Section 2. Protocol

This section contains a complete reference copy of the MTN 004 protocol. At the time of this printing, protocol Version 3.0, dated 30 June 2008; and Letter of Amendment #1, dated 15 May 2009, reflects current protocol specifications.

To ensure that this manual continues to reflect current protocol specifications in the future:

- Upon receipt of any protocol clarification memos, add a copy of the memo to this section.
- Upon receipt of any letters of amendment, add a copy of the letter of amendment to this section.
- Upon receipt of any full protocol amendments, replace the contents of this section with the amended protocol. However, retain the previous version(s) in your MTN 004 essential document file.

Further information on the content and required handling of protocol clarification memos, letters of amendment, and full amendments is available in Section 9 of the MTN Manual of Operations which is available at: http://www.mtnstopshiv.org

LETTER OF AMENDMENT #01 TO:

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 3.0 / 30 June 2008

IND # 62,482

Letter of Amendment Date: 15 May 2009

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the MTN-004 study and must be forwarded to your Institutional Review Board (IRB) and/or Ethics Committee (EC) as soon as possible for their information and review. IRB/EC approval is required before implementation of the revisions contained in this LoA.

The following information will also impact the sample informed consent. Site IRB/ECs are responsible for assessing whether and how the changes included in this LoA are to be communicated to study participants. All IRB/EC requirements must be followed.

Please file this LoA and all associated IRB/EC correspondence in your essential documents files for MTN-004.

Summary of Revisions and Rationale

This LoA adds an additional study site to the MTN-004 protocol. This LoA also clarifies language regarding specimen collection and archive in the Enrollment and Storage and Future Testing of Specimens Sample Informed Consent documents. Changes previously noted in CM # 02, dated October 3, 2007, and CM #03, dated September 3, 2008, are also included in this LoA.

Changes to the Protocol Team Roster are also noted here.

Implementation

This LoA is official MTN-004 protocol documentation. Prior to implementing the revisions listed below, the MTN-004 study sites will submit this LoA to all relevant regulatory authorities and the IRB/EC. Starpharma Pty Ltd, will submit this LoA to the United States Food and Drug Administration for inclusion in Investigational New Drug (IND) application # 62,482. Upon receipt of all required regulatory and IRB/EC approvals, the protocol revisions listed below will be implemented.

With the exception of modifications to the Protocol Team Roster, detailed modifications of the protocol text are indicated by ~~strikethrough~~ (for deletions) and **bold** for additions.

Detailed Listing of Revisions

1. The Protocol Team Roster is updated to reflect updates to the study team.

The following protocol team members have been added to the roster:

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The following protocol team members have updated roster information:

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The following listings are deleted from the Protocol Team Roster: Pat Farrell, Pamina Gorbach, Corey Kelly and Karen Patterson.

2. As previously noted in CM #03, Sections 6.2.6, 7.6.3, and 8.3.1 are updated.

In Section 6.2.6, Retrieval of Unused Study Products, third and fourth sentences are updated:

All unused study products must be returned **by the participant** to the site**, placed in a biohazard container** and then **destroyed at the site. Unused study product remaining in the pharmacy must be** forwarded to the MTN CORE **pharmacist for destruction** after the study is completed or terminated unless otherwise instructed by the MTN CORE.

In Section 7.6.3, Enrollment Visit, Table 13: Enrollment Visit, Study Supplies row, is updated to maintain consistency with Version 3.0 of the protocol:

Study Supplies	• Dispense two cartons (20 applicators) of study gel, male condoms and panty liners, and/or pads~~, and resealable plastic bags~~ • Participant to insert first dose in study clinic

In Section 8.3.1, Adverse Events, fourth paragraph, second sentence is deleted and fourth sentence modified to omit AE reporting for male partners:

Second sentence
~~Participants will be encouraged to report to the study clinician any problems experienced by their male partners that might be potentially related to study product.~~

Fourth sentence
Study site staff will document on study CRFs all AEs reported by or observed in enrolled study participants~~ or their partners~~ from the time of their first dose of study gel through the Three-Week Clinic Visit or early termination, regardless of severity and presumed relationship to study gel or applicators.

3. Throughout the protocol, text is updated to reflect the addition of a new study site.

In the Schema, participating sites, study design, and study duration are updated:

Participating Sites:
- University of South Florida, Tampa, Florida
- University of Puerto Rico, San Juan, Puerto Rico
- **Pitt CRS, Pittsburgh, Pennsylvania**

Study Design: Phase 1, three arm, ~~two~~ **three** site, randomized, double blind, placebo-controlled trial comparing VivaGel®, VivaGel® placebo, or HEC placebo gel (HEC Gel) applied vaginally twice daily for 14 days

Study Duration: Approximately 21 days per participant, ~~nine~~ **fourteen** calendar months of accrual, and ~~ten~~ **fifteen** months total planned study duration

In Section 1.4, Study Investigators is updated:

Site Investigator: Beatrice Chen, MD MPH
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In Section 4.1, Identification of Study Design, first and last sentences are updated:

MTN-004 is a ~~two~~ **three** site, Phase I, double blind, randomized, controlled comparison with 14 days of twice daily exposure to VivaGel®, VivaGel® placebo, or HEC gel, and follow-up among HIV-uninfected sexually active women. Participants in all three arms will receive male condom counseling and free male condoms on an ongoing basis. The study will be conducted at ~~two~~ **three** sites: University of South Florida**,** ~~and~~ University of Puerto Rico**, and the Pitt CRS.**

In Section 4.4, Time to Complete Enrollment is updated:

The approximate time to complete study enrollment is expected to be ~~nine~~ **fourteen** months.

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, is updated:

Enrollment Period	Follow-Up Period	Total Duration
~~9~~ **14** months	1 month	1~~0~~**5** months

In Section 4.8, Sites, the number of participating sites is updated:

~~Two~~ **Three** study sites are planned for this trial: University of South Florida**,** ~~and~~ University of Puerto Rico**, and Pitt CRS**.

In Section 5.1, Selection of the Study Population, second paragraph, second and third sentences are updated:
Participants will be recruited from a variety of venues. There are ~~two~~ **three** sites: University of South Florida**,** ~~and~~ University of Puerto Rico**, and Pitt CRS**. ~~Each site will enroll approximately 30 participants.~~ **A total of approximately 61 participants will be enrolled among the three sites.** Additional participants may be enrolled if non-adherent participants need to be replaced**.** ~~or if enrollment "slots" need to be shifted from one site to another.~~

In Section 5.1.2, Recruitment, first and third sentences are updated:

Members of the research teams at ~~both~~ **all** study sites will recruit women from various clinical sites at which they are providing direct patient care to potential study participants. Study staff will contact volunteers from previous research studies if those participants have previously signed an authorization permitting this type of contact. Site IRB-approved media advertisements, telephone scripts, and fliers will be used. These materials will be

presented and discussed with the community advisory boards at ~~both~~ **all** sites before submission to the local IRBs. Written informed consent will be obtained prior to the initiation of any study-related procedures.

In Section 6.4.4, Required Medications and Procedures, second paragraph, Male Condoms subsection, first sentence is updated:

~~Both s~~**S**tudy site pharmacies will be provided with a single brand of lubricated male condoms by MTN CORE to distribute to participants in quantities expected to be sufficient according to study-specific procedures when study product is dispensed.

In Section 6.4.4, Required Medications and Procedures, third paragraph, Panty Liners and Pads subsection, first sentence is updated:

~~Both s~~**S**tudy site pharmacies will be provided with single brands of panty liners and pads by the MTN CORE to distribute to participants in quantities expected by the participant to be sufficient when study product is dispensed.

Section 7.4.3.1 Quality Control and Quality Assurance Procedures is updated:

Network Laboratory staff will conduct visits as needed to ~~both~~ **all** sites to assess the implementation of on-site laboratory quality control procedures, including the proper maintenance of laboratory testing equipment, etc.

In Section 7.7, Colposcopy, first sentence is updated:

Experienced staff at ~~both~~ **all three** sites will conduct colposcopic examinations of the study participants. In addition, an MTN Safety Physician will provide specialized training in colposcopy for the evaluation of vaginal products.

In Section 8.1, Safety Monitoring, first sentence is updated:

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, ~~both~~ **all** Site PIs, FHI Protocol Coordinator, DAIDS and NICHD Medical Officers, and DAIDS Clinical Operations Study Coordinator, will serve as the Protocol Safety Review Team (PSRT).

In Section 8.3.1, Adverse Events, first paragraph, third sentence is updated:

This definition will be applied to ~~both~~ **all** treatment arms.

Section 10.1, Overview and General Design, is updated:

This is a ~~two~~ **three** site, Phase I, double blind, randomized, controlled comparison with 14 days of twice daily exposure to VivaGel®, VivaGel® placebo, or HEC gel, and follow-up among HIV-uninfected sexually active women.

In Section 10.9, Participant Accrual and Follow-Up, fourth sentence is updated:

Accrual is anticipated to take approximately ~~9~~ **14** months. Monthly accrual targets will be available in the SSP.

4. **Throughout the protocol, text is updated for applicability to MTN sites, in addition to ATN sites.**

Section 1.2, Sponsor and Monitor Identification, is updated to reflect PPD as the monitor for DAIDS sites:

Monitor: **PPD, Inc.**
929 North Front Street
Wilmington, NC 28401-3331 USA

In Section 12, Clinical Site Monitoring, first paragraph is updated to reflect PPD as the monitor for DAIDS sites:

Study monitoring **for the Tampa and San Juan sites** will be carried out by Westat (Rockville, MD)**, and by PPD, for the Pitt CRS**. On-site study monitoring will be performed in accordance with DAIDS policies. Site monitoring visits will be conducted to assess compliance with Health and Human Services (HHS) Regulations 45 CFR Part 46 and 21 CFR Parts 50, 56, and 312. Study monitors will visit the site to:

In Section 13.5, Participant Confidentiality, first paragraph, first and second sentences, and second paragraph, first and second sentences are updated:

Members of the study staff **at all** sites are ~~all~~ trained in patient confidentiality for their participation in ~~the ATN~~**MTN-004**. ~~The only sites at which this study will be performed are both ATN Trials Units (ATU).~~ The log of study participant names and other protected health information will be kept in a double-locked area. All computer information about study volunteers will be kept on a computer with log-on passwords. Laboratory specimens are labeled with study numbers and date, and are delivered or shipped by study staff. The study sites' data management and clinical staff are the only personnel with access to the protected health information of study volunteers. Each member of the staff has log-on identification and password, logs off before leaving a computer screen unattended, and closes their office door when out of the office. All research records will be kept indefinitely following closure of this study.

To further protect the privacy of the study participants, the ATN has obtained a Certificate of Confidentiality from the U.S. Department of Health and Human Services (DHHS). **The MTN has also obtained a Certificate of Confidentiality which applies to MTN sites.** With this Certificate in place, ~~the ATN~~ researchers cannot be forced to turn over identifying information about a study participant in any Federal, State, or local criminal, administrative, legislative, or other proceedings. This Certificate does not prevent a study participant from volunteering to turn over their research information nor does it prevent researchers from providing research-related information to others when requested by the study participant.

Section 13.2, Protocol Registration is updated to reflect protocol registration for the Pitt CRS.

A subheading is added to the original language in Section 13.2 to clarify the separate protocol registration procedures for the University of South Florida and the University of Puerto Rico:

Protocol Registration for the University of South Florida and the University of Puerto Rico

The text for protocol registration for the University of South Florida and the University of Puerto Rico remains unchanged.

A separate protocol registration subsection is added for Pitt CRS:

Protocol Registration for Pitt CRS

The study site will complete protocol registration with the DAIDS RCC Protocol Registration Office. For additional information, refer to the protocol registration documents located at http://rcc.tech-res.com/forms.htm. Protocol registration must occur as a condition for site-specific study activation; no participants may be screened or enrolled in this study prior to obtaining protocol registration approval and completing all other study activation requirements. MTN CORE (FHI) staff will notify the study site when all activation requirements have been met by issuing a site-specific study activation notice. Study implementation may not be initiated until the activation notice is issued.

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chairs and the NIAID Medical Officer and NICHD Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB(s) and the RCC prior to implementing the amendment.

5. **The Sample Informed Consent documents are updated to reflect changes to the study sites, anticipated duration of the study, clarify language related to the collection and long-term storage of plasma archive specimens, and to include modifications previously made in CM #02, dated October 3, 2007.**

The following changes have been made to Appendix V: Sample Informed Consent document (Screening):

In the Why Are These Screening Exams and Tests Being Done? subsection, fourth paragraph, second, third, and fourth sentences are updated:

A total of approximately 61 women from Florida**,** ~~and~~ Puerto Rico, **and Pennsylvania** will join this study ~~(about 30 in Florida, and about 30 in Puerto Rico). About 30 women will be in the study here at [INSERT NAME OF SITE].~~ The whole study will take about ~~ten~~ **fifteen** months to finish.

The following changes have been made to Appendix VI: Sample Informed Consent document (Enrollment):

In the Why is this Study Being Done? subsection, fifth paragraph, second, third, and fourth sentences are updated:

A total of 61 women from Florida**,** ~~and~~ Puerto Rico**, and Pennsylvania** will join this study ~~(about 30 in Florida, and about 30 in Puerto Rico). About 30 women will be in the study here at [INSERT NAME OF SITE].~~ The whole study will take about ~~ten~~ **fifteen** months to finish.

In the What Do I Have To Do If I Am In This Study? Enrollment subsection, the second bullet is updated:

- Give blood for tests to check on the health of your blood cells, liver, and kidneys and to confirm that there is no SPL7013 already in your blood (about 30 mL or about 2 tablespoons). **If you consent to the long-term storage of specimens, a portion of this blood sample will be stored for potential future testing.**

As previously noted in CM #02, Telephone Call subsection, the first sentence is modified:

Two **to four** days after you have your Enrollment Visit, you will have a phone call with study staff to talk about any problems you might have with the gel applicator.

As previously noted in CM #02, One-Week Clinic Visit subsection, the sixth bullet is omitted:

~~• Complete a computerized questionnaire about your use of the study gel.~~

In the How Many Women Will Take Part in this Study? subsection, the second sentence is updated:

Approximately 61 women will take part in this study. ~~About 30 women will be from Florida, and about 30 women will be from Puerto Rico.~~

In Appendix VII: Sample Informed Consent Document (Storage and Future Testing of Specimens), How Will You Get The Samples From Me? subsection is modified:

The research doctors want to **collect and** save ~~any extra~~ blood and cervical fluid ~~leftover from your tests~~ during the study. This ~~leftover~~ blood and cervical fluid **(including any leftover specimens)** will be kept and used for future research.

MTN-004
Phase 1 Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel®) Applied Vaginally in Sexually Active Young Women

A Study of the Microbicide Trials Network

In Cooperation with:
Adolescent Medicine Trials Network for HIV/AIDS Interventions

Sponsored by:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institute of Child Health and Human Development
US National Institutes of Health

Grant #:
5-U01-AI068633-03

DAIDS Protocol #:
10492

Starpharma Protocol #:
SPL7013-006

Co-Sponsored by:
Starpharma Pty Ltd

IND # 62,482

Protocol Chair:
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Version 3.0
30 June 2008

MTN-004

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

TABLE OF CONTENTS

TABLE OF FIGURES

MTN-004
Phase 1 Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel®) Applied Vaginally in Sexually Active Young Women

LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALP	alkaline phosphatase
ALT	alanine transaminase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
ATN	Adolescent Medicine Trials Network for HIV/AIDS Interventions
ATU	ATN Trials Units
BV	bacterial vaginosis
BUN	blood urea nitrogen
CBC	complete blood count
CFR	code of federal regulations
cGMP	current Good Manufacturing Practices
CONRAD	Contraceptive Research and Development Organization
CPST	Center for Pharmaceutical Science and Technology
CRF	case report form
CT	Chlamydia trachomatis
DAIDS	Division of AIDS
DMID	Division of Microbiology and Infectious Diseases
DNA	deoxyribonucleic acid
DOC	Data and Operations Center (Westat)
EAE	expedited adverse event
EDTA	ethylenediaminetetraacetic acid
FDA	(United States) Food and Drug Administration
FHI	Family Health International
GC	Neisseria gonorrhea
GCP	Good Clinical Practices
GRAS	Generally Recognized As Safe
HEC	Hydroxyethylcellulose
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
HSV-1, HSV-2	Herpes Simplex Virus type 1, type 2
IATA	International Air Transport Association
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonization
ID_{50}	intravaginal dose
IRL	Industrial Research Limited
IWGM	International Working Group on Microbicides
IND	investigational new drug
IRB	Institutional Review Board
IUD	intrauterine device
KOH	potassium hydroxide
LDMS	Laboratory Data Management System
LLOQ	lower limit of quantification

LIST OF ABBREVIATIONS AND ACRONYMS (Continued)

µg	microgram
mg	milligram
mL	milliliter
MOP	Manual of Procedures
MTN	Microbicide Trials Network
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
N	number
N-9	Nonoxynol-9
NIAID	National Institute of Allergy and Infectious Disease
NICHD	National Institute of Child Health and Development
NIH	National Institutes of Health
nM	nanomolar
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Nonnucleoside reverse transcriptase inhibitor
NOEL	no-observed-effect-level
PAB	DAIDS Pharmaceutical Affairs Branch
PAMA	Pediatric, Adolescent and Maternal AIDS
PBS	phosphate-buffered saline
PCR	polymerase chain reaction
PI	Principal Investigator
PID	pelvic inflammatory disease
PSRT	Protocol Safety Review Team
PTID	Participant Identification
qs	*quantum sufficiat;* a sufficient quantity
RBC	red blood cell
RCC	Regulatory Compliance Center
RNA	ribonucleic acid
RPR	rapid plasma reagin
RT	reverse transcriptase
RTI	reproductive tract infection
SADR	serious adverse drug reaction
SAE	serious adverse event
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SDA	strand displacement assay
SDMC	Statistical Data Management Center
SHIV	Simian-Human Immunodeficiency Virus (SIV/ HIV hybrid virus)
SLPI	secretory leukocyte protease inhibitor
SOP	standard operating procedure(s)
SSP	study specific procedure(s)
STD	sexually transmitted disease
STI	sexually transmitted infection
STICTG	Sexually Transmitted Infections Clinical Trials Group
ULN	upper limits of normal
UNAIDS	Joint United Nations Program on AIDS
WB	Western blot
WBC	white blood cell
w/w	weight for weight

MTN-004
Phase 1 Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel®) Applied Vaginally in Sexually Active Young Women

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MTN-004
Phase 1 Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel®) Applied Vaginally in Sexually Active Young Women

INVESTIGATOR SIGNATURE FORM

Version 3.0
30 June 2008
A Study of the Microbicide Trials Network (MTN)

Sponsored by:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institute of Child Health and Human Development
US National Institutes of Health

Co-Sponsored by:
Starpharma Pty Ltd

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation for at least two years following the date of marketing approval for the study gel for the indication in which it was studied, unless otherwise specified by the Division of AIDS (DAIDS), Starpharma Pty Ltd, or the Microbicide Trials Network (MTN) Coordinating and Operations Center. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the U.S. Food and Drug Administration (FDA) is notified that the Investigational New Drug application (IND) is discontinued. Publication of the results of this study will be governed by MTN policies. Any presentation, abstract, or manuscript will be submitted to the MTN Manuscript Review Committee, DAIDS, and Starpharma Pty Ltd for review prior to submission.

