria for prisoner participation per US 45 Code of Federal Regulations (CFR) 46.306 (a)(2)(D). MTN-004 is not suitable for further reviews by local IRBs for the inclusion of prisoners.~~

120. In Section 14, Publication Policy, first sentence: DAIDS and MTN policies and a Memorandum of Agreement (MOA) between MTN and ATN, and a Clinical Trial Agreement (CTA) between Starpharma, **NICHD** and NIAID, will govern publication of the results of this study.

121. In Appendix I: Schedule of Study Visits and Evaluations:

Male Condom Counseling	X	**X**	X		X	X		▲

122. In Appendix II: Outcomes, Diagnostics, and Follow-Up Evaluations:

CONDITION	PRODUCT USE	EVALUATION	FOLLOW-UP AND TREATMENT ACTION
Deep Epithelial Disruption (Ulceration) **excluding findings observed by colposcopy only**	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) **excluding findings observed by colposcopy only**	Continue	Naked eye evaluation ~~and/or~~ **with or without** colposcopy	Re-evaluate by speculum examination in 48 - 72 hours. If condition is significantly worse, hold study gel. Otherwise continue gel use.
Localized	Continue	Naked eye	If asymptomatic, re-

erythema or edema: area of less than 50% of vulvar surface or combined vaginal and cervical surface **excluding findings observed by colposcopy only**		evaluation ~~and/or~~ **with or without** colposcopy	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 **excluding findings observed by colposcopy only**	Hold ~~S~~**s**tudy ~~G~~**g**el (until evaluated)	Naked eye evaluation ~~and/or~~ **with or without** 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 ~~S~~**s**tudy ~~G~~**g**el (until evaluated~~),~~ ~~except for asymptomatic Candida vaginitis)~~	Perform wet mount for Candida vaginitis, trichomoniasis, and BV	Provide treatment and **permanently discontinue** ~~reevaluate in 48 - 72 hours. If resolved reinstate~~ 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~~	~~Hold Study Gel (until evaluated)~~ **Continue (at**	Naked eye evaluation ~~and/or~~ **with or without**	If determined to be **due to deep epithelial disruption,**

~~B~~**b**leeding~~/Spotting~~	**clinician's discretion).**	colposcopy	**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~~)	~~Continue (at clinician's discretion)~~ **Hold study gel (until evaluated)**	Evaluate for *N. gonorrhoeae* and *C. trachomatis*	~~Re-evaluate in 48 - 72 hours. If condition is worse, hold gel use until further evaluation is scheduled.~~ **Provide treatment and permanently discontinue gel use for all cases of cervicitis.**
Genital ~~P~~**p**etechial~~**(e) Hemorrhage~~ **excluding findings observed by colposcopy only**	Continue	Naked eye evaluation ~~and/or colposcopy~~	~~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.~~ **No further evaluation or treatment required.**
Genital ~~E~~**e**cchymosis **excluding findings observed by colposcopy only**	Continue	Naked eye evaluation ~~and/or~~ **with or without** colposcopy	~~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.~~ **No further evaluation or treatment required.**
EAE that is judged by the site investigator or designee to be	For Grades 1, 2, and 3 - Hold ~~S~~**s**tudy ~~G~~**g**el (until evaluated)	Evaluate as according to current clinical practice at the site	Provide treatment as clinically indicated, when resolved reinstate gel use at

definitely, probably, possibly, or probably not related to the study gel or applicator	For Grade 4 – Permanent Discontinuation	Not applicable	clinician's discretion. Not applicable

123. Former Appendix IV: DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS, Publish Date: December 2004 is deleted as current version of table is available on the RCC website.

124. In Appendix V: Sample Informed Consent Document (Screening), Why Are These Screening Exams and Tests Being Done?, first paragraph, third, fourth, and fifth sentences: About ~~half~~ **one-third** of the women in the research study will place VivaGel® into the vagina twice a day for two weeks. ~~About half~~ **One-third** of the women will place a **VivaGel®** placebo (inactive) gel into the vagina twice a day for two weeks**, and one-third will place a different kind of placebo (inactive) gel, called HEC placebo, into the vagina twice a day for two weeks**. Women will be in the group getting VivaGe**l®, the group getting VivaGel® Placebo Gel** or the group getting **HEC** Placebo Gel, depending on a selection process that will use random chance (like flipping a coin) to decide the groups.

125. In Appendix V: Sample Informed Consent Document (Screening), Why Are These Screening Exams and Tests Being Done?, first paragraph, last sentence: ~~This study will also check the gel applicators to see if a dye test can tell if they were put into the vagina or not.~~

126. In Appendix V: Sample Informed Consent Document (Screening), Why Are These Screening Exams and Tests Being Done?, third paragraph, second and third sentences: A total of approximately ~~40~~ **61** women from Florida and Puerto Rico will join this study (**about** ~~2~~**3**0 in Florida and **about** ~~2~~**3**0 in Puerto Rico). About ~~2~~**3**0 women will be in the study here at [INSERT NAME OF SITE].

127. In Appendix V: Sample Informed Consent Document (Screening), Why Are These Screening Exams and Tests Being Done?, fourth paragraph, third and fourth sentences: The whole study will take about ~~seven~~ **ten** months to finish. Each woman will be in the study for about ~~six~~ **eight** weeks.