I have read and understand the information in the Investigator's Brochure(s), including the potential risks and side effects of the products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

_____
Name of Investigator of Record

_____ _____
Signature of Investigator of Record Date

MTN-004
Phase 1 Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel®) Applied Vaginally in Sexually Active Young Women

SCHEMA

Short Title: Safety and Acceptability of VivaGel® in Sexually Active Women

Clinical Phase: 1

IND Sponsor: Starpharma Pty Ltd

Protocol Chair: Ian McGowan, MD, PhD, FRCP

Sample Size: Approximately 61 women, including 7 participants enrolled under Version 2.0 of the MTN-004 protocol

Study Population: US sexually active, HIV-negative women between the ages of 18 and 24 years with a normal genital tract

Participating Sites:

- University of South Florida, Tampa, Florida
- University of Puerto Rico, San Juan, Puerto Rico

Study Design: Phase 1, three arm, two site, randomized, double blind, placebo-controlled trial comparing VivaGel®, VivaGel® placebo, or HEC placebo gel (HEC Gel) applied vaginally twice daily for 14 days

Study Duration: Approximately 21 days per participant, nine calendar months of accrual, and ten months total planned study duration

Study Regimen:

Arm	Description	N	Frequency
1	VivaGel®	*18	Twice daily for fourteen consecutive days
2	VivaGel® placebo	*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.

Primary Objective:

- To assess the safety of VivaGel® when administered for 14 consecutive days on the vulvar and cervicovaginal mucosa of healthy sexually active HIV-negative women aged 18-24 years

Primary Endpoints:

- Abnormal genital symptoms judged by the Investigator to be possibly, probably, or definitely related to product use
- Abnormal pelvic exam findings (excluding abnormal findings observed by colposcopy only) judged by the Investigator to be possibly, probably, or definitely related to product use
- Grade 3 or higher laboratory values (as defined by the DAIDS Toxicity Tables) for hematology, liver function, creatinine level and coagulation judged by the Investigator to be possibly, probably, or definitely related to product use
- Adverse experiences judged by the Investigator to be possibly, probably, or definitely related to product use

Secondary Objectives:

- To assess the adherence to a short-term regimen of VivaGel® among healthy sexually-active HIV-negative women aged 18-24 years
- To evaluate product acceptability among healthy sexually-active HIV-negative women aged 18-24 years
- To assess the effect of a twice daily short-term regimen of VivaGel® on the vaginal microflora of healthy sexually-active HIV-negative women aged 18-24 years

Secondary Endpoints

Consistent with the secondary study objectives to assess adherence to, and acceptability of, a short-term regimen of VivaGel®, and to assess the effect of this regimen on vaginal microflora, the following endpoints will be assessed:

- The proportion of participants who report via adherence questionnaire that they were adherent to the product use regimen, with adherence defined as the application of at least 80% of the expected number of doses of study product over the two weeks of product use.
- The proportion of participants who at their Two-Week Clinic Visit report via the acceptability questionnaire that they would be very likely to use the candidate microbicide during sexual intercourse in the future.
- Reported positive and negative aspects of using study product
- Changes in vaginal flora

Exploratory Objectives

- Determine the pattern of cytokine/chemokine, innate immune factor changes, and functional activity associated with use of VivaGel® in the lower reproductive tract of healthy sexually active HIV-negative women aged 18-24 years.
- Determine the extent of SPL7013 absorption into the blood following the completion of product dosing
- To assess the effects of VivaGel® on colposcopic findings

Exploratory Endpoints

- Changes in cervical cytokine, innate immune factor (secretory leukocyte protease inhibitor (SLPI) and lactoferrin) expression, and functional activity (antiviral and antibacterial) in cervicovaginal secretions
- Detection of SPL7013 in blood samples at Day 0 and Two-Week Clinic Visit (Target Day 14)
- Assessment of colposcopic findings

1 KEY ROLES

1.1 Protocol Identification

Protocol Title:	Phase 1 Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel®) Applied Vaginally in Sexually Active Young Women
MTN Protocol Number:	MTN-004
Co-Sponsor Number:	SPL7013-006
Date:	30 June 2008

1.2 Sponsor and Monitor Identification

Sponsor:	Division of AIDS (DAIDS)/National Institute of Allergy and Infectious Diseases (NIAID) National Institutes of Health (NIH) 6700 B Rockledge Drive Bethesda, MD 20892
Co-Sponsor:	National Institute of Child Health and Human Development (NICHD)/NIH Pediatric, Adolescent and Maternal AIDS Branch (PAMA) 6100 Executive Blvd Bethesda, MD 20892
Co-Sponsor:	Starpharma Pty Ltd Level 6, Baker Building 75 Commercial Road Melbourne VIC 3004 Australia
Monitor:	Westat 1650 Research Boulevard Rockville, MD 20850-3195

1.3 Medical Officers

DAIDS Medical Officer:	Jeanna M. Piper, MD Division of AIDS, NIAID National Institutes of Health 6700 B Rockledge Drive, Room 5248 Bethesda, MD 20892

NICHD Medical Officer: Bill G. Kapogiannis, MD
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1.4 Site Investigators

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1.5 Clinical Laboratories

Network Laboratory: MTN Network Laboratory
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Pittsburgh, PA 15213

Starpharma Laboratory: Starpharma Pty Ltd Bioanalytical Laboratory
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75 Commercial Road
Melbourne, 3004, VIC Australia

Site Laboratory: All Children's Hospital
801 6th Street South
St. Petersburg, FL 33701

Site Laboratory: Tampa General Hospital
2 Columbia Drive
2nd Floor West Pavilion
Tampa, FL 33606

Site Laboratory: University of Puerto Rico
Medical Science Campus
Department of Pathology, Lab 606A
San Juan, Puerto Rico, 00936

1.6 Data Center

Data Center: Statistical Center for HIV/AIDS Research & Prevention
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue N., LE-400
PO Box 19024
Seattle, WA 98109-1024

1.7 Study Operations

Study Operations: Family Health International (FHI)
PO Box 13950
Research Triangle Park, NC 27709

2 INTRODUCTION

2.1 HIV/AIDS Prevention and Microbicides

According to UNAIDS, an estimated 33.2 million (30.6 million–36.1 million) people worldwide were living with human immunodeficiency virus (HIV) in 2007. An estimated 2.5 million (1.8 million–4.1 million) became newly infected with HIV and an estimated 2.1 million (1.9 million–2.4 million) lost their lives to acquired immunodeficiency syndrome (AIDS)(1). Given these statistics, it is clear that available prevention options today have been insufficient to stem the tide of the AIDS epidemic, particularly for women, who continue to comprise a growing proportion of new HIV infections around the world. There is an urgent need for prevention methods that women can initiate and control themselves. Topical microbicides represent one such method, and a growing body of data suggests that a safe and effective topical microbicide will be a real option for women in the future. Many candidate microbicides are currently in various stages of preclinical and clinical investigation; VivaGel® is a dendrimer-based topical microbicide candidate with significant promise as a safe and effective means of prevention of HIV transmission.

2.2 The MTN Research Agenda

The MTN microbicide development plan has been designed to move candidate microbicides such as VivaGel® from the preclinical evaluation phase through to licensure. Candidate microbicides are considered for MTN development if they meet the following minimum criteria; (i) the International Working Group on Microbicides (IWGM) criteria for advancement into Phase 1 human studies, (ii) the commercial sponsor must be able to provide sufficient quantities of the candidate to undertake Phase 1 studies, (iii) the sponsor must have a formulation appropriate for human administration or be prepared to subcontract formulation development to agencies such as the NIAID/DAIDS formulation subcontract, (iv) the IND should have been submitted, and (v) an updated Investigator's Brochure must be available. VivaGel® is a product that meets all of these criteria.

2.3 Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN)

The MTN will collaborate with the ATN to carry out MTN-004. The ATN has been the only national network focused on studying the emerging HIV epidemic in teens infected through sex or drug-injecting behaviors. The scientific findings generated within this network inform the nation's adolescent-specific HIV/AIDS scientific agenda to improve HIV prevention efforts and the medical and psychosocial management of HIV-infected teens. The National Institute of Child Health and Human Development (NICHD) supports the ATN and its infrastructure with the capacity for behavioral, microbicidal, prophylactic, therapeutic, and vaccine trials to take full advantage of results gleaned from detailed observational and laboratory-intensive studies.

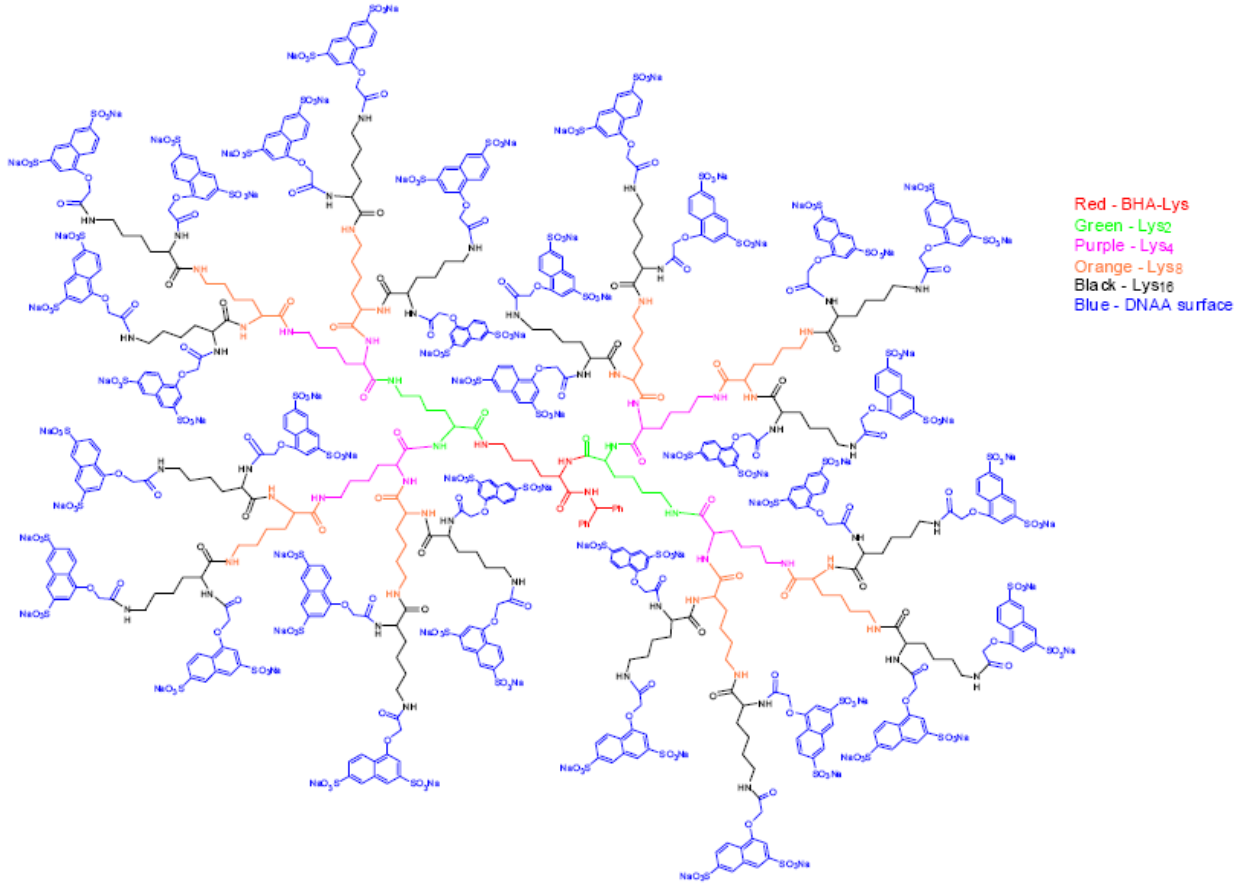
The primary mission of the ATN is to conduct research, both independently and in collaboration with existing research networks on promising behavioral, microbicidal, prophylactic, therapeutic, and vaccine modalities in HIV-infected and HIV-at-risk adolescents, ages 12 through 24 years. The ATN brings expertise and resources to collaborative protocol development that ensures feasible and acceptable study design as well as experience in recruiting and retaining this unique population. For the purposes of collaborative research, the resources in the ATN support the site-specific and negotiated participant-specific costs entailed in collaborative research activities, and do not duplicate but draw upon the regulatory, drug repository, laboratory, forms design, database management, and statistical capacity available in the NIH-funded research networks which choose to collaborate with the ATN.

2.4 SPL7013

SPL7013 is the active pharmaceutical ingredient (API) which, when formulated into a vaginal gel, is known as SPL7013 Gel or VivaGel®. Dendrimers are a relatively new class of macromolecules characterized by multiple layers of subunits branching out from a central core; they are constructed by repeated stepwise addition of branching units to a core(2). During lead optimization for dendrimer-based microbicides with HIV and herpes simplex virus (HSV) antiviral potential by Starpharma Pty Ltd, SPL7013 emerged as a candidate with significant antiviral properties. In addition it was the easiest to prepare on large scale as a single molecular species, having the optimal formulation compatibility and an excellent stability profile. Under IND 62,482, VivaGel® was granted "Fast Track" status by the U.S. Food and Drug Administration (FDA) for the HIV prevention indication. Further information on the formulation of VivaGel® is noted in Section 6. A sufficient body of preclinical and clinical safety data exists to support further clinical testing of VivaGel®. This section summarizes *in vitro*, animal, and clinical studies to date. Further detailed information is available in the SPL7013 Gel (VivaGel®) Investigator's Brochure(3).

The chemical name for SPL7013 is 2,6-bis-{(1-napthalenyl-3,6-disulfonic acid)-oxyacetamido}-2,6-bis-2,6-bis-2,6-bis-(2,6-diamino-hexanoylamino)-2,6-diamino-hexanoic acid (diphenylmethyl)-amide, polysodium salt. The underlying dendrimer architecture of SPL7013 is created by the addition of (L)-lysine molecules in layers or generations radiating out from a divalent core (the benzhydrylamine amide of (L)-lysine). The last step in the synthesis of SPL7013 involves attachment of 32 copies of a naphthalene-3, 6-disulfonate derivative to form the outer surface. The completed structure is an example of a polylysine dendrimer and the molecular weight is 16,582 Da). The structure of SPL7013 is noted in Figure 1.

Figure 1. Chemical structure of SPL7013



SPL7013 is a member of the class of compounds called dendrimers, a chemically diverse array of macromolecules. As pharmaceuticals, dendrimers offer a unique single-molecule structure for the presentation of multiple copies of a given surface group which are attached to the underlying dendrimer architecture through linkers(4). VivaGel® is a water-based Carbopol® gel buffered to a physiologically compatible pH (Table 1: VivaGel® Formulation).

Table 1: VivaGel® Formulation

Ingredient	Function in Formulation	Amount (weight for weight (w/w))
SPL7013	Antiviral	3.0%
Purified Water, USP	Solvent	qs to 100%
Methylparaben, NF	Antimicrobial preservative	0.18%
Propylparaben, NF	Antimicrobial preservative	0.02%
EDTA	Antioxidant	0.1%
Carbopol® 971P	Gelling agent	5.0%
Propylene glycol, USP	Emollient	1.0%
Glycerin, USP	Emollient	1.0%
2N NaOH	pH adjusting agent	qs to pH 5.0

2.4.1 Strength of Active Product

This protocol will utilize the 3% w/w SPL7013 Gel (VivaGel®).

2.4.2 Mechanism of Action

Dendrimers can be synthetically engineered to have properties that prevent virus entry and infection(5). In particular, polyanionic dendrimers are able to block virus attachment to cells or interfere with virus adsorption. SPL7013 is able to interact at multiple target sites, a factor which also enhances its antiviral activity(6).

2.5 Condom Integrity

The effect of VivaGel® on latex condoms has been assessed in a number of studies. VivaGel® did not compromise the integrity of non-lubricated, silicone lubricated, and aqueous lubricated condoms, as assessed by burst pressure, time to burst, burst volume, and tensile strength. The dimensions of the condoms after exposure to the gel also appeared to be unchanged.

2.6 Anti-HSV Activity

In vitro and *in vivo* studies in mice on a selection of dendrimer-based compounds have reported potent inhibition of HSV-1 and HSV-2(7). In a mouse model, unformulated SPL7013 provided significant protection from genital herpes disease and infection at concentrations as low as 1 mg/mL and for at least 1 hour following topical (vaginal) administration of 10 mg/mL(6). SPL7013 formulated into VivaGel® and two related formulations was further evaluated in mouse and guinea pig models of genital herpes infection. In the murine evaluations each of the formulations provided significant protection at concentrations of 10 and 50 mg/mL. Formulated SPL7013 provided protection for at least 1 hour at a concentration of 10 mg/mL. The VivaGel® formulation was chosen for dose ranging experiments using the guinea pig model of vaginal genital herpes. The guinea pig evaluations suggested that doses of 30 to 50 mg/mL were required for optimal protection. The results of these evaluations indicate that SPL7013 shows significant promise as a microbicidal product with antiviral activity.

2.7 Anti-HIV-1 Activity

In vitro studies of SPL7013 have demonstrated antiviral activity against HIV type 1 (IC_{50}=1.90 µg/mL), HIV type 2 (IC_{50}=4.38 µg/mL) and chimeric-simian human immunodeficiency viruses (SHIV) (IC_{50}=0.25 µg/mL). The antiviral properties of polyanionic dendrimers are mediated by multiple mechanisms including inhibition of viral transmission, attachment, fusion, and replication.

Studies of inhibition of attachment, fusion, and viral replication found no significant cytotoxic effects of SPL7013 at concentrations up to 100 µg/mL (highest concentration tested). The cellular cytotoxicity of SPL7013 in human PBMCs was reassessed against

two previously tested strains (one type of HIV-1 Clade D and one type of HIV-1 Clade O); this study confirmed SPL7013 efficacy against these strains, with therapeutic indices of >676 and >1348 against Clade D and O, respectively.

Cervical and colorectal explant cultures were exposed to HIV-1 in the presence or absence of 5% SPL7013. In the absence of SPL7013, the cervical and colorectal explant cultures replicated HIV-1, which peaked approximately by day 14 of culture. SPL7013 blocked infection in 3 of 4 colorectal explant cultures and in 2 of 2 cervical explant cultures. This was significant inhibition of HIV-1 infection in these tissues.

A SHIV-challenge study of female pigtailed macaques (8 animals/untreated, 8 animals/placebo, 6 animals/active treatment group, up to 5% w/w SPL7013 Gel, single dose) found that 3-5% w/w SPL7013 Gels were effective in blocking vaginal transmission of a single virus challenge with SHIV(8). Neither SPL7013 nor placebo gel produced any adverse effects following the single application.

Table 2: Effects of SPL7013 Gels on Vaginal Transmission of $SHIV_{89.6P}$ in Macaques

Treatment Group	Number of Animals	Virus Isolation*	Viral DNA PCR*	Plasma Viral RNA*	CD4 Cell Depletion*	Anti-SHIV Antibody*	% Infection
5% w/w SPL7013 Gel	6	0	0	0	0	0	0
3% w/w SPL7013 Gel	6	1	1	1	1	1	16.7
1% w/w SPL7013 Gel	6	4	4	4	4	2	66.7
Placebo Gel	8	7	7	7	7	5	87.5
Untreated control	8	8	8	8	8	6	100

*Results of each assay expressed as number of positive macaque(s) per total tested.

2.8 *In vitro* Studies

2.8.1 Cytotoxicity

In vitro studies of cytotoxicity suggest that SPL7013 has a significant therapeutic index, with little potential for cytotoxicity. An investigation of SPL7013 5% formulation in colorectal and urogenital epithelial cell lines and primary immune cells found the microbicide to be relatively non-toxic as determined by an ATP-dependent luminescence assay. SPL7013 did not affect an intact, polarized epithelial monolayer, a potential marker for product safety on mucosal epithelia(9).

Human cervical explant cultures were used to evaluate potential toxicity of SPL7013 Gel. Histological analysis of cervical tissues exposed to 5% w/w SPL7013 Gel and placebo showed regenerated epithelium and an intact lamina propria similar to the untreated control. Further, an MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay confirmed these results(10). A recent study utilized a human colorectal

explant culture to evaluate the potential toxicity of SPL7013 Gel, among others(11). 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. An MTT assay confirmed these results. Viability of tissues treated with SPL7013 was not significantly different from that of the control media. Spermatozoa Motility
SPL7013 was not shown to be spermicidal in a modified Sander-Cramer assay. Motile spermatozoa were noted following a room temperature incubation of semen with an SPL7013 dilution.

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. In an *in vivo* rat micronucleus study, SPL7013 administered intravenously did not increase the incidence of micronucleated polychromatic erythrocytes(12). SPL7013 was negative in this genetic toxicity assay.

2.9 Animal Studies

2.9.1 Oral administration

Multiple toxicity studies performed in rats have suggested a low risk for acute toxicity from SPL7013(12). An oral gavage study of acute toxicity in rats (3 animals/group, 3 groups, up to 1600 mg/kg/day) had no mortality and no clinical signs or effects on animals' body weight were reported. Based on this study, the no-observed-effect-level (NOEL) was estimated to be greater than 1600 mg/kg. 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.

2.9.2 Intravenous Administration

A study of intravenous administration of SPL7013 in rats (20 male, 20 female, 5/sex/dosage group, single-dose up to 75 mg/kg) noted signs of toxicity (both clinically and on necropsy) in some animals at the 50 mg/kg and 75 mg/kg dose levels. The NOEL was determined to be 25 mg/kg for the intravenous administration route. A study of intravenous administration in rabbits (2 animals/group, 4 groups, up to 75 mg/kg, single dose) found a dose of 25 mg/kg (the NOEL) well tolerated, but noted adverse effects by clinical and necropsy evaluation in some animals at the 50 and 75 mg/kg dose levels.

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.

2.9.3 Vaginal Administration

Animal studies of vaginal administration of SPL7013 Gel have suggested a low risk for acute toxicity(12). A study of acute toxicity in rats (5 animals/group, 2 groups, placebo vs. 5% gel, 0.1 mL single vaginal dose) found no clinical signs of toxicity or vaginal irritation in either group. No effects were noted in body weight gain. There were no macroscopic changes in systemic organs on necropsy. The NOEL was calculated as 28.6 mg/kg. A study of vaginal administration of SPL7013 Gel in rabbits (3 animals/group, 2 groups, placebo vs. 5% w/w SPL7013 Gel, single dose 1.0 mL test article volume) noted no clinical signs of systemic toxicity in either group, and no effects on body weights, body weight gains, or food consumption. No differences were observed between groups with respect to vaginal irritation following a single vaginal dose.

Studies of repeat-dose toxicity in rats, rabbits, dogs, and macaques also found a lack of evidence for systemic toxicity. A study of rats (10 animals/group, 5 groups, up to 25 mg/kg/day, single daily 0.1 mL dose, 14-day exposure) found minimal vaginal irritation in all dose groups, with no systemic toxicity noted (NOEL >25 mg/kg). Rabbits receiving vaginal SPL7013 Gel (5 animals/group, 5 groups, up to 5% w/w SPL7013 Gel, single daily 1.0 mL dose, 14-day exposure) were not observed to have significant vaginal irritation or signs of systemic toxicity (NOEL >12.5 mg/kg). Dogs receiving vaginal SPL7013 Gel (2 animals/group, 4 groups, up to 5% w/w SPL7013 Gel, single daily 1.0 mL dose, 14-day exposure) were not observed to have significant vaginal irritation or signs of systemic toxicity (NOEL >5% w/w SPL7013 Gel). A dose-related increase in the severity of subacute inflammation was noted in the cervix and vagina (proximal, mid, and distal sections) of the dogs. This occurred in all animals from all groups, including the vehicle control.

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(12). 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.

A study in pigtailed macaques (6 animals/group, 3 groups, receiving 0%, 1%, 3% and 5% w/w SPL7013 Gel in a 1.5 mL volume, four consecutive daily applications) examined the vaginal safety of SPL7013(13). Vaginal safety measures included colposcopy, vaginal pH, and microflora determinations. Cervicovaginal tissue disruption and/or friability were noted in four of six animals receiving the 5% w/w SPL7013 formulation. None of the animals treated with the 1% or 3% w/w SPL7013 Gel formulation demonstrated cervicovaginal irritation. Observations of subepithelial vasculature were noted in the majority of animals from each arm of the study. Statistically significant decreases in vaginal pH were noted 30 minutes after the application of each SPL7013 Gel formulation, and remained lower than baseline at 24 hours after application. These values were recovered to baseline at the Day 8 measurement. Differences in vaginal pH were not statistically significant in comparison to values noted after application of placebo gel (base formulation without added SPL7013) at these time points.

In the same macaque study, when quantities of vaginal microflora between placebo and treatment groups were compared, there were few significant differences. Of the daily comparisons, significant differences were found between the placebo-treated group and the 3% w/w SPL7013 Gel treated group concerning H_2O_2-producting lactobacillus on day 4 and between the placebo-treated group and the 5% w/w SPL7013 Gel treated group concerning H_2O_2-producing lactobacilli on day 5. No significant differences were noted on the other study days. Due to the small sample size, the investigators did not conclude that these were true differences, and no pattern of product-induced suppression of these organisms emerged.

Profiles of vaginal and cervical biopsy specimens collected from macaques in the same study 24 hours after the final application of 1%, 3%, and 5% w/w SPL7013 Gel were mostly similar to baseline profiles assessed in these studies (layers of epithelial cells, presence of polymorphonuclear cells, plasma cells and lymphocytes). Biopsy specimens from animals that received the test gel had histologic profiles similar to those that received placebo. Although statistical analyses indicate an increase in presence of plasma cells in the 1% SPL7013 treated animals, these increases reflected no more than one cell greater than the normal profile range (0-4 cells per high power field). No clinical significance was attached to these findings (unpublished data). Overall, repeated daily vaginal use of 1% and 3% w/w SPL7013 Gels resulted in an acceptable safety profile, as evaluated by colposcopy, pH determination, microflora evaluation, and histology, compared to the profiles achieved with the placebo gel.

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.

2.9.4 Penile Administration

A study of penile administration in dogs (3 animals/group, 2 groups, placebo vs. 3% w/w SPL7013 Gel) found the test article to be well tolerated, with no effects noted on clinical observations, including degree of erythema, edema, body weights, or food consumption (NOEL >3.4 mg/kg).

2.9.5 Rectal Administration

A study of rectal administration in macaques (8 animals, crossover design, 3% w/w SPL7013 Gel vs. placebo vs. no product, 3 daily applications of single dose 2.5 mL gel or no product) found 3% w/w SPL7013 Gel to be well tolerated by rectal tissues and microflora compared to tolerance of the placebo gel(13).

2.9.6 Developmental Toxicology

A study of vaginal administration in rats (25 animals/group, 4 groups, up to 5% w/w SPL7013 Gel, 0.1 mL daily dose for 12 days) found no evidence of teratogenicity at any dose (NOEL >25 mg/kg or 5% w/w SPL7013 Gel). A study of vaginal administration in rabbits (23 animals/group, 4 groups, up to 5% w/w SPL7013 Gel, 1.0 mL daily dose for 14 days) did not find evidence of developmental toxicity. This study reported maternal deaths, but based on follow-up studies and histopathological evaluation, these mortalities were concluded to be the result of a local, facility/procedure related and species-specific response that has an understood pathogenesis. Further details are available in the Investigator's Brochure.

2.9.7 Pharmacokinetics

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. The identified lower limit of quantification (LLOQ) of SPL7013 in these plasma samples was 0.2 to 0.5 µg/mL (12 to 30 nM).

2.9.8 Contraceptive Activity

The effect of 3% w/w SPL7013 Gel, or 3% w/w of the active ingredient, SPL7013, in hydroxyethylcellulose (HEC) gel, on contraception in female New Zealand White rabbits has been studied. Animals were artificially inseminated with 0.5 mL of sperm 5 minutes after vaginal administration of 2mL of the gels containing SPL7013. HEC gel was used as a placebo control. Contraceptive efficacy was determined 15 days post insemination

by assessing whether or not the animal became pregnant, and by comparing the number of implanted embryos in pregnant animals.

Out of 8 rabbits pre-treated with 3% w/w SPL7013 Gel, only 2 became pregnant, with 6 and 7 embryos counted in each of the pregnant does. Out of 8 rabbits pre-treated with 3% w/w SPL7013 in HEC Gel, again only 2 became pregnant. There was only one embryo in each of the pregnant does. In contrast, 9 of 11 rabbits in the HEC placebo control group became pregnant with a total of 75 embryos. Preliminary observations were also made to determine the duration of contraceptive effect. The combined results demonstrated that 3% w/w SPL7013 Gel was a highly effective contraceptive approximately 24 hours after application. The results also suggest that contraceptive efficacy diminished 2 days after application, and was no longer present at 7 days.

2.10 Clinical Studies

Clinical experience so far with SPL7013 Gel is comprised of three completed Phase 1, randomized, placebo-controlled studies(12). 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)(12). 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)(12). 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)(12). 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(12). 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.

Table 3: Design of First Clinical Study in Women

Group	N	Dose Level	Doses	Interval
1	12 (8 active, 4 placebo)	0.5% w/w SPL7013 Gel	7	24-hour
2	12 (8 active, 4 placebo)	1.0% w/w SPL7013 Gel	7	24-hour
3	13 (9 active, 4 placebo)	3.0% w/w SPL7013 Gel	7 for 12 participants, 3 for 1 participant	24-hour

Safety evaluations included clinical symptom assessment, vital sign measurements, clinical laboratory diagnostic results, colposcopic examination of the vulva, vagina, and cervix, and examination of the vaginal microflora. No serious adverse events (SAEs) were reported in this trial. Adverse events (AEs) were experienced by 31 of 37

participants, with a total of 13 events having a possible causal relationship to study treatment (active or placebo). All reported AEs were deemed to be of mild or moderate intensity except for a tension headache of severe intensity reported by a participant who received the placebo gel, but this event was not considered to be related to study treatment. Of the moderate intensity AEs, the only one judged possibly related to study treatment was a rash on the jaw-line, experienced by a participant receiving placebo gel. All other AEs, which were possibly related to study treatment, were of mild intensity.

Table 4: Reported AEs Possibly Related to Study Treatment

AE	Participants Receiving Active	Participants Receiving Placebo
Mild abdominal pain	4	1
Mild dysuria	1	0
Mild genital pruritus	0	1

Common AEs judged unlikely to be or not related to study treatment included headache, metrorrhagia, and venipuncture site bruise. No identifiable trends in AEs were observed when analyzed by type or by dose of study agent. On colposcopy, no participants showed signs of vulvar, vaginal or cervical inflammation or other pathology related to gel exposure. Analysis of vaginal flora in both active and placebo groups noted lower concentrations of normal lactobacilli, higher concentration of facultative gram-negative rods, and a decrease in proportion of anaerobic forms. This change in flora was not associated with any cases of vaginal infection, and flora generally returned to pre-gel levels by the Day 14 follow-up visit. Most participants experienced leakage of the gel across all SPL7013 Gel treatment groups (24 out of 25) on at least one occasion during the dosing period, but the volume of discharge was small, and was transitory. The discharge in all instances was not associated with vaginal burning, pruritus or malodor, and was easily tolerated. No clinically relevant changes in vital sign measurements or laboratory values were noted. SPL7013 plasma concentrations were measured by a validated, bioanalytical capillary electrophoresis method in all participants who received the highest dose level (3.0% w/w SPL7013 Gel). No SPL7013 was detected in any plasma sample analyzed during the study (LLOQ = 0.5 µg/mL [30nm]).

Study No. SPL7013-002: 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(12).
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.

As with the study in females, no discernible trends in AEs were observed in this study, and no SPL7013 was detected in any plasma sample analyzed during the study.

Study No. SPL7013-004: A total of 54 healthy women were enrolled in the study with 35 receiving SPL7013 Gel and 19 receiving placebo(12).

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.

2.11 VivaGel® Placebo

The VivaGel® placebo for this study is the base formulation without SPL7013. The placebo gel to be used in this study is formulated primarily from water, but also contains Carbopol® and other ingredients as outlined in Section 6.2. Carbopol® is one of the most widely used excipients for thickening topical lotions, creams and gels. Carbopol®

and other types of similar polymers are also used to modify the rheology (flow properties) of water-based systems and to stabilize multi-phase systems such as emulsions and suspensions(14). Also known as carbomer, this type of thickener is a high-molecular weight polymer that is not absorbed by body tissues.

Table 5: VivaGel® Placebo Formulation

Ingredient	Function in Formulation	Amount (w/w)
Purified Water, USP	Solvent	qs to 100%
Methylparaben, NF	Antimicrobial preservative	0.18%
Propylparaben, NF	Antimicrobial preservative	0.02%
EDTA	Antioxidant	0.1%
Carbopol® 971P	Gelling agent	5.0%
Propylene glycol, USP	Emollient	1.0%
Glycerin, USP	Emollient	1.0%
2N NaOH	pH adjusting agent	qs to pH 5.0

2.11.1 *In vitro* Studies

Carbopol®, the gelling agent in the placebo gel, has been the subject of numerous *in vitro* studies. Biological oxygen demand tests have demonstrated that the biological oxygen demand of Carbopol® crosslinked polyacrylic acid polymers is zero, contributing to an excellent shelf life in severe environments(15). The Carbopol®-based aqueous placebo gel planned for use in this study was found to be not disruptive to transepithelial resistance at a nontoxic product concentration. Using a cervical explant culture model, a Carbopol®-containing placebo did not affect tissue viability as compared to the control based on the MTT assay(16). Further, tissue architecture appeared histologically normal. A subsequent study utilizing a human colorectal explant culture model found explants treated with this placebo gel to be histologically normal. Results from an MTT assay showed a non-significant reduction in viability of intestinal explants exposed to SPL7013 compared to those exposed to the medium control.

2.11.2 Animal Studies

Carbomer is the generic name adopted by United States Pharmacopeia (USP) for various Carbopol® homopolymers. Acute oral studies with rats, guinea pigs, mice and dogs showed that carbomers have low toxicities when ingested. No mortalities occurred in rabbits injected intravenously with 1%, 2% or 3% carbomer in aqueous solution at a dose of 5 mL/kg. Rabbits showed minimal skin irritation when tested with 100% carbomer, and zero to moderate eye irritation when tested with carbomers and/or their various salts at concentrations of 0.20-100%(17).

Single and repeated dose oral, intravenous and vaginal administration in rats and rabbits of the base placebo gel (base formulation without added SPL7013) planned for this protocol was not associated with significant adverse clinical effects or systemic toxicity. Repeat dose penile administration in dogs of this placebo gel was also well tolerated and not associated with adverse clinical effects or systemic toxicity.

A study in pigtailed macaques (6 animals/group, 3 groups, placebo, 1 and 5% w/w SPL7013 Gel, followed by a separate assessment of the 3% w/w SPL7013 Gel controlled by a repeat of the placebo arm) examined the vaginal safety of SPL7013 and the base placebo gel [12]. Mild erythema was noted in 2 of 12 placebo-treated animals. There were no statistically significant differences in pre- and post-application pHs with the placebo gel in this study. Rectal administration of the placebo gel in pigtailed macaques was associated with a slightly increased level of epithelial desquamation(13).

2.11.3 Clinical Studies

Powdered Carbopol® polymers have a long history of safe use in cosmetic and pharmaceutical products(15). Clinical studies with carbomer and its various salts showed that these polymers have low potential for skin irritation and sensitization at concentrations up to 100%. Propylene glycol and glycerin (other ingredients in the placebo gel formulation) are both generally recognized as safe (GRAS) for use in humans. Methylparaben and propylparaben are affirmed GRAS Direct Food Substances in the USA at levels up to 0.1%, and are widely used in vaginal formulations at levels of 0.1-0.18% and 0.02-0.1%, respectively.

MTN-004 will utilize as the placebo gel the same Carbopol®-based aqueous gel that was utilized in clinical protocol number SPL7013-001, SPL7013-002, and SPL7013-004(12). 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). The only AE reported of severe intensity was a tension headache in a placebo recipient, although this was not deemed related to study product or procedures. Eleven participants who received placebo gel reported product leakage on one or more occasions, but without complaints of burning, itching or unpleasant odor. One participant who received placebo gel reported itching without associated discharge. No participants receiving placebo gel had colposcopic findings consistent with inflammation or other pathology related to study agents. Lower concentrations of vaginal lactobacilli with a concomitant increase in colonization with facultative gram-negative rods were noted on vaginal culture during placebo gel use, but no cases of bacterial vaginosis or any intermediate Nugent score were identified. No clinically relevant changes were noted in vital signs or clinical laboratory diagnostic results.

In study SPL7013-002, 5 genital AEs were reported by 33% of study participants in the placebo group (4 of 12 men)(12). 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.

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(18). 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
Hydroxyethylcellulose, 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(18). 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(19). 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(18).

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(19). 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)(18). 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)(19).

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(19). *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(19). 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(19). 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(20). 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(21).

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(21). 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(22). 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(23). 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(18).

2.18 Study Hypothesis and Rationale

2.18.1 Study Hypothesis

MTN-004 hypothesizes that VivaGel® will be safe, well-tolerated and acceptable for twice daily vaginal application among healthy sexually active young women.

2.18.2 Rationale for Sexually Active Study Population

This will be the first study of VivaGel® in a sexually active study population. Studies of safety and acceptability in a sexually active population of women are important for understanding the potential of a candidate microbicide for several reasons. A vaginal microbicide, if approved, is intended for use by sexually active women, and thus must be evaluated for acceptability by this population. In addition, the product should have its safety profile evaluated in women who are experiencing the mechanical effects of intercourse on vaginal and cervical epithelial integrity.

Based upon protocol stipulations and preclinical investigations of the study product to date, neither VivaGel® nor either type of placebo gel is expected to be associated with adverse effects or toxicity in male partners of female study participants. Female volunteers will be informed at the Screening Visit and then reminded at all subsequent study visits that male partner knowledge of study participation is encouraged and left to the volunteers' discretion, and that male condom use is a protocol-specified requirement for study participation. According to the results of male condom integrity studies, VivaGel® does not compromise the integrity of latex male condoms, as assessed by

burst pressure, time to burst and burst volume, with no apparent change in dimension of male condoms after exposure to the gel. Volunteers who are unwilling or unable to comply with the male condom requirements of this protocol will not be enrolled. Based on a study of penile administration in dogs, no toxicity in male partners is expected in the event of inadvertent exposure. A Phase 1 study of the safety of VivaGel® (3% w/w) in male volunteers 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).

In the event that a study participant did not follow protocol guidelines specifying male condom use, it is unlikely that the product would lead to any significant exposure in sexual partners. No quantifiable or significant systemic absorption in female participants is expected. The single completed Phase 1 study of vaginal exposure to VivaGel® was conducted in sexually inactive volunteers who remained in a Phase 1 clinical trial unit for the duration of the dosing period, and therefore did not include partner consent. While male partner consent will not be a part of this study, reported instances of unprotected intercourse at any time during the study period will be reported as participant non-adherence to the protocol, as defined by study-specific procedures, with these cases being referred to the physician site investigator for further evaluation according to study-specific procedures if necessary.

2.18.3 Justification of Dosing

The utilization of a 3% w/w SPL7013 dose concentration is based on considerations of safety, potential efficacy, and physical properties of VivaGel®. In a study of pig-tailed macaques described above, the safety profile following the use of the 5% SPL7013 formulation did indicate some deleterious effects on the cervicovaginal environment assessed by colposcopy, as compared to the 3% w/w SPL7013 formulation. Investigators evaluating unformulated and formulated dendrimer-based microbicide candidates in mouse and guinea pig models of HSV-2 infection concluded that concentrations of 3% or higher of the formulated SPL7013 product may be necessary for optimal protection against genital herpes. As reviewed above, macaques treated with SPL7013 showed a dose-dependent resistance to SHIV viral challenge, with 3-5% w/w SPL7013 Gels effective in blocking vaginal transmission of SHIV in macaques after single gel application followed by single virus challenge. Studies also indicate that the SPL7013 Gel formulation decreases in viscosity as the concentration of SPL7013 increases. Given these considerations, it seems most scientifically appropriate that clinical research for vaginal application proceed with the 3% w/w SPL7013 Gel formulation.

The dose volume of 3.5 g (equivalent to 3.5 mL) of 3% w/w SPL7013 Gel has been selected as the dose that is intended to provide optimum vaginal and cervical coverage while minimizing leakage of product from the vagina. This balance between coverage and leakage has been investigated using other potential vaginal microbicide candidate gels with similar physicochemical properties to SPL7013 Gel. These studies showed that 3.5 mL of gel provides adequate coverage with minimal leakage(24). 14

consecutive days of dosing is considered to be the maximum length of time in which menses does not overlap with product application and/or follow up visit. Twice daily dosing for 14 days represents the accepted duration of exposure during Phase 1 microbicide studies as this level of product exposure exceeds the likely frequency of gel administration during efficacy studies, which will be driven by coital frequency.

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."

3 OBJECTIVES

3.1 Primary Objective

- To assess the safety of VivaGel® when administered for 14 consecutive days on the vulvar and cervicovaginal mucosa of healthy sexually active HIV-negative women aged 18 – 24 years.

3.2 Secondary Objectives

- To assess the adherence to a short-term regimen of VivaGel® among healthy sexually-active HIV-negative women aged 18 – 24 years.

- To evaluate product acceptability among healthy sexually-active HIV-negative women aged 18 – 24 years.

- To assess the effect of a twice daily short-term regimen of VivaGel® on the vaginal microflora of healthy sexually-active HIV-negative women aged 18-24 years.

3.3 Exploratory Objectives

- Determine the pattern of cytokine/chemokine, innate immune factor changes, and functional activity associated with use of **VivaGel®** in the lower reproductive tract of healthy sexually active HIV-negative women aged 18 – 24 years.

- Determine the extent of SPL7013 absorption into the blood following the completion of product dosing.

- To assess the effects of VivaGel® on colposcopic findings

4 STUDY DESIGN

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 VivaGel®, VivaGel® placebo, or HEC gel, and follow-up among HIV-uninfected sexually active women. Participants in all three arms will receive male condom counseling and free male condoms on an ongoing basis. The study will be conducted at two sites: University of South Florida and University of Puerto Rico.

Table 7: Study Design

Arm	Description	N	Frequency
1	VivaGel® daily use	*18	Twice daily for fourteen consecutive days
2	VivaGel® placebo daily use	*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.

4.2 Summary of Major Endpoints

Primary Endpoints

- Abnormal genital symptoms judged by the Investigator to be possibly, probably, or definitely related to product use
- Abnormal pelvic exam findings (excluding findings observed by colposcopy only) judged by the Investigator to be possibly, probably, or definitely related to product use
- Grade 3 or higher laboratory values (as defined by the DAIDS Toxicity Tables) for hematology, liver function, creatinine level and coagulation judged by the Investigator to be possibly, probably, or definitely related to product use

- Adverse experiences judged by the Investigator to be possibly, probably, or definitely related to product use

Secondary Endpoints

Consistent with the secondary study objectives to assess adherence to, and acceptability of, a short-term regimen of VivaGel®, and to assess the effect of this regimen on vaginal microflora, the following endpoints will be assessed:

- The proportion of participants who report via adherence questionnaire that they were adherent to the product use regimen, with adherence defined as the application of at least 80% of the expected number of doses of study product over the two weeks of product use;

- The proportion of participants who at their Two-Week Clinic Visit report via the acceptability questionnaire that they would be very likely to use the candidate microbicide during sexual intercourse in the future;

- Reported positive and negative aspects of using study product;

- Changes in vaginal flora.

Exploratory Endpoints

- Changes in cervical cytokine, innate immune factor (secretory leukocyte protease inhibitor (SLPI) and lactoferrin) expression, and functional activity (antiviral and antibacterial) in cervicovaginal secretions;

- Detection of SPL7013 in blood samples at Day 0 and Two-Week Clinic Visit (Target Day 14);

- Assessment of colposcopic findings.

4.3 Description of Study Population

The study population will include 18 to 24 year old US women who are HIV-negative, non-pregnant, sexually active, and healthy with a normal genital tract who are using adequate contraception.

4.4 Time to Complete Enrollment

The approximate time to complete study enrollment is expected to be nine months.

4.5 Study Groups

Three study arms including a total of 61 women are planned. Of these 61 women seven were randomized at a 1:1 ratio to VivaGel® or VivaGel® placebo, and a total of approximately 54 women will be randomized at a 1:1:1 ratio stratified by site to VivaGel® VivaGel® placebo, or HEC gel, with all three groups applying the product vaginally twice daily (approximately every 12 hours) for 14 days. Additional participants may be enrolled to ensure that a total of approximately 61 evaluable participants complete the three-week study.

4.6 Sequence and Duration of Trial Periods

Table 8: Sequence and Duration of Trial Periods for Individual Participants

Screening 1 Visit	Screening 2 Visit	Enrollment Visit	1-Week Clinic Visit	2-Week Clinic Visit	3-Week Clinic Visit
DAY -36 or less		DAY 0	DAY 6-8	DAY 13-15	DAY 20-24

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

Enrollment Period	Follow-Up Period	Total Duration
9 months	1 month	10 months

4.7 Expected Duration of Participation

The expected duration of participation for individual enrolled participants is 21 days. Participants who have Adverse Events (AEs) which are not resolved at the 3-Week/Early Termination Visit will be followed beyond the 3-Week/Early Termination Visit until a clinically acceptable resolution of the AE(s) (at the discretion of the Site PI or NIH Medical Monitors) has been documented, including resolution date, if possible. No further study data (for purposes of data analysis) will be collected for these participants after the 3-Week/Early Termination Visit, except in cases of pregnancy to capture data on pregnancy outcome. In the unlikely event that a participant is pregnant at the time of her 3-Week/Early Termination Visit, sites will make every attempt to follow the participant until documentation can be completed regarding her pregnancy outcome.

4.8 Sites

Two study sites are planned for this trial: University of South Florida and University of Puerto Rico.

5 STUDY POPULATION

5.1 Selection of the Study Population

A total of 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. For the purposes of MTN-004, "normal" is defined as:

- Anatomically normal pelvic exam at Screening 1, according to clinical judgment of the examiner
- Without evidence of genital infection at Screening 1, as defined by eligibility criteria
- Without evidence of deep disruption of the genital epithelium at Screening 1

Participants will be recruited from a variety of venues. There are two sites: University of South Florida and University of Puerto Rico. Each site will enroll approximately 30 participants. Additional participants may be enrolled if non-adherent participants need to be replaced or if enrollment "slots" need to be shifted from one site to another.

5.1.1 Composition

It is anticipated that the study population will be primarily composed of Hispanic-Latina female volunteers, although women of all racial/ethnic backgrounds will be included. As this study is primarily examining the safety of a vaginally applied product, only female volunteers will be enrolled.

5.1.2 Recruitment

Members of the research teams at both study sites will recruit women from various clinical sites at which they are providing direct patient care to potential study participants. Study staff will contact volunteers from previous research studies if those participants have previously signed an authorization permitting this type of contact. Site IRB-approved media advertisements, telephone scripts, and fliers will be used. These materials will be presented and discussed with the community advisory boards at both sites before submission to the local IRBs. Written informed consent will be obtained prior to the initiation of any study-related procedures.

5.1.3 Retention

Each site will establish participant retention procedures to target an average retention rate of 95% at 3 weeks. Study site staff members at each site are responsible for developing and implementing site-specific SOPs to target this goal.

5.1.4 Co-Enrollment Guidelines

Women with participation in any other investigational drug trial in the 30 days prior to enrollment will not be enrolled in this study. Study participants will be required to refrain from enrollment in other clinical trials involving investigational or prohibited drugs during their involvement in this study. Participants who report after enrollment their concurrent participation in such trials will be discussed by the PSRT and may be discontinued from use of study product. In this case they will be encouraged to remain in the study and will be followed with all safety evaluations deemed clinically appropriate by the Investigator and the NIH medical monitor.

5.2 Inclusion Criteria

- Age 18-24 years at screening and enrollment, inclusive, and verified per site SOP. For the Puerto Rico site, participants aged 18-20 years will be eligible if legally emancipated, with relevant local IRB waiver, or with parental consent.
- Willing and able to provide written informed consent for screening and enrollment
- General good health as determined by the site clinician at screening and enrollment
- HIV-uninfected (per HIV Antibody Testing Algorithm, Appendix III)
- Normal Pap result at screening or able to document normal result from Pap done within the 12 calendar months prior to screening
- Predictable menstrual cycle, per participant report, with $\geq$ 21 days between menses (does *not* apply to participants who report using a hormonal method of contraception at enrollment, e.g., Depo-Provera)
- Sexually active (penile-vaginal intercourse by participant report at a minimum average of one episode per week in the 30 days prior to screening) and intention to continue penile-vaginal intercourse at the same approximate frequency for the duration of study participation
- Willing to abstain from oral-vaginal and penile-anal intercourse for the duration of study participation.
- Visualization of vaginal and cervical anatomy that, in the clinical judgment of the colposcopist, lends itself to colposcopy
- Use of an effective method of contraception at enrollment, and intention to use effective method of contraception for the duration of study participation including one month after finishing study product application. 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)
- Willing to abstain from the use of other intravaginal products and/or devices including sex toys from 72 hours prior to enrollment through the 3-Week/Early Termination Visit
- Willing to use VivaGel® , VivaGel® placebo, or HEC gel as required by protocol
- Agree to not participate in other drug or device study during study participation
- Urine negative for pregnancy test at screening and enrollment

- Agree to have partner use study provided condoms for each act of intercourse during study participation
- Willing to participate as required by protocol, including assessments and follow-up schedule

5.3 Exclusion Criteria

- History of adverse reaction to latex or to any component of the study products
- Reported history of male sex partner having an allergic reaction to latex
- Using a diaphragm, vaginal ring, and/or spermicide for contraception at enrollment, and/or intention to use a diaphragm, vaginal ring, and/or spermicide for contraception during study participation
- Pregnant or breastfeeding at screening or enrollment, or has had any form of pregnancy within 90 days of enrollment
- Grade 3 or higher liver function, creatinine, coagulation, or hematology abnormality in accordance with DAIDS toxicity table values (normal values based on site specific laboratory criteria) at screening and confirmed by retest/and or redraw
- Gynecologic surgical procedure in 90 days prior to enrollment (e.g., biopsy, tubal ligation, dilation and curettage, etc.)
- 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
- Sexually transmitted infection (STI) or reproductive tract infection (RTI) according to the 2006 Center for Disease Control (CDC) guidelines via lab tests at screening, or examination at screening or enrollment, and requiring treatment, including symptomatic bacterial vaginosis (BV) (clinical criteria or Gram stain evidence plus symptomatic discharge, odor, or itching), symptomatic candidiasis, other vaginitis, trichomoniasis, Chlamydia, gonorrhea, syphilis, active HSV lesions (HSV-2 seropositive not excluded except with active lesions), chancroid, pelvic inflammatory disease (PID), genital sores or ulcers, cervicitis, genital warts of the labia minora, vagina, or cervix, or any other symptomatic genital warts. *Note: Signs of asymptomatic BV may include the presence of white to grey homogeneous discharge, positive whiff test (amine odor) with addition of potassium hydroxide (KOH), pH greater than 4.5, presence of clue cells, a decrease in lactobacilli morphotypes, and increase in non-lactobacilli morphotypes. Women with clinical criteria or evidence of BV and with symptoms (symptomatic discharge, odor, itching) will be excluded. Women without symptoms, but with clinical or laboratory evidence of BV, are still eligible.*
- In the six months prior to enrollment, diagnosed with or treated for any STI (except genital HSV recurrence) or pelvic inflammatory disease
- Use of oral and/or vaginal preparations of antibiotic or antifungal medications, at Screening or within 30 days prior to the enrollment visit
- Participation in any other drug or device study within 30 days prior to enrollment visit
- Injected non-therapeutic drugs in the 12 calendar months prior to enrollment

- At screening or enrollment, any social or medical condition that, in the investigator's opinion, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

6 STUDY PRODUCT

6.1 Regimen

The regimen for the study products will be as follows:

Table 10: Study Product Regimen

Arm	Description	N	Dose, Route, and Frequency
1	VivaGel® daily use	*18	One 3.5 g applicator per vagina twice daily for fourteen consecutive days
2	VivaGel® placebo daily use	*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.

Study staff will instruct participants on the proper methods of storing and applying the products. Beginning on Day 0, participants in all three arms of the study will utilize one single-dose, pre-filled applicator containing 3.5 g of study product (VivaGel®, VivaGel® placebo, or HEC gel) twice daily, for fourteen consecutive days. The participant will insert the first dose of study product at the Enrollment Visit. Target doses are in the morning and in the evening (approximately every 12 hours). The evening dose should be administered before longest period of rest (usually night).

If a participant misses a dose, she should make up the missed dose as soon as possible, unless the next application is due within 2 hours or less. 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 the next dosing time to insert the study gel.

Participants may continue their usual hygiene practices with the exception of any products applied directly to the vulva or vagina. In particular, participants will be educated and counseled about the risks of douching and advised to avoid this practice. Participants will be informed that tampons, sanitary pads, swimming, bathing, and sauna use are permitted. Participants will be advised to not use other participants' study gel, or to distribute their own study gel to other women. Study participants will be instructed to wash their hands before and after using the applicator to insert study gel.

6.2 Study Product Supply and Accountability

6.2.1 Study Product Supply

VivaGel® and VivaGel® placebo are manufactured and packaged in single-use applicators and analyzed/released under current good manufacturing practices (cGMP).

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

VivaGel®,VivaGel® Placebo, and 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 (VivaGel®, VivaGel® placebo or HEC gel). Both active and placebo gels are clear and are of similar viscosity. Each product (VivaGel®,, VivaGel® placebo, and HEC gel) will be packaged in cartons containing 10 pre-filled, single use applicators per carton.

The applicator measures approximately 11.4 cm long and 1.05 cm wide, and has a barrel-and-plunger design with screw-on cap to be removed before product usage. The applicator has a tapered, rounded tip for easy insertion into the vagina. A mechanism on the applicator prevents refilling and reuse. The seal inside the barrel is made from non-latex rubber. The same type of applicator is widely used for other vaginal products, including Monistat®.

6.2.2 Study Product Receipt

Site pharmacists will be required to maintain complete study records of all study product supplies received. These records will contain documentation of receipt as well as dispensing of all study supplies

6.2.3 Storage

In accordance with documented 12-month stability data, VivaGel® and VivaGel® placebo 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. 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).

Storage conditions for protocol-provided study products will include segregation, security, and temperature monitoring, as well as appropriate conditions of light, moisture, ventilation and sanitation. Study products should be stored in a limited access area that is locked when not in use. The study products should be accessible only to authorized personnel, such as the Pharmacist of Record and his/her pharmacist designee.

Study participants will be instructed to store their applicators at the recommended storage conditions, and away from direct sources of light and heat, in an area out of reach of children. Study products will be stored in accordance with the protocol.

6.2.4 Dispensing

Study products will be dispensed only to enrolled study participants, or to study staff on behalf of the participant, upon receipt of a written prescription from an authorized prescriber. An authorized prescriber includes the Investigator of Record (IoR) or a licensed clinician directly responsible to the IoR as noted on the FDA 1572.

Twenty individually wrapped pre-filled applicators dispensed in two cartons of ten applicators each will be provided at the Enrollment Visit. At the One-Week Clinic Visit, participants will receive an additional carton containing ten applicators.

Participants will be instructed to contact the study site to request additional supplies in the event that additional supplies between visits are needed. All circumstances resulting in this additional supply will be documented fully by the Site Principal Investigator or designee. The pharmacist will record the dispensing of any additional study product on the documents maintained by the Pharmacist of Record or designee.

6.2.5 Accountability

Study product accountability will be performed and documented. The study pharmacist must maintain complete records of study gel 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.

6.2.6 Retrieval of Unused Study Products

Study participants will be instructed to bring all unused study products back to the enrollment site at the Two-Week Clinic Visit. In the event that unused study products are not returned to the enrollment site, study staff members will make attempts to retrieve unused study products. All unused study products must be returned to the site and then forwarded to the MTN CORE after the study is completed or terminated unless otherwise instructed by the MTN CORE.

6.3 Assessment of Participant Adherence

Data on adherence to self-administration of a study gel will be collected at the Two-Week Clinic Visit via a web-based questionnaire (see acceptability and adherence questionnaire in Section 7.2, Behavioral Measures). This questionnaire will collect data on the number of times participants used the gel during the trial and reasons that may have prevented participants from adhering to protocol requirements.

Adherence counseling will be provided to all study participants upon enrollment into the study, and as needed thereafter to help ensure high rates of study product use. Counseling will include client-centered strategies to remember to use the product as directed both in the home and away from home. In addition, counseling will cover the importance of contacting study staff with questions about study product use and requests for additional supplies. For participants who anticipate or report adherence difficulties at the One-Week Clinic Visit, every effort will be made to identify strategies that will help increase their rates of correct product use throughout participation in the study. Section 10 outlines how data on participant adherence will be incorporated into analysis of the study results.

6.4 Concomitant Medications and Procedures

Throughout the course of the study, all concomitant medications, including those used to treat AE's, will be recorded in the participant's chart on forms designed for that purpose. Prescription medications, over-the-counter preparations, vitamins and nutritional supplements, and herbal preparations will all be recorded as concomitant medications. Medications/procedures not listed below under precautionary and prohibited medications and procedures are permitted.

6.4.1 Permitted Medications and Procedures

With the exception of those not permitted under inclusion/exclusion criteria, concomitant medications will be permitted. These include both prescription and non-prescription medications.

6.4.2 Prohibited Medications and Procedures

Several concomitant medications/devices will not be permitted, including spermicides, diaphragms, contraceptive vaginal rings, and oral and vaginal preparations of antibiotic or antifungal medication. These medications will be not allowed in order to protect the integrity of the lower genital tract and reduce the possibility of adverse events due to agents other than the study gel and applicator. Oil-based lubricants are also known to risk damage to the integrity of latex male condoms and are prohibited.

Potential participants who report current or recent use of these medications will not be enrolled in the study. Participants already enrolled who report concurrent use will be reviewed by the PSRT and may be discontinued from study product use. These participants will continue to be followed for safety assessment through study exit. All concomitant medications will be recorded on Concomitant Medication records.

6.4.3 Precautionary Medications and Procedures

There are no known precautions for concomitant use with the study products/interventions.

6.4.4 Required Medications and Procedures

Latex male condom use is required for all acts of penile vaginal intercourse by participants enrolled in this study. As noted above, latex male condoms will be provided to participants.

Male condoms
Both study site pharmacies will be provided with a single brand of lubricated male condoms by MTN CORE to distribute to participants in quantities expected to be sufficient according to study-specific procedures when study product is dispensed. These male condoms will not be impregnated or coated with any type of spermicide. Male condoms will be required for all sexual encounters with a male partner during the study period. In the event that a participant needs additional male condoms between visits, she may request these from study sites at any time. Participants will be provided with a list of approved brands that can be used in place of the study provided condoms to help encourage condom use by their male partners.

Panty Liners and Pads
Both study site pharmacies will be provided with single brands of panty liners and pads by the MTN CORE to distribute to participants in quantities expected by the participant to be sufficient when study product is dispensed. In the event that a participant needs additional panty liners or pads between visits, she may request these from study sites at any time. It is hoped that women enrolled in the study will not be menstruating during the two weeks of study drug administration. However, if women do menstruate they will be able to use sanitary towels or tampons of their own choice.

7 STUDY PROCEDURES

This section outlines study procedures according to visit schedule for participants. The study visits included here are the Screening 1 Visit, Screening 2 Visit, 1-Week Clinic Visit, 2-Week Clinic Visit, 3-Week Clinic Visit, and the Safety Visits.

7.1 Clinical Evaluations and Procedures

- Medical history, including medical-surgical history, allergy history, menstrual history, contraception use
- Medications history, including current prescription and non-prescription medications
- Counseling procedures, including condom use counseling, HIV pre- and post-test counseling, other laboratory test results counseling
- Questionnaires, including adherence, sexual behavior, history of vaginal product use, product acceptability
- Vital signs, including heart rate, blood pressure, and temperature

- Abdominal exam, including inspection and palpation
- Pelvic exam, including speculum exam and bimanual exam
- Colposcopic exam

7.2 Behavioral Measures

Each study site will have a computer terminal connected to the Web that the participants will use three times during the study to respond to Behavioral Measures. This computer terminal will be placed in such way to assure the confidentiality of the participants' responses (i.e. the screen will be out of site of staff members or other participants while answers are being entered). Behavioral Measures will be the Baseline Behavioral Questionnaire, taken at the Enrollment Visit, the Acceptability and Adherence Questionnaire, taken at the 2-Week Clinic visit, and the Study Burden Questionnaire taken at the 3-Week Clinic Visit (see Appendix I, Schedule of Study Visits and Evaluations).

7.2.1 Baseline Behavioral Questionnaire

A staff member will access the Web page for the questionnaire and enter a password to log in. Next, the staff member will enter the participant's ID and date and let the participant complete the rest of the questionnaire. Initially, the participant will be presented simple practice questions (e.g., "choose all that applies," "indicate how many times," "choose one of a fixed set of answers"). Once the practice has been successfully completed, the participant will read a statement encouraging her to respond to all questions as truthfully as possible. Next, she will proceed to the Baseline Behavioral Questionnaire. This questionnaire will assess different types of sexual behavior (vaginal/anal/oral), condom use per act (with/without), partner gender (male/female), partner type (significant other/casual partner), and partner HIV status (positive, negative, unknown) in the recent past. It will also include questions on past use of vaginal hygiene products, medications, desiccants, douches, tampons, and vaginal pregnancy prevention methods. Participants will also be asked to report on substance use, and likelihood of using a microbicide in the future.

7.2.2 Acceptability and Adherence Questionnaire

At theTwo-Week Clinic Visit, the participant will once again fill in a Web-based survey. This time it will be the Acceptability and Adherence Questionnaire that will explore the experiences the participant had during the prior 14 days using the gel vaginally, her likes and dislikes concerning the gel, the applicator, the application process, any changes she may have introduced or may wish to introduce in the volume used, any problems (e.g. leakage) she may have had, partner's reaction, sexual enjoyment, condom use during sexual intercourse using the gel, changes in her habitual sexual behavior, and likelihood of using a microbicide in the future. This last section will have items worded very similar to those of the same section applied at baseline, so that

comparisons can be made regarding the anticipated likelihood of future microbicide use before and after becoming familiarized with the product.

7.2.3 Study Burden Questionnaire

At the 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.

If any participant discontinues trial participation, she will be encouraged to respond to the Acceptability and Adherence Questionnaire and the Study Burden Questionnaire at the time of trial discontinuation.

7.3 Laboratory Evaluations

- Urinalysis
- Qualitative urine pregnancy test
- Urine SDA for *N. gonorrhoeae* and *C. trachomatis*
- HIV antibody screen
- Rapid plasma reagin (RPR)
- Complete blood count (hemoglobin, WBC with differential, platelets)
- Liver function panel (AST, ALT)
- Creatinine level
- Coagulation panel (PTT and INR)
- Plasma SPL7013 level
- Pap smear of cervix unless documented normal Pap available within the last year
- Vaginal swab pH
- Vaginal wet preparation slide for yeast, bacterial vaginosis, and trichomoniasis
- Gram-stained vaginal smear
- Quantitative vaginal cultures
- Cervical cytokine panel and innate immune factors (secretory leukocyte protease inhibitor (SLPI) and lactoferrin)
- As clinically indicated: urine culture and sensitivity, herpes culture, Genprobe Aptima, rapid plasma reagin (RPR), treponemal confirmation, HIV Western blot

7.4 Specimen Collection and Processing

Each study site will adhere to the standards of good clinical practice, the MTN Network Laboratory Manual, the study-specific procedures manual, and local standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens at the local laboratory. Specimen collection, testing, and storage at the site laboratories will be documented using the Laboratory Data Management System (LDMS).

The MTN Network Laboratory has confirmed that the study gels do not inhibit or otherwise interfere with the pregnancy test and dipstick urinalysis methodology selected for this study. The study gel has been determined to interfere with SDA testing for Chlamydia and gonorrhea. Chlamydia and gonorrhea testing is only done at Screening, unless indicated at follow-up visits; in these cases, the testing will be done via Genprobe Aptima, which has been determined to be unaffected by the study gel.

7.4.1 Local Laboratory Specimens

The following types of specimens will be collected at the study site and tested at the local laboratory: urine, vaginal, cervical, blood, and (as needed) other pelvic swabs.

Urine Samples
The Local Laboratory or Site Research Staff will perform urinalysis and pregnancy tests.

Vaginal Samples
The Local Laboratory or Site Research Staff will test vaginal swabs for bacterial vaginosis, candidiasis, and trichomoniasis.

Cervical Samples
The Study Site Laboratory will examine ectocervical and endocervical Pap smear specimens.

Other Pelvic Samples
The Local Laboratory will test pelvic swabs for HSV-2 via culture as needed.

Blood Samples
Study site staff will collect blood samples for the following testing at the local laboratory: complete blood count, liver function, creatinine level, and coagulation testing. Study site staff or Local Laboratory staff will also obtain blood for HIV-1 Antibody Test, and perform testing per SOP.

7.4.2 Starpharma Laboratory Specimens

Plasma samples will be assayed for SPL7013 levels using a validated capillary electrophoresis bioanalytical method at the Starpharma Pty Ltd bioanalytical laboratory in Melbourne, Australia.

7.4.3 Network Laboratory Specimens

Vaginal and cervical specimens listed below will be collected at the study site and tested at the MTN Network Laboratory. These include: vaginal gram stain, quantitative vaginal cultures, cervical cytokines, cervical innate factors, and urine SDA for *C. trachomatis* and *N. gonorrhoeae* testing. As indicated, Genprobe Aptima testing may be performed on urine specimens for the detection of Chlamydia and gonorrhea.

Vaginal Specimens

The assessment of vaginal flora will be based on the Nugent Scoring System for Gram-Stained Vaginal Smears as well as assessment of several groups of organisms. These organisms will include *Lactobacillus* species, *Gardnerella vaginalis*, *Escherichia coli*, *Staphylococcus aureus*, anaerobic gram-negative rods (Bacteroides, Prevotella, Porphyromonas), Enterococcus species, Group B Streptococcus, and Candida species.

Gram-stained vaginal smears will have leukocytes quantified according to Network Laboratory SOP.

Cervical Specimens

Cervical cytokines and innate factors will be handled and measured according to policies outlined in the SSPs for this study. Cytokines to be measured include: IL-1β, IL-6, GM-CSF, TNF-α, IFN-γ, MIP-1α, and IL-12p40. Cytokines will be measured according to Network Laboratory SOP via the Luminex® 100TM Instrument (Luminex Co., Austin, TX), using concentrations extracted from an 8-point standard curve via the Luminex® 100TM IS software. Cervical innate factors (SLPI and lactoferrin) will be measured by ELISA. Levels of cytokines and innate factors will be correlated to functional assays that will measure the anti-viral (HSV-2) and anti-bacterial (*Escherichia coli* and *Staphylococcus aureus*) activity as a surrogate marker of mucosal immunity. These activities will be measured according to policies outlined in the SSPs.

Urine Specimens

C. trachomatis and *N. gonorrhoeae* will be detected using an amplified DNA (SDA) assay and measured according to policies outlined in the SSP. As indicated, Genprobe Aptima testing may be performed on urine specimens for the detection of Chlamydia and gonorrhea.

7.4.3.1 Quality Control and Quality Assurance Procedures

Network Laboratory staff will conduct visits 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.

7.4.3.2 Specimen Storage and Possible Future Research Testing

Plasma and cervical specimens will be stored at the MTN Network Laboratory for possible future research testing. The informed consent process will include appropriate consent to obtain and store these samples.

7.5 Specimen Preparation, Handling, and Shipping

All specimens will be shipped in accordance with International Air Transport Association (IATA) specimen shipping regulations. All shipments will be documented using the LDMS. Details on specimen preparation, handling, shipping, and biohazard containment are included in the SSP.

7.6 Sequence of Procedures/Evaluations

Protocol Appendix I summarizes the expected sequence of procedures and evaluations for MTN-004. Upon indicating interest in the study, a brief telephone-screening interview with the prospective participant may be conducted to determine participant preliminary eligibility for this study.

7.6.1 Screening 1 Visit

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 is in the MTN Manual of Procedures.

Table 11: Screening 1 Visit

Screening 1 Visit (within -36 days)	
Component	**Procedure/Analysis**
Study Communications	• Explain study requirements • Informed consent document • Assign Participant ID (PTID) • Collect contact information • Collect demographic information • Administer behavioral eligibility assessment • Collect medical and menstrual history • Provide HIV pretest and post-test counseling • Provide male condom counseling • *Treat or refer for treatment and/or further counseling (including STI treatment and/or counseling) • Schedule Screening 2 Visit as appropriate • Provide reimbursement for study visit
Urine	• Pregnancy test • Urinalysis • *Culture and sensitivity • SDA for GC/CT
Blood	• Complete blood count • Liver function panel • Creatinine level • Coagulation panel • Rapid Plasma Reagin/*Confirmatory testing • HIV-1 Antibody Test/*Confirmatory testing
Targeted Physical Exam	• Vital signs (temperature, blood pressure, pulse) • Abdominal exam
Pelvic Exam	• Clinical gynecologic exam (speculum and bimanual) • Vaginal swabs for pH and wet prep • Gram-stained vaginal smears with leukocyte quantification • *Herpes culture • Pap smear (if no written report from prior year)

*If clinically indicated

7.6.2 Screening 2 Visit

The purpose of the Screening 2 Visit is to review with potential study participants their results from Screening 1, as well as to ensure that eligibility criteria are met before

scheduling an Enrollment Visit. 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.

Table 12: Screening 2 Visit

Screening 2 Visit (within -36 days)	
Component	**Procedure/Analysis**
Study Communications	• Update contact information • Update medical and menstrual history • Administer behavioral eligibility assessment • Male condom counseling • Provide other test results as available, with associated counseling • When clinically indicated, treat or refer for treatment and/or further counseling (including STI treatment and/or counseling) • Schedule follow-up appointment as appropriate. If participant is eligible for enrollment, conduct Enrollment Visit or schedule Enrollment Visit for a later date (within the 36-day window). • Provide reimbursement for study visit
Laboratory Measures	• Pregnancy test • *Repeat collection of screening laboratory specimens

*only in cases where sample was judged to be inadequate, or in cases of no result

7.6.3 Enrollment Visit

The Enrollment Visit will take place at or less than 36 days following the Screening 1 Visit, approximately 1 to 2 days after the complete cessation of menses. The Screening 2 Visit and the Enrollment Visit can also occur on the same day.

Table 13: Enrollment Visit

Enrollment Visit (Day 0)	
Component	**Procedure/Analysis**

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

Behavioral Measures	• Administer baseline behavioral and vaginal product use questionnaire
Urine	• *Pregnancy test (required only if Enrollment does not take place on the same day as the Screening 2 Visit) • *Urinalysis • *Culture and sensitivity • *SDA for GC/CT
Blood	• Complete blood count • Liver function panel • Creatinine level • Coagulation panel • SPL7013 level • *Rapid Plasma Reagin/*Confirmatory testing • Plasma archive
Targeted Physical Exam	• Vital signs (temperature, blood pressure, pulse) • Abdominal exam
Pelvic Exam	• Clinical gynecologic exam (speculum and bimanual) • Vaginal swabs for pH and wet prep • Gram-stained vaginal smears with leukocyte quantification • Cervical swabs for cytokines and innate factors • Quantitative vaginal cultures • Colposcopy of vulva, vagina, and cervix

Randomization	• Follow study-specific procedures for randomization
Study Supplies	• Dispense two cartons (20 applicators) of study gel, male condoms and panty liners, and/or pads, and resealable plastic bags • Participant to insert first dose in study clinic

*If clinically indicated

** In the event that Enrollment does not take place on the same day as the Screening 2 Visit, the following screening procedures must additionally be completed on the day of Enrollment to confirm participant eligibility prior to Enrollment:

- Review of all prior screening documentation, with update of medical and menstrual history and/or current medications if applicable
- Review contact information and update as necessary
- Re-confirmation (by participant self-report) that participant is not currently using other intravaginal products, and is not planning to use other intravaginal products during her study participation
- Re-confirmation that the participant has not used prohibited products as outlined in Section 6.4.2 in the last 30 days
- Re-confirmation (by participant self-report) that participant has not participated in any other drug or device study in the last 30 days, and is not planning to participate in any other drug or device study during her study participation
- Re-confirmation (by participant self-report) that participant is currently using an effective method of contraception (hormonal method (except vaginal ring), IUD inserted at least 30 days prior to Enrollment, sterilization, or sexual activity with a documented vasectomized partner) and plans to do so for the duration of her study participation
- Re-confirmation (by participant self-report) that participant is not currently using a diaphragm, vaginal ring, and/or spermicide for contraception, and does not plan to use these for the duration of her study participation
- Re-confirmation (by participant self-report) that the participant has not been diagnosed with or treated for any STI (except genital HSV recurrence) or pelvic inflammatory disease in the last 6 months
- Pregnancy test
- Male condom counseling
- Re-confirmation (by participant self-report) that the participant has not been pregnant, given birth, or had a pregnancy outcome, and has not breastfed in the last 90 days
- Re-confirmation (by participant self-report) that the participant has not had a gynecological surgical procedure in the last 90 days
- Re-confirmation (by participant self-report) that the participant has not injected non-therapeutic drugs in the last 12 calendar months
- Any other clinically indicated behavioral, clinical, or laboratory assessments

7.6.4 Phone Assessment

For the Phone Assessment, study staff will ask participants if they are having any difficulty with the study gel or applicator, and review applicator and/or study product-related instructions as needed. Any adverse events will be recorded and followed with safety visits if deemed necessary by the site investigator. This contact may be initiated by study staff or the participant on Study Day 2-4 (Target Day 2), as agreed upon prior to the call.

7.6.5 One-Week Clinic Visit

The One-Week Clinic Visit is outlined below. The One-Week Clinic visit will take place within the window of Days 6-8 post enrollment.

Table 14: One-Week Clinic Visit

One-Week Clinic Visit (Day 6-8)	
Component	**Procedure/Analysis**
Study Communications	• Update contact information • Update medical and menstrual history • Update Concomitant Medications Form (if applicable) • Record Adverse Events (if applicable) • Male condom counseling • Provide test results as available, with associated counseling • *Treat or refer for treatment and/or further counseling • Reinforce study product usage instructions • Schedule 2-Week Clinic Visit • Provide reimbursement for study visit
Behavioral Measures	• Administer adherence assessment
Urine	• Pregnancy test • *Urinalysis • *Culture and sensitivity • *Genprobe Aptima for GC/CT
Blood	• Complete blood count • Liver function panel • Creatinine level • Coagulation panel • *Rapid Plasma Reagin/*Confirmatory testing
Targeted Physical Exam	• Vital signs (temperature, blood pressure, pulse) • Abdominal exam

Pelvic Exam	• Clinical gynecologic exam (speculum and bimanual) • Vaginal swabs for pH and wet prep • Gram-stained vaginal smears with leukocyte quantification • Cervical swabs for cytokines and innate factors • Quantitative vaginal cultures • *Colposcopy of vulva, vagina, and cervix • *Herpes culture
Study Supplies	• Count returned unused applicators • Dispense one carton (ten applicators) of study gel • Dispense more male condoms and panty liners and/or pads if needed

*If clinically indicated

7.6.6 Two-Week Clinic Visit

The Two-Week Clinic Visit is outlined below. The Two-Week Clinic Visit will take place within the window of days 13-15 post enrollment

Table 15: Two-Week Clinic Visit

Two-Week Clinic Visit (Day 13-15)	
Component	**Procedure/Analysis**
Study Communications	• Update contact information • Update medical and menstrual history • Update Concomitant Medications Form (if applicable) • Record and/or update Adverse Events (if applicable) • Male condom counseling • Provide test results as available, with associated counseling • *Treat or refer for treatment and/or further counseling • Schedule 3-week Clinic Visit • Provide reimbursement for study visit
Behavioral Measures	• Administer acceptability assessment • Administer adherence assessment
Urine	• Pregnancy test • *Urinalysis • *Culture and sensitivity • *Genprobe Aptima for GC/CT
Blood	• Complete blood count • Liver function panel • Creatinine level • Coagulation panel • SPL7013 level

	• *Rapid Plasma Reagin/Confirmatory testing • Plasma archive
Targeted Physical Exam	• Vital signs (temperature, blood pressure, pulse) • Abdominal exam
Pelvic Exam	• Clinical gynecologic exam (speculum and bimanual) • Vaginal swabs for pH and wet prep • Gram-stained vaginal smears with leukocyte quantification • Cervical swabs for cytokines and innate factors • Quantitative vaginal cultures • Colposcopy of vulva, vagina, and cervix • *Herpes culture
Study supplies	• Count returned unused applicators

*If clinically indicated

7.6.7 Three-Week Clinic/Early Termination Visit

The Three-Week Clinic Visit will be the final scheduled study visit at the study site and will take place within a five-day window (days 20-24 from enrollment). Any additional study visits will occur only on an as-needed basis as determined by study-specific criteria. Study staff will attempt to record resolution dates for any outstanding AEs and/or concomitant medications at this visit, if possible.

Table 16: Three-Week Clinic/Early Termination Visit

Three-Week Clinic/Early Termination Visit (Day 20-24)	
Component	**Procedure/Analysis**
Study Communications	• Update contact information • Update medical and menstrual history • Update Concomitant Medications Form (if applicable) • Record and/or update Adverse Events (if applicable) • Provide test results as available, with associated counseling • *Treat or refer for treatment and/or further counseling • Provide reimbursement for study visit • *Schedule additional visits to resolve ongoing adverse events
Behavioral Measures	• Administer Study Burden Assessment
Urine	• Pregnancy test • *Urinalysis • *Culture and sensitivity • *Genprobe Aptima for GC/CT

Blood	• *Complete blood count • *Liver function panel • *Creatinine level • *Coagulation panel • *Rapid Plasma Reagin/*Confirmatory testing
Targeted Physical Exam	• Vital signs (temperature, blood pressure, pulse) • Abdominal exam
Pelvic Exam	• Clinical gynecologic exam (speculum and bimanual) • Vaginal swabs for pH and wet prep • Gram-stained vaginal smears for leukocyte quantification • Cervical swabs for cytokines and innate factors • Quantitative vaginal cultures • *Colposcopy of vulva, vagina, and cervix • *Herpes culture
Study Supplies	• *Count returned unused applicators (if not already returned at previous visit)

*If clinically indicated

Note for all follow-up visits: If a participant has her menses at the time of her study visit, all visit procedures except the pelvic exam, colposcopy, and associated specimen collections should be performed at that time. The pelvic exam, colposcopy, and associated specimen collections required for the given visit may be rescheduled for a date as soon as practical after the end of the participant's menses.

7.6.8 Interim Contacts and Safety Visits

At any time during the study, a participant may be seen for an unscheduled visit if requested by the participant or deemed necessary by an investigator. Study staff will utilize case report forms designed especially for interim contacts and visits.

Participants will have a urine pregnancy test at each interim visit. If deemed necessary by the examining clinician, the participant will be scheduled for colposcopy. Participants reporting vaginal bleeding or spotting other than expected menstrual bleeding will be evaluated via colposcopy. Unexpected intermenstrual bleeding, unexpected menstrual bleeding (menorrhagia or metrorrhagia), bleeding associated with new or changed findings, and bleeding from no obvious source will be considered adverse events.

Some interim visits may occur for administrative reasons. For example, the participant may have questions for study staff or require additional study supplies. Other interim contacts and visits may occur in response to AEs experienced by study participants. When interim contacts or visits are completed in response to participant reports of AEs,

study staff will assess the reported event clinically and provide or refer the participant to appropriate medical care; all AEs associated with genital symptoms will be evaluated according to the pelvic exam procedures described for the regularly scheduled follow up visits, and diagnosis and follow up of any observed abnormalities will proceed according to Appendix II.

7.7 Colposcopy

Experienced staff at both sites will conduct colposcopic examinations of the study participants. In addition, an MTN Safety Physician will provide specialized training in colposcopy for the evaluation of vaginal products.

7.8 Colposcopic Images

Records of digital colposcopic images are 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 there are findings on follow-up visits, the clinician should retain digital video images in order to complement documentation of baseline findings, abnormal findings or injury. The informed consent document will include consent to obtain these digital images.

7.9 Final Contact

The Two-Week Clinic Visit for all participants will include laboratory testing for complete blood count, liver panel, creatinine level, and coagulation panel. If the results are not available at the Three-Week Clinic visit for participants, a final contact (in person or by telephone [except for HIV test results]) may be required to provide the final study test results, post-test counseling, and treatment from these visits. In addition, for participants who become pregnant prior to the study end date, an additional contact may be required to ascertain the participant's pregnancy outcome. Study sites may complete the final contact visit(s) at the study site or at community based locations, depending on site capacities and site and participant preferences. All final contacts must be documented in participant study records.

8 ASSESSMENT OF SAFETY

8.1 Safety Monitoring

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, both Site PIs, FHI Protocol Coordinator, DAIDS and NICHD Medical Officers, and DAIDS Clinical Operations Study Coordinator, will serve as the Protocol Safety Review Team (PSRT). Close cooperation between the PSRT and other study team members will be necessary to monitor participant safety and respond to occurrences of toxicity in a timely manner.

8.2 Clinical Data Safety Review

A multi-tiered safety review process will be followed for the duration of this study. 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.

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. The SDMC Clinical Affairs staff review AEs, events requiring expedited reporting to DAIDS, and events that meet safety pause criteria.

During the active product use phase of the trial, the PSRT will review clinical and laboratory safety reports (blinded to treatment assignment) and conduct calls every two weeks, or as needed, to review the data as appropriate. The content, format and frequency of these reports will be agreed upon by the PSRT and the SDMC in advance of study implementation. In addition to these routine safety data reviews, the PSRT will convene on an ad hoc basis to make decisions regarding the handling of any significant safety concerns. If necessary, experts external to the MTN representing expertise in the fields of microbicides, biostatistics, and medical ethics may be invited to join the PSRT safety review.

After the product use and the final safety visits are completed, less frequent reporting and safety reviews may be conducted at the discretion of the MTN-004 PSRT.

Decisions regarding permanent discontinuation of study gel in individual participants will be made by the PSRT based on careful review of all relevant data and may involve sponsor consultation with the US Food and Drug Administration (FDA).

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 or toxicity endpoint, defined as:

1. Having at least one grade 3 or higher adverse experience during follow up judged by the investigator to be definitely, probably, or possibly related to the study gel or applicator, or:

2. 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.

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. If the PSRT pauses overall study product use and then lifts the pause following a safety review, participants in active follow-up at the time of the pause will discontinue further product use. Such participants will continue to be followed up through study exit for safety follow-up. Adverse events assessed as probably not related, not related, or pending will not be considered when determining whether or not a safety pause shall occur. A decision to stop the trial may be recommended by a quorum of the PSRT at this time or at any such time that the team agrees that an unacceptable type and/or frequency of AEs has been observed. The quorum will consist of the DAIDS Medical Officer, a NICHD Medical Officer, and one of the MTN safety physicians.

In the unlikely event that the protocol team has serious safety concerns that lead to a decision to permanently discontinue study gel for all participants and stop accrual into the study, the protocol team will request an unblinded review of the data by the NIAID Data and Safety Monitoring Board (DSMB) before recommending that the study be stopped. Members of the NIAID DSMB will be independent investigators with no financial interest in the outcomes of this study. If at any time, a decision is made to discontinue study gel in all participants, Starpharma Pty Ltd after consultation with the DAIDS and the protocol team will inform the US FDA. The Site PI's will notify the responsible IRBs expeditiously.

8.3 Adverse Events Definitions and Reporting Requirements

8.3.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product. This definition will be applied to both treatment arms. The term "investigational product" for this study refers to VivaGel®, VivaGel® placebo, and HEC gel as well as the study gel delivery applicators.

Study participants will be provided a 24-hour telephone number and instructed to contact the study clinician to report any AEs they may experience, except for life-threatening events, for which they will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek medical care where the study clinician is based, and to request that the clinician be paged or otherwise contacted upon their arrival. With appropriate permission of the participant, whenever possible records from all non-study medical providers related to

AEs will be obtained and required data elements will be recorded on study case report forms. All participants reporting an AE will be followed clinically, until the AE resolves (returns to baseline) or stabilizes.

Participants who are found to have clinical findings or microscopic evidence consistent with bacterial vaginosis or vaginal candidiasis or both, but who do not report associated symptoms, will not have those diagnoses (asymptomatic bacterial vaginosis, asymptomatic vaginal candidiasis) reported as adverse events.

Participants who develop any pelvic exam abnormality, excluding findings observed by colposcopy only, will be followed until the AE resolves or stabilizes. Participants will be encouraged to report to the study clinician any problems experienced by their male partners that might be potentially related to study product. The study clinician will suggest follow up care or a referral for such care if deemed appropriate. Study site staff will document on study CRFs all AEs reported by or observed in enrolled study participants or their partners from the time of their first dose of study gel through the Three-Week Clinic Visit or early termination, regardless of severity and presumed relationship to study gel or applicators. 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 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 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.

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 and Addendum 1 to the table. These tables are available at: http://rcc.tech-res.com/eae.htm.

8.3.3 Serious Adverse Event

Serious Adverse Event (SAE) will be defined per 21 CFR 312.32 guidelines. A serious adverse event is any adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity, or
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Study sites will report any SAEs to Starpharma within 24 hours of their knowledge of the SAE. SAEs will be reported to the FDA by Starpharma Pty Ltd. SAE reports sent to the FDA will be simultaneously sent by Starpharma Pty Ltd to the DAIDS and NICHD Medical Officers.

8.3.4 Adverse Event Relationship to Study Product

Relatedness is an assessment made by a study clinician of whether or not the event is related to the study agent. Degrees of relatedness will be categorized as one of the following.

Definitely related: adverse event and administration of study agent are related in time, and a direct association can be demonstrated with the study agent.

Probably related: adverse event and administration of study agent are reasonably related in time, and the adverse event is more likely explained by the study agent than by other causes.

Possibly related: adverse event and administration of study agent are reasonably related in time, and the adverse event can be explained equally well by causes other than the study agent.

Probably not related: a potential relationship between administration of study agent and adverse event could exist, but is unlikely, and the adverse event is most likely explained by causes other than the study agent.

Not related: the adverse event is clearly explained by another cause unrelated to administration of the study agent. Reportable events must have documentation to support the determination of “not related”.

8.4 Expedited Adverse Event Reporting Requirements

This section outlines Expedited Adverse Event (EAE) reporting requirements for MTN-004. Study sites will receive training on EAE reporting prior to the onset of study enrollment.

8.4.1 Expedited Adverse Event Reporting to DAIDS and Starpharma Pty Ltd

The EAE reporting requirements and definitions for this study and the methods for expedited reporting of AEs to the DAIDS RCC Safety Office are defined in "The Manual for Expedited Reporting of Adverse Events to DAIDS" (DAIDS EAE Manual) **dated May 6, 2004**. The DAIDS EAE Manual is available on the RCC website: http://rcc.tech-res-intl.com/. The DAIDS EAE Manual is also available in the MTN-004 Study Operations Manual.

AEs reported on an expedited basis must be documented on the DAIDS Expedited Adverse Event Reporting Form (EAE Reporting Form) available on the RCC website: http://rcc.tech-res-intl.com.

EAEs must be faxed to DAIDS and Starpharma Pty Ltd as outlined in the SSP. Medical Officers from both DAIDS and NICHD are also to receive timely and synchronous communications of any adverse event reported to the RCC from the sites. They will engage in any necessary dialogue or consultation with each other in order to render a decision. If agreement cannot be reached, the ultimate decision will be rendered by the Medical Officer from the MTN's primary sponsoring institute (NIAID/DAIDS) (or the individual designated to cover for them in their absence).

8.4.2 EAE Reporting Requirements for this Study

EAE Reporting Level
This study uses the **Intensive Level** of expedited AE reporting as defined in the DAIDS EAE Manual.

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, VivaGel®, VivaGel® placebo, and HEC 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, VivaGel®,, VivaGel® placebo, and HEC gel.

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Grading Severity of Events
The DAIDS AE Grading Table, Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies) will be the primary tool for grading adverse events for this protocol, with the exception of asymptomatic bacterial vaginosis and asymptomatic candidiasis 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, Dec 2004. In cases where an AE is covered in both tables, the Female Genital 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.

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December, 2004 is available on the RCC website at http://rcc.tech-res.com/eae.htm. The DAIDS AE Grading Table is also available in the MTN-004 Study Specific Procedures (SSP) Manual.

EAE Reporting Periods

AEs must be reported on an expedited basis at the **Intensive Level** during the Protocol-defined EAE Reporting Period, which is:

> The entire study duration for an individual participant (from study enrollment until study completion or discontinuation of the participant from study participation for any reason).

After the end of the Protocol-defined EAE Reporting Period stated above, sites must report serious, unexpected, clinical suspected adverse drug reactions if the study site staff becomes aware of the event on a passive basis, i.e., from publicly available information.

8.5 Local Regulatory Requirements

Site investigators will submit AE information in accordance with local regulatory agencies' or other local authorities' requirements. This reporting will include site IRB-mandated reporting of AEs, SAEs, and other relevant safety information.

9 CLINICAL MANAGEMENT

This section summarizes guidelines for clinical management for individual participants in the case of unplanned health events, including product toxicity, other disease events, and pregnancy.

9.1 Toxicity Management

Based on results from the first Phase 1 study of VivaGel®, toxicity in study participants is not expected in this trial. In response to AEs reported by study participants and/or observed upon exam by study staff, the study site principal investigator or designee will recommend either continuation or withholding study gel use consistent with the criteria in Appendix II.

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. Unless the participant withdraws her consent, she will remain in the study to complete the safety

evaluations (unless clinically contraindicated) according to Appendix I, and/or as specified in Appendix II.

9.2 Other Disease Events

Management of confirmed sexually transmitted infections/sexually transmitted diseases, commonly referred to as STIs or STDs, and other forms of vaginitis and cervicitis will be in accordance with CDC Guidelines.

9.3 Pregnancy

All participants will be instructed to report pregnancies to site investigator or to the study staff who will in turn report to the site investigator; the site investigator will inform PSRT. The site investigator will counsel the participant and discuss possible risks if the pregnancy is continued according to site-specific SOPs.

Participants who are found to be pregnant during the study period will continue to be followed for safety reasons until the end of their study participation (study exit visit). Participants who are pregnant at the time of the study exit visit will continue to be followed until the pregnancy outcome is ascertained or it is determined that, after multiple attempts, pregnancy outcome cannot be ascertained. The site PIs will attempt to ascertain the pregnancy outcome, and pregnancy outcomes will be reported to SCHARP on the Pregnancy Outcome form. Any pregnancies will be reported to the PSRT. Pregnancies with abnormal outcomes will be reported according to all applicable EAE guidelines listed in Section 8.4.

Sites will provide a single brand of lubricated (non-N-9 or -spermicide containing), male, latex condoms for the purpose of this study, and facilitate participants' access to all contraceptive methods. In the event of pregnancy, sites will counsel participants and will facilitate access to services, according to the site-specific SOPs. However, sites will not be responsible for paying for pregnancy-related care. Participants who become pregnant during the course of the study will discontinue study gel use while they are pregnant, but will not routinely be withdrawn from the study. Rather, if the participant does not withdraw her consent, every effort will be made to complete the safety evaluations according to Appendix I.

For participants who become pregnant, all protocol-specified procedures will continue except:

- Administration of study gel (The site staff will make every effort to recover any unused study product once pregnancy is diagnosed.)

9.4 Criteria for Discontinuation of Study Product, and Discontinuation of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. The principal investigators may withdraw participants to protect their safety, and/or if participants are unable or unwilling to comply with study procedures. The investigators may withdraw a participant from the study if any condition in the opinion of the investigator would impose a health risk to the participant or interfere with the evaluation of the study product. Participants withdrawn for safety reasons by the investigator will continue to be followed with the protocol-determined schedule of follow-up visits, unless consent is withdrawn.

Discontinuation of study participation will occur only if certain conditions below are met. These conditions are related to safety as well as impact on reaching planned study endpoints.

9.4.1 Criteria for Permanent Study Product Discontinuation for an Individual Participant

The criteria for permanent discontinuation of further study product use for an individual participant are:

- Signs or symptoms of STI(s)/RTI(s) requiring treatment according to the judgment of the investigator
- Study product-related toxicity (see Section 9.1)
- Pregnancy or breastfeeding
- Completion of regimen as defined in the protocol
- Request by participant to terminate treatment
- Clinical reasons determined by the physician

The participant will continue to be followed with the participant's permission if study product is discontinued. No subsequent modifications to the visit schedule and duration of continued follow-up will be made, except no study product will be administered.

9.4.2 Criteria for Premature Study Discontinuation for an Individual Participant

Safety or other considerations may make it appropriate to have a participant prematurely discontinue the study. The criteria for premature discontinuation from the study for an individual participant are:

- Lost to follow-up as evidenced by failure by the participant to attend two consecutive clinic visits
- Participant repeatedly non-compliant with study treatment as prescribed (e.g. non-compliant with instructions for dosage, route, regimen, or male condom use)
- Request by participant to withdraw

- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant

10 STATISTICAL CONSIDERATIONS

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 VivaGel®, VivaGel® placebo, or HEC gel, and follow-up among HIV-uninfected sexually active women.

10.2 Study Endpoints

10.2.1 Primary Endpoint

Consistent with the primary study objective to assess the safety of study drug when administered twice daily for 14 consecutive days on vulvar and cervicovaginal mucosa, the following primary endpoints will be assessed:

- Abnormal genital symptoms judged by the Investigator to be possibly, probably, or definitely related to product use;

- Abnormal pelvic exam findings, (excluding findings observed by colposcopy only), judged by the Investigator to be possibly, probably, or definitely related to product use;

- Grade 3 or higher laboratory values (as defined by the DAIDS Toxicity Tables) for hematology, liver function, creatinine level and coagulation judged by the Investigator to be possibly, probably, or definitely related to product use;

- Adverse experiences judged by the Investigator to be possibly, probably, or definitely related to product use.

10.2.2 Secondary Endpoints

Consistent with the secondary study objectives to assess adherence to, and acceptability of, a short-term regimen of VivaGel®, and to assess the effect of this regimen on vaginal microflora, the following endpoints will be assessed:

- The proportion of participants who report via adherence questionnaire that they were adherent to the product use regimen, with adherence defined as the application of at least 80% of the expected number of doses of study product over the two weeks of product use;

- The proportion of participants who at their Two-Week Clinic Visit report via the acceptability questionnaire that they would be very likely to use the candidate microbicide during sexual intercourse in the future;

- Reported positive and negative aspects of using study product;

- Changes in vaginal flora.

10.2.3 Exploratory Endpoints

- Changes in cervical cytokine, innate immune factor (secretory leukocyte protease inhibitor (SLPI) and lactoferrin) expression, and functional activity (antiviral and antibacterial) in cervicovaginal secretions

- Detection of SPL7013 in blood samples at Day 0 and Two-Week Clinic Visit (Target Day 14)

- To assess the effects of VivaGel® on colposcopic findings

Changes within each arm and between arms will be reported.

10.3 Study Hypothesis

MTN-004 hypothesizes that VivaGel® will be safe, well-tolerated and acceptable for twice daily vaginal application among healthy sexually active young women.

10.4 Sample Size

The primary aim of the study is to assess the local and systemic safety of vaginal application of VivaGel® versus placebo gel among HIV uninfected women. The proposed total sample size is approximately n=61 evaluable participants with approximately 36 included in comparisons between VivaGel® 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). This sample size is based upon the size of similar Phase 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. 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.

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 minimum sample size of 18 women using VivaGel® for various “true” event rates:

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

Event Rate	P (0 events | n=18)	P (≥1 event | n=18)	P (≥2 events | n=18)
1%	0.83	0.17	0.01
5%	0.40	0.60	0.23
10%	0.15	0.85	0.55
15%	0.05	0.95	0.78
25%	<0.01	>0.99	0.96
35%	<0.01	>0.99	>0.99
45%	<0.01	>0.99	>0.99

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) 18 women exposed to VivaGel® is 0.60.

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

10.5 Randomization Procedures

Women will be randomized at a 1:1:1 ratio to one of the three arms. Randomization will be stratified by site to ensure balanced assignment to each product (VivaGel®, VivaGel® placebo, or HEC gel) within each site. The randomization scheme will be generated and maintained by the SDMC. The SDMC will provide each study site with one set of randomization envelopes to be stored and used in the study clinic. Clinic staff will assign these envelopes in sequential order, by envelope number, to eligible participants. Additional envelopes will be provided to each site for the purpose of enrolling >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.

Assignment of the randomization envelope is considered the effective act of participant enrollment/randomization. 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 (VivaGel®, VivaGel® placebo, or

HEC gel) to which the participant was assigned. Multiple codes will be utilized to conceal and protect the randomization assignments in this study. Clinic staff will store assigned randomization envelopes and copies of the study prescription in participants' study charts.

10.6 Justification for Placebo Gels

Inclusion of placebo gels 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 gels (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) that have been shown to have good safety profiles and low likelihoods of inducing mucosal damage.

10.7 Blinding

Study staff and participants will be blinded to the random assignments of all study participants. All study gels will be supplied in identical, single-use applicators packaged in individual wrappers. Blinding will be maintained until all data are entered into the study database, all study endpoint data and other data included in the final analysis have been cleaned and verified, and the data are ready for final analysis. This will be explained to participants as part of the study.

10.8 Maintenance of Trial Randomization Codes

Trial randomization codes will be maintained by unblinded staff at the SDMC. There are no circumstances under which it is expected that unblinding to blinded study staff or participants will be necessary for the provision of medical treatment or to otherwise protect the safety of study participants.

As described in Section 9.4, in the event that an Investigator is concerned that a participant might be put at an undue risk by continuing product use, the Investigator may discontinue use by this participant; however, knowledge of the specific product to which the participant was assigned should not be necessary to guide further follow up and/or treatment. If an Investigator feels that specific product knowledge is necessary to protect participant safety, the Investigator will notify the PSRT to consider and rule upon the request.

10.9 Participant Accrual and Follow-Up

Based on previous studies of vaginal products with similar eligibility requirements, the accrual of eligible participants with normal reproductive tracts is expected to require the screening of approximately 160 volunteers. The target for retention will be 95% of enrolled participants over the 21-day follow-up period. Therefore, it is anticipated that

approximately 64 women will be enrolled in the study. Accrual is anticipated to take approximately 9 months. Monthly accrual targets will be available in the SSP.

10.10 Data and Safety Monitoring and Analysis

10.10.1 Study Monitoring Committee (SMC)

In addition to the safety monitoring done by the PSRT (described in section 8.1), the MTN SDMC will prepare study progress reports and reports of AEs experienced by study participants (blinded to treatment assignment) for review by the MTN Study Monitoring Committee (SMC). The SMC will conduct interim reviews of study progress (blinded to treatment assignment), including rates of participant accrual, retention, rates of adherence to study gel use, and product safety. These reviews will take place approximately every 90 days, or as needed. At the time of these reviews, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued.

10.10.2 Data Analysis

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.

When the use of descriptive statistics to assess group characteristics or differences is required, the following methods will be used: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles and range (minimum, maximum). Within-treatment group assessment of the change from the baseline measurement to a follow-up measurement will be analyzed using McNemar's test (for categorical response variables) or the paired t-test or Wilcoxon signed-ranks test (for continuous variables). When use of formal testing to assess differences between users of the control gel and 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.

To assess the adequacy of the randomization, control gel and VivaGel® participants will be compared for baseline characteristics including demographics, pelvic examination, and laboratory measurements using descriptive statistics. Due to the small sample size, formal comparisons will not be done.

Primary Analyses

The primary aim of the study is to assess the toxicity of VivaGel® on vulvar and cervicovaginal mucosa. All visits in which a woman has been exposed to the study product will be included in the primary analysis of safety. Secondary intent to treat analyses may also be performed. To assess safety, the number and the percentages of participants experiencing at least one AE, and the number and percentage experiencing each specific AE will be tabulated by study arm. Each participant will contribute once in each category (i.e. only for highest severity AE for each participant) for the calculation of event rates. The number and percentage of participants experiencing each type of AE (including AEs leading to study discontinuation) will be tabulated by severity and relationship to treatment for each treatment group. AEs that lead to study product discontinuation will be listed in a separate data listing. Overall summaries by treatment group include the number and percentage of participants experiencing: (1) any experience; (2) any moderate, severe, or life-threatening experience. The number and percentage of participants with an AE judged possibly, probably or definitely related to study treatment will be summarized for each treatment group. Grade 3 or higher toxicity for hematology, coagulation function, liver function, or creatinine level is also a primary endpoint. Baseline and Two-Week visit laboratory measures will be summarized and the change in function, defined by the difference between Two-Week and baseline measurements, will be evaluated by treatment group.

Secondary Analyses

One secondary study objective is to assess adherence to a short-term regimen of VivaGel®. To assess adherence, the proportion of participants who applied 80% of the expected number of doses of study product over the two weeks of product use will be calculated by treatment arm. All enrolled women will be included in this analysis.

An additional secondary study objective is to evaluate aspects of product acceptability. To evaluate acceptability, the proportion of participants who at their Two-Week Follow-up Visits report via acceptability questionnaire that they would be extremely likely to use the candidate microbicide during sexual intercourse in the future will be calculated by treatment arm. In addition, positive and negative aspects of using the study drug will be listed in order of frequency. All enrolled women with a Two-Week follow-up visit will be included in these analyses.

The final secondary study objective is to assess the effect of a twice-daily short-term regimen of VivaGel® on the vaginal microflora of sexually active HIV-uninfected women. To assess the effect of SPL7013 on vaginal flora, clinically significant changes in vaginal flora will be evaluated by the Nugent score with shift tables from baseline (Enrollment) to follow-up visits. The Nugent score is graded 1 to 10 as follows:

1. Normal, 0 to 3
2. Intermediate, 4 to 6
3. BV, 7-10

Any shift from normal at baseline to intermediate or BV at a follow-up visit, or intermediate at baseline to BV at a follow-up visit, will be considered a clinically meaningful change in vaginal flora. Changes within each treatment arm will be reported. In addition, differences between the treatment groups in the distribution of Nugent scores at follow-up visits will be formally tested.

In addition to looking at shifts in the Nugent score, within treatment arm descriptions, and between treatment arm comparisons, will be done to assess clinically meaningful changes in quantitative measures of vaginal flora (defined by more than $\geq$1 log change in dominant members of the microflora, including *Lactobacillus* (H_2O_2 positive and negative strains), anaerobic gram negative rods, *Gardnerella vaginalis*, *Escherichia coli*, *Staphylococcus aureus*, *Candida* species, Group B *Streptococcus*, and *Enterococcus* species) and to assess differences in the quantitative levels of these flora between treatment arms during follow-up.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Study case report forms will be developed by the SDMC. Quality control reports and queries routinely will be generated and distributed to the study sites for verification and resolution.

11.2 Source Documents and Access to Source Data/Documents

The investigator will maintain, and store securely, complete, accurate and current study records throughout the study. In accordance with U.S. regulations, the investigator will retain all study records indefinitely. Study records will not be destroyed prior to receiving approval for record destruction from DAIDS and Starpharma. Applicable records include source documents, site registration documents and reports, correspondence, informed consent forms, and notations of all contacts with the participant.

11.3 Quality Control and Quality Assurance

Dr. Sharon Hillier, who completed a training program in clinical and public health microbiology certified by the American Board of Medical Board of Microbiology, directs the Site Support and Diagnostic Training Core in the MTN Network Laboratory at Magee-Womens Research Institute. This laboratory is Clinical Laboratory Improvement

Amendments (CLIA)-inspected and maintains its own CLIA license. Thus, all testing done in this research laboratory is performed with the same level of quality control as required in a licensed clinical laboratory.

Dr. John Mellors directs the Virology Core in the MTN Network Laboratory at the University of Pittsburgh School Of Medicine. This laboratory is CLIA-certified and has consistently met proficiency standards for HIV-1 RNA testing established by the DAIDS-sponsored Virology Quality Assurance program. All HIV-1 endpoint confirmations will be done in this laboratory.

See Section 12 for site monitoring plan.

11.4 Study Coordination

Starpharma Pty Ltd holds the IND application for this study (#62,482). Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement executed by DAIDS, NICHD, and Starpharma Pty Ltd. Study site staff will be provided with the DAIDS SOPs for Source Documentation and Essential Documents, the Manual for Expedited Reporting of Adverse Events to DAIDS, and the DAIDS AE Grading Table. Training and written instructions outlining management and reporting, study gel dispensing, product accountability, and other study operations will be provided by Family Health International, the Statistical Center for HIV/AIDS Research & Prevention (SCHARP), and the MTN Network Laboratory. The final study report will be consistent with both DAIDS and ICH E3 guidelines.

12 CLINICAL SITE MONITORING

Study monitoring will be carried out by Westat (Rockville, MD). On-site study monitoring will be performed in accordance with DAIDS policies. Site monitoring visits will be conducted to assess compliance with Health and Human Services (HHS) Regulations 45 CFR Part 46 and 21 CFR Parts 50, 56, and 312. Study monitors will visit the site to:

- Verify compliance with human subjects and other research regulations and guidelines, including confidentiality procedures, informed consent process, and regulatory documentation

- Assess adherence to the study protocol, study-specific procedures manual, and local counseling practices, including compliance related to study product management and pharmacy-related procedures

- Confirm the quality and accuracy of information collected at the study site and entered into the study database, including the validation of data reported on case report and DataFax forms

- Assess the resolution of any past or ongoing issues identified at previous monitoring visits

A minimum of three monitoring visits per site will occur for this study, including a visit shortly after study initiation, one at the perceived midpoint for enrollment, and a third for study closeout.

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the MTN CORE, MTN NL, Family Health International, Statistical Center for HIV/AIDS Research & Prevention, NIAID, NICHD, Starpharma Pty Ltd, FDA, and US regulatory authorities. A site visit log will be maintained at the study site to document all visits.

13 HUMAN SUBJECTS PROTECTIONS

The investigators will make efforts to minimize risks of this new product to human participants. Volunteers will take part in a thorough informed consent process throughout their participation in the study. Before beginning the study, the investigators will have obtained IRB approval and the protocol will have been submitted to the FDA. The investigators will permit audits by the NIH, Starpharma Pty Ltd or the FDA or any of their appointed agents.

13.1 Institutional Review Boards

Each participating institution is responsible for assuring that this protocol and the associated informed consent documents and study-related documents are reviewed by an Ethics Committee (EC) or Institutional Review Board (IRB) prior to implementation of the protocol. Any amendments to the protocol, informed consents, or other study-related documents must be approved by the EC/IRB, NICHD, and DAIDS prior to implementation.

13.2 Protocol Registration

Each participating institution will complete protocol registration with the NICHD via Westat. After study sites have received final approval from their local IRB, they must submit protocol registration materials to the Data and Operations Center (DOC) at Westat in accordance with ATN requirements. When the DOC has received all required registration materials, the DOC will approve the site's protocol registration and notify the site that it may begin protocol enrollment. Protocol registration must occur before the site can enroll any participants into the study.

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair, NIAID Medical Officer, and NICHD Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB(s), and where necessary by Starpharma to the FDA, prior to implementing the amendment.

Following ethical review and approval, study sites will submit required administrative documentation to the ATN DOC, Westat. NICHD has delegated responsibility for review and approval of protocol-specific regulatory documentation to Westat. Included in this step will be MTN CORE review of each site-specific study informed consent form.

13.3 Risk/Benefit Statement

Risks

Before testing in humans VivaGel® and the active ingredient were tested in animals. VivaGel® was well tolerated in a number of animal studies using rats, mice, guinea pigs, dogs, rabbits and monkeys. At one laboratory, some rabbits died when they received VivaGel® in the vagina at various doses similar to those that will be used in this study. However, this effect was not seen in other studies when VivaGel® was applied to the vaginas of female rats, dogs, monkeys, and in other studies in rabbits at one other laboratory, in which no rabbits died. Further investigation indicated that the deaths of the rabbits were likely to be related to the procedure used at that laboratory to administer the VivaGel® to the vagina. Rabbits have a place in the vaginal wall where blood vessels are concentrated. It was concluded that damage was caused to that area of the vaginal wall by the dosing procedure, which in turn caused bleeding. Humans, monkeys and rats do not have this concentration of blood vessels in the vagina. It is considered that the effects seen in that rabbit study do not represent a risk to the participants in this or any other clinical trial of VivaGel®. However, the researchers could not determine the exact cause of death in these rabbits.

It is not expected that this trial will expose participants to unreasonable risk. The intervention used in this study is unlikely to cause uncomfortable side effects. An unpublished clinical study suggests a low incidence of side effects, both in the VivaGel® and placebo gel groups.

In the first clinical study of VivaGel® (Starpharma Protocol Number SPL7013-001), volunteers reported the following adverse events that were deemed at least possibly related to study product: vaginal pruritus, vaginal discharge (including product leakage), abdominal discomfort or pain, and dysuria. A rare but potentially life-threatening risk of exposure to either study agent would be anaphylaxis (has not yet been reported for either VivaGel® or placebo gel). Use of a vaginal applicator may cause discomfort, and rarely, vaginal or cervical injury. Colposcopy may also cause mild discomfort secondary to speculum placement in the vagina for the 10-15 minute examination. Collection of cervical cells by Cytobrush® may cause discomfort or spotting during specimen

collection. Phlebotomy may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection.

Male sexual partners will be protected from potential risks of study drug exposure by the use of condoms throughout the study.

Disclosure of STI status may cause sadness or depression in volunteers. Disclosure of HIV-positive status has been associated with depression, suicidal ideation, and denial, as well as social isolation. Participation in clinical research includes the risks of loss of confidentiality and discomfort with personal nature of questions.

Benefits

Participation in this Phase 1 trial likely will have no direct benefit to volunteers other than access to screening for STIs and appropriate referral if STIs are diagnosed. Some volunteers may have the opportunity to access expedient treatment and decreased morbidity due to early diagnosis and treatment of abnormalities in serology, blood count, coagulation, liver or kidney function tests. Pap smear and colposcopy may offer the opportunity for early detection of a cervical and/or vaginal abnormality with expedient referral if an abnormality is detected. Lastly, the participant may appreciate the opportunity to contribute to the body of knowledge in the field of microbicide research. However, there is no guarantee that volunteers will receive any of these benefits.

13.4 Informed Consent Process

Written informed consent will be obtained from all potential study participants prior to the initiation of any study-related procedures. In obtaining and documenting informed consent, the investigators will comply with applicable local and domestic regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Prior to the beginning of the trial, site investigators will have the IRB/EC's written approval/favorable opinion of the protocol, informed consent forms, and any other study-related information to be provided to participants. This study does not plan to enroll children under 18 or illiterate individuals. All study related materials including the informed consent forms will be available in English and Spanish as required by each study site.

The informed consent process will give individuals all of the relevant information they need in order to decide whether to participate, or to continue participation, in this study. Potential research participants will be permitted to ask questions and to exchange information freely with the study investigators. Only listed study investigators may obtain informed consent from potential study participants. The investigators will keep research participants fully informed of any new information that could affect their willingness to continue study participation.

13.5 Participant Confidentiality

Members of the study staff sites are all trained in patient confidentiality for their participation in the ATN. The only sites at which this study will be performed are both ATN Trials Units (ATU). The log of study participant names and other protected health information will be kept in a double-locked area. All computer information about study volunteers will be kept on a computer with log-on passwords. Laboratory specimens are labeled with study numbers and date, and are delivered or shipped by study staff. The study sites' data management and clinical staff are the only personnel with access to the protected health information of study volunteers. Each member of the staff has log-on identification and password, logs off before leaving a computer screen unattended, and closes their office door when out of the office. All research records will be kept indefinitely following closure of this study.

To further protect the privacy of the study participants, the ATN has obtained a Certificate of Confidentiality from the U.S. Department of Health and Human Services (DHHS). With this Certificate in place, the ATN researchers cannot be forced to turn over identifying information about a study participant in any Federal, State, or local criminal, administrative, legislative, or other proceedings. This Certificate does not prevent a study participant from volunteering to turn over their research information nor does it prevent researchers from providing research-related information to others when requested by the study participant.

13.6 Special Populations

This section outlines considerations made for the inclusion or exclusion of special populations in this study.

13.6.1 Pregnant Women

Pregnancy is an exclusion criterion because there are no current recommendations for the use of VivaGel® during pregnancy. A urine pregnancy test will be performed on all women at all clinic visits, and positive tests will be noted on the Eligibility Criteria form. During the informed consent process, women will be informed that VivaGel® is not known to prevent pregnancy and that the effect of VivaGel® on a developing human fetus is unknown. All potential participants will be required by the Eligibility Criteria for Screening and Enrollment to be currently using a reliable method of contraception, such as hormonal contraception (except vaginal ring), intrauterine device, or sterilization. Women who become pregnant during the study period following randomization and exposure to study product will discontinue product use but not be excluded from analysis.

13.6.2 Children

The NIH has mandated that children be included in research trials when appropriate. This study will enroll women aged 18 to 24 who are able to give informed consent. This study meets "Justifications for Exclusion" criteria for younger children as set forth by the NIH. Specifically, "insufficient data are available in adults to judge potential risk in children" and "children should not be the initial group to be involved in research studies.

13.7 Incentives

Pending IRB approval, participants will be compensated for their time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. Site-specific reimbursement amounts will be specified in the study informed consent forms.

13.8 Communicable Disease Reporting

Study staff will comply with all applicable local requirements to report communicable diseases including HIV identified among study participants to local health authorities. Participants will be made aware of all reporting requirements during the study informed consent process.

13.9 Access to HIV-Related Care

This section outlines study participants' access to HIV-related care, including HIV counseling and testing, as well as care for participants identified as HIV-infected.

13.9.1 HIV Counseling and Testing

HIV pretest and post-test counseling will be provided to all potential study participants who consent to undergo HIV screening to determine their eligibility for this study. Participants must receive their HIV test results to take part in this study. The investigators do not expect a screening population at high risk for HIV infection. However, trained clinical staff will refer participants who are confirmed to be HIV-infected per the HIV Antibody Testing Algorithm in Appendix III to a physician for follow-up testing and care. Participants who have positive or indeterminate results will have standard post-test counseling as well as limited follow-up confirmatory testing provided by the study. Referral for additional counseling related to testing or diagnosis will occur if needed or requested by the participant.

13.9.2 Care for Participants Identified as HIV-Infected

Study staff will provide participants with their HIV test results in the context of post-test counseling. According to site SOPs, study staff will refer participants found to be HIV-infected to available sources of medical and psychological care, social support, and local research studies for HIV-infected women.

13.10 Study Discontinuation

This study may be discontinued at any time by NIAID, NICHD, the MTN, Starpharma, the US FDA, other government or regulatory authorities, or site IRBs.

14 PUBLICATION POLICY

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. Any presentation, abstract, or manuscript will be submitted by the Investigator to the MTN Manuscript Review Committee, DAIDS, NICHD and Starpharma Pty Ltd, for review prior to submission.

APPENDICES

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 2-4	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	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	▲

X=protocol-defined procedure; ▲=performed as clinically indicated; Plasma archive will only apply if participant has signed the consent for Storage of Specimens

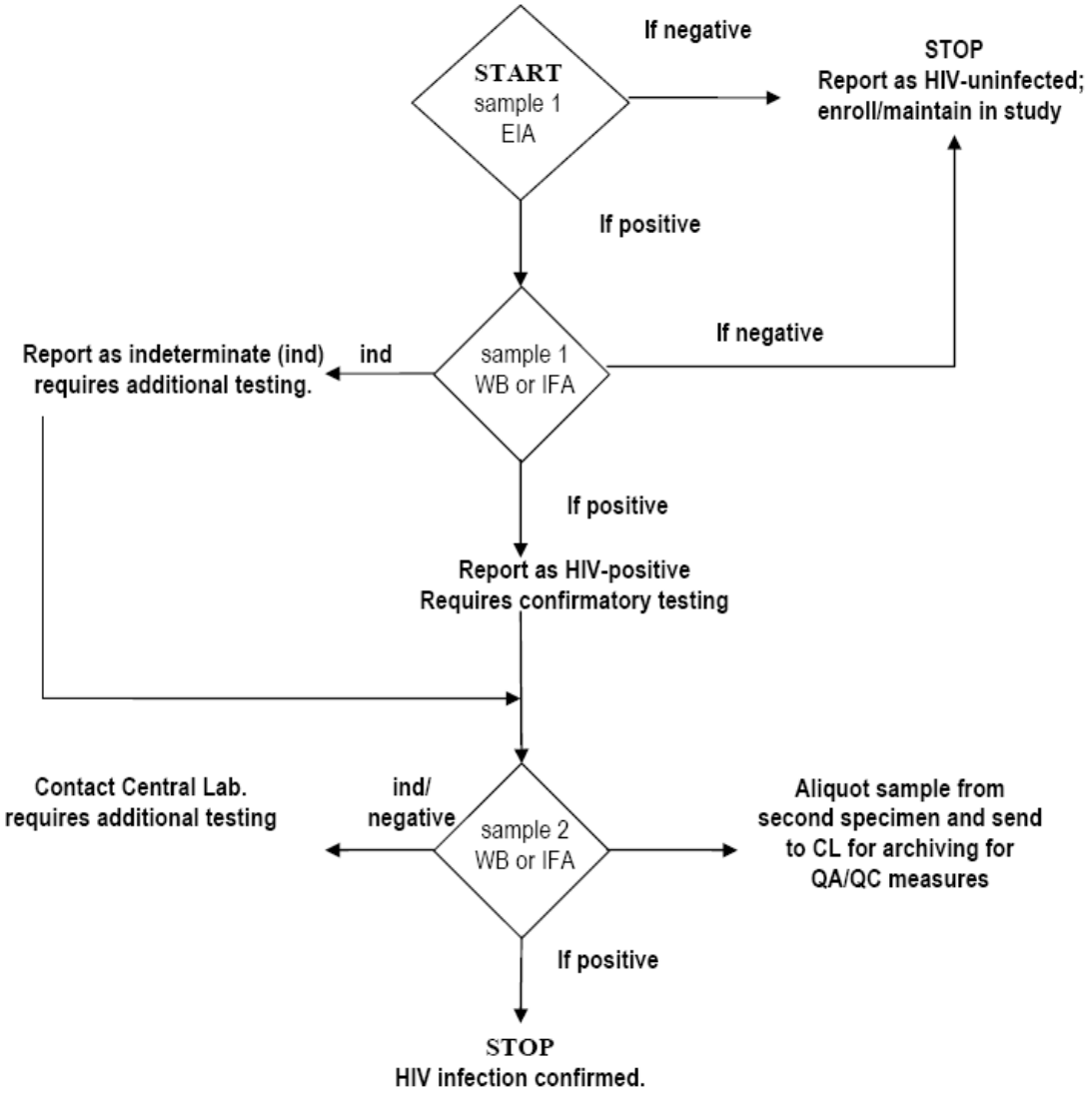
APPENDIX II: OUTCOMES, DIAGNOSTICS, AND FOLLOW-UP EVALUATIONS

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 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 erythema or edema: area of less than 50% of vulvar surface or combined vaginal and cervical surface excluding findings observed by colposcopy only	Continue	Naked eye evaluation with or without 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 excluding findings observed by colposcopy only	Hold study gel (until evaluated)	Naked eye evaluation 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.
Abnormal vaginal discharge	Hold study gel (until evaluated)	Perform wet mount for Candida vaginitis, trichomoniasis, and	Provide treatment and permanently discontinue gel use for all cases of trichomoniasis,

		BV	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 bleeding	Continue (at clinician's discretion)	Naked eye evaluation with or without colposcopy	If determined to be due to deep epithelial disruption, refer to guidelines in this table. Otherwise continue gel use.
Presumed cervicitis (findings on exam such as mucopurulent cervical discharge)	Hold study gel (until evaluated)	Evaluate for *N. gonorrhoeae* and *C. trachomatis*	Provide treatment and permanently discontinue gel use for all cases of cervicitis.
Genital petechia(e) excluding findings observed by colposcopy only	Continue	Naked eye evaluation	No further evaluation or treatment required.
Genital ecchymosis excluding findings observed by colposcopy only	Continue	Naked eye evaluation with or without colposcopy.	No further evaluation or treatment required.
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

APPENDIX III: HIV ANTIBODY TESTING ALGORITHM



Note: HIV positive results will only be reported to participants once the result is confirmed by Western Blot Testing. Once a participant's HIV status is confirmed, sites will follow site specific SOPs for notification to local agencies.

APPENDIX IV: MANUAL FOR EXPEDITED REPORTING OF ADVERSE EVENTS TO DAIDS

May 6, 2004

Table of Contents

1.0 PURPOSE OF MANUAL

1.1 Purpose

The purpose of this Manual is to describe the criteria and method for expedited reporting of certain serious and other reportable adverse events to the Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), through the DAIDS Safety Office.

1.2 Scope

This Manual applies only to those clinical studies/trials requiring expedited reporting of adverse events to the DAIDS Safety Office as stated in the protocol. This Manual applies to all study agents specified in the protocol as requiring expedited reporting to DAIDS. Although not covered under this Manual, note that DAIDS may require MedWatch reporting (using e.g., Form FDA 3500A or CIOMS I Form) to the Food and Drug Administration (FDA) and/or DAIDS for some studies. MedWatch reporting may only be applied to studies/trials of US FDA-approved study agents. Any requirements for MedWatch reporting will be identified in the study/trial protocol.

1.3 Introduction

For adverse events requiring expedited reporting to DAIDS, sites must follow the general reporting requirements and procedures described in this Manual. In order to fully define the expedited adverse event reporting requirements that apply to an individual study/trial, the protocol will specify:

- One of three Levels of Adverse Event Reporting (Section 3.1) and any other adverse events to be reported on an expedited basis (Section 3.2).
- The duration of the protocol-defined expedited reporting period.
- The name or category of each study agent (US FDA-approved or investigational) that requires expedited reporting of adverse events to DAIDS. This may include study agents in addition to those provided by the study/trial.

2.0 DESCRIBING AN ADVERSE EVENT BY SERIOUSNESS, SEVERITY, RELATIONSHIP TO STUDY AGENT, AND EXPECTEDNESS

The criteria for expedited reporting of adverse events to the DAIDS Safety Office include the seriousness of the outcome of the event, the severity (intensity) of the event, its relationship to study agent, and (only for the Targeted Level) expectedness, i.e., whether the adverse event is expected or unexpected.

2.1 Seriousness

The first consideration for expedited reporting of adverse events to DAIDS is the seriousness of the outcome of the event. The April 1996 International Conference on Harmonisation (ICH) guidance, “Good Clinical Practice: Consolidated Guidance,” (ICH E6) defined a serious adverse event (SAE) as “any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect."

"Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above" may also be considered to be serious (October 1994 ICH guidance (E2A), "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting").

2.2 Severity (Intensity)

The second consideration for expedited reporting of adverse events to DAIDS is the severity (intensity) of the event. In order to maintain consistency among studies/trials and sites, DAIDS has developed a list of common clinical and laboratory adverse events and defined grade 1 – 5 severity parameters to generate the Division of AIDS Tables for Grading Adult and Pediatric Adverse Experiences (also known as "the toxicity tables"). These tables are located on the DAIDS Safety Office website at http://rcc.tech-resintl.com. Unless stated otherwise in the protocol, study staff is required to use the Division of AIDS Tables for Grading Adult and Pediatric Adverse Experiences to determine the intensity of adverse events in order to establish consistency in adverse event reporting to DAIDS. Specific protocols may include additional or modified criteria for grading adverse events that are not included in the current versions of the Division of AIDS Tables for Grading Adult and Pediatric Adverse Experiences.

2.3 Seriousness vs. Severity (Intensity) of Adverse Events and Reporting Criteria

For expedited reporting to DAIDS, the term "severity" (or "intensity") is described as the grade for a specific event, i.e., mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4). This is *not* the same as "serious," which is based on subject/event *outcome or action* criteria usually associated with events that pose a threat to a subject's life or functioning (ICH E2A).

2.4 Relationship to Study Agent

The third consideration for expedited reporting of adverse events to DAIDS is the judgment of causal association (relationship) between an adverse event and the study agent. The protocol must specify by name or category each study agent (either approved or investigational) that requires expedited reporting of adverse events to DAIDS. The study physician makes the site's final assessment of the causal association based upon the temporal relationship to administration of the study agent(s), the pharmacology of the study agent(s), and his/her clinical

judgment. The terms used in DAIDS studies/trials to assess relationship of an event to study agent are:

- **Definitely Related**. The adverse event and administration of study agent are related in time, and a direct association can be demonstrated.
- **Probably Related**. The adverse event and administration of study agent are reasonably related in time, and the adverse event is more likely explained by study agent than other causes.
- **Possibly Related**. The adverse event and administration of study agent are reasonably related in time, and the adverse event can be explained equally well by causes other than study agent.
- **Probably Not Related**. A potential relationship between study agent and the adverse event could exist (i.e., the possibility cannot be excluded), but the adverse event is most likely explained by causes other than the study agent.
- **Not Related**. The adverse event is clearly explained by another cause not related to the study agent.
- **Pending.** Pending may be used as a temporary relationship assessment only for death and only if data necessary to determine relationship to study agent are being collected. The site is required to submit a final assessment within 3 business days after reporting the death. If no final assessment is made within 3 business days after the date of submission, the event will be assessed as possibly related to study agent. Any additional information received at a later time, including an autopsy report, should be submitted as a Follow-up Report.

A **suspected adverse drug reaction (SADR)** is an adverse event that could potentially have a causal relationship to the study agent (definitely, probably, possibly, probably not related, or for deaths, pending).

2.5 Expectedness (Expected vs. Unexpected)

Expected refers to the perspective of events previously observed, *not* on the basis of what might be anticipated from the pharmacological properties of the study agent. (ICH E2A) Unexpected refers to events whose nature or severity (intensity) is not consistent with those included in the package insert/summary of study agents that have been approved by the US FDA or in the Investigator's Brochure. (ICH E2A)

3.0 ADVERSE EVENTS REQUIRING EXPEDITED REPORTING AND THE STUDY/TRIAL REPORTING PERIOD

3.1 Levels of Adverse Event Reporting

The protocol will specify one of three Levels of Adverse Event Reporting. The Level of Adverse Event Reporting chosen for expedited reporting is based primarily upon the degree of risk that may be associated with the study agent.

3.1.1 Standard Level

Report all adverse events following any exposure to study agent that:

- Result in death **regardless** of relationship to study agent.
- Are congenital anomalies, birth defects, or fetal losses **regardless** of relationship to study agent.
- Result in persistent or significant disabilities or incapacities **regardless** of relationship to study agent.
- Are a **suspected adverse drug reaction**, i.e., definitely, probably, possibly, and probably not related, to a study agent that requires or prolongs existing hospitalization, or requires intervention to prevent significant/permanent disability or death.
- Are life-threatening (including all Grade 4 adverse events) **suspected adverse drug reactions**, i.e., definitely, probably, possibly, and probably not related to a study agent.

3.1.2 Intensive Level

In addition to all adverse events reported for the Standard Level, also report all Grade 3 suspected adverse drug reactions, i.e., definitely, probably, possibly, and probably not related to a study agent. (The Intensive Level includes reporting Grades 3 and 4 SADRs.)

3.1.3 Targeted Level

Use of the Targeted Level of reporting is limited to non-IND studies/trials of US FDA-approved agents and doses for approved indications and populations. Report **only** the following adverse events:

- All events that result in death **regardless of relationship** to study agent.
- All congenital anomalies, birth defects, or fetal losses **regardless of relationship** to study agent.
- All persistent or significant disability or incapacity **regardless of relationship** to study agent.
- **Unexpected* suspected adverse drug reactions**, i.e., definitely, probably, possibly, and probably not related to a study agent, that require or prolong existing hospitalization, or require intervention to prevent death or significant/permanent disability.
- **Unexpected*** life-threatening clinical **suspected adverse drug reactions**, i.e., definitely, probably, possibly, and probably not related to a study agent. **DO NOT report** Grade 4 laboratory values that are not associated with a life-threatening clinical event.

*Unexpected events are events whose nature or severity is not consistent with the package insert/summary of product characteristics for a US FDA-approved study agent.

3.2 Additional Protocol-Required Expedited Reporting Requirements

In addition to specifying one of the reporting levels above, a protocol may require other adverse events to be reported on an expedited basis. In this case, the protocol will explicitly state the additional adverse events to be reported to

DAIDS. For example, in rare instances a protocol may specify use of the Intensive Level and also require Grades 1 and 2 SADRs to be reported, or a protocol may require reporting of a specific type of adverse event regardless of grade.

3.3 Additional Adverse Events That Should Be Reported for Any Study/Trial Requiring Expedited Reporting to DAIDS

In addition to the reporting requirements described above, sites should report any of the following adverse events on an expedited basis:

- Suspected adverse drug reactions, i.e., definitely, probably, possibly, and probably not related to a study agent, that **do not meet the protocol-required reporting criteria**, but the Investigator believes are of sufficient concern to be reported on an expedited basis to DAIDS. This includes adverse events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent a serious adverse event. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm or blood dyscrasias or convulsions that do not result in hospitalization.

- Unexpected, serious suspected adverse drug reactions, i.e., definitely, probably, possibly, and probably not related to a study agent, that occur at any time **after the protocol-defined expedited reporting period** if the study staff become aware of its occurrence. These events include deaths, permanent disabilities, congenital anomalies, hospitalizations, and life-threatening clinical events. (Do not report Grade 4 laboratory values unless associated with a life-threatening clinical event.)

- Serious adverse events that are not related to a study agent, but could be associated with **study participation or procedure** (e.g., pulmonary embolism secondary to an intravenous catheter placed for study agent administration).

3.4 Protocol-Defined Expedited Adverse Event Reporting Period

The protocol-specified reporting level continues throughout the study/trial period (from enrollment of a subject through the end of study follow-up visits for that subject). The protocol may also require the same level of adverse event reporting to be continued beyond the end of study follow-up for each subject, and if so, the protocol must specify the duration of this additional reporting period.

4.0 METHOD AND TIMEFRAME FOR EXPEDITED REPORTING OF INDIVIDUAL ADVERSE EVENTS

All information requested on the DAIDS Expedited Adverse Event Reporting Form must be provided and the form submitted to the DAIDS Safety Office. This form can be found at the web site for the DAIDS Safety Office. Contact information for the DAIDS Safety Office is provided in Appendix B. The timeframe for expedited reporting of individual adverse events begins when the

site recognizes that an event fulfills the criteria outlined in this Manual for expedited reporting to DAIDS. Sites must submit adverse events requiring expedited reporting to the DAIDS Safety Office as soon as possible, **but no later than 3 business days**, after the site's recognition that the event fulfills the criteria for expedited reporting.

5.0 ADDITIONAL EXPEDITED REPORTING REQUIREMENTS

5.1 Follow-up Reporting of Adverse