128. In Appendix VI: Sample Informed Consent Document (Enrollment), Why Is This Study Being Done?, first paragraph: You may have heard of this study before since this study began enrolling participants in August 2007, but was paused for a short time because some participants had some side-effects that were probably caused by the gel. The researchers decided to stop the study for a little while so that they could study these side-effects to make sure the gel was safe to use. The researchers found that the side-effects were minor and the participants got better quickly. These types of side-effects are normal for this kind of study. At the beginning of this study, the researchers were comparing 2 different

products-VivaGel® and VivaGel® placebo, a gel with the same ingredients as VivaGel®, but without the active study drug. The new version of this study includes a second kind of placebo gel called HEC gel. Several other studies have shown HEC gel to be safe and well-tolerated in humans. Because of this, it is used as the comparison product in many other microbicide studies. The addition of HEC gel to this study will help the researchers understand the effects of VivaGel® and the VivaGel® placebo.

129. In Appendix VI: Sample Informed Consent Document (Enrollment), Why Is This Study Being Done?, second paragraph, second, third, and fourth sentences: About ~~half~~ **one-third** of the women in the research study will place VivaGel® into the vagina twice a day for two weeks. ~~The other half~~ **One-third** of the women will place a VivaGel® ~~p~~**P**lacebo (inactive) Gel into the vagina twice a day for two weeks**, and one-third will place a different kind of placebo gel called HEC Placebo Gel into the vagina twice a day for two weeks.** Women will be in the group getting VivaGel®, ~~or~~ **the** group getting VivaGel® Placebo Gel**, or the group getting HEC Placebo Gel,** depending on a selection process that will use random chance (like flipping a coin) to decide the groups.

130. In Appendix VI: Sample Informed Consent Document (Enrollment), Why Is This Study Being Done?, second paragraph, last sentence: ~~This study will also check the gel applicators to see if a dye test can tell if they were put into the vagina or not.~~

131. In Appendix VI: Sample Informed Consent Document (Enrollment), Why Is This Study Being Done?, fifth paragraph, second , third, fourth and fifth sentences: A total of ~~40~~ **61** women from Florida and Puerto Rico will join this study (**about** ~~2~~**3**0 in Florida and **about** ~~2~~**3**0 in Puerto Rico). About ~~2~~**3**0 women will be in the study here at [INSERT NAME OF SITE]. The whole study will take about ~~seven~~ **ten** months to finish. Each woman will be in the study for about ~~six~~ **eight** weeks.

132. In Appendix VI: Sample Informed Consent Document (Enrollment), What Do I Have To Do If I Am In This Study?, first paragraph, first four sentences: If you decide to join this study, and your tests and answers to the questions show you can join, you will be placed in one of t~~wo~~**hree** study groups. One group will get VivaGel®, ~~and the other~~ **one** group will get VivaGel® Placebo, and one group will get HEC Placebo Gel. ~~The placebo gel is a gel that looks and feels like VivaGel®, and it is made up of all the same ingredients except SPL7013 (the active ingredient). Both groups will use the study gel twice daily for 14 days.~~

133. In Appendix VI: Sample Informed Consent Document (Enrollment), What Do I Have To Do If I Am In This Study?, second paragraph, first sentence: ~~Both~~ **All three** groups are important to this study.

134. In Appendix VI: Sample Informed Consent Document (Enrollment), What Do I Have To Do If I Am In This Study?, fifth paragraph, third sentence: You will

return all of your ~~used and~~ unused applicators to the study sites at the Week 1 and Week 2 visits in the bags given to you for this purpose.

135. In Appendix VI: Sample Informed Consent Document (Enrollment), Enrollment Visit, seventh paragraph, first sentence: If you are eligible to join the study, you will be given 20 tubes of either ~~SPL7013 gel~~ **VivaGel®** or placebo gel **(VivaGel® Placebo or HEC Placebo)** already packaged inside applicators.

136. In Appendix VI: Sample Informed Consent Document (Enrollment), One-Week Clinic Visit, previous eleventh bullet: ~~Give back all of your used applicators to the clinic in the plastic bags that will be given to you for this reason. A laboratory test will be done on some of the applicators to check if the test can tell whether or not the applicators were put in the vagina or not.~~

137. In Appendix VI: Sample Informed Consent Document (Enrollment), Two-Week Clinic Visit, last bullet: Return all of your ~~used and~~ unused (if you have any unused) applicators to the clinic. ~~A laboratory test will be done on some of the applicators to check if the test can tell whether or not the applicators were put in the vagina or not.~~

138. In Appendix VI: Sample Informed Consent Document (Enrollment), How Many Women Will Take Part In This Study?: ~~40~~ **61** women will take part in this study. About ~~2~~**3**0 women will be from Florida and about ~~2~~**3**0 women will be from Puerto Rico.

139. In Appendix VI: Sample Informed Consent Document (Enrollment), Enrollment Visit, second paragraph, first bullet:

Give urine for a pregnancy test~~.~~ **if your second screening visit took place on a day other than today.**

140. In Appendix VI: Sample Informed Consent Document (Enrollment), Enrollment Visit, seventh paragraph, last bullet: It is ok for you to **use tampons,** take a bath or go swimming while you are using the study gel.

141. In Appendix VI: Sample Informed Consent Document (Enrollment), Risks of VivaGel®, second paragraph, second sentence: Some possible effects are dryness, itching, burning, **redness, a sore** or pain in the genital area.

142. In Appendix VII: Sample Informed Consent Document (Storage and Future Testing of Specimens), What About Confidentiality?, second paragraph, second sentence: In addition to the efforts of the study staff to help keep your personal information private, we have ~~applied for~~ **obtained** a Certificate of Confidentiality from the U.S. Federal Government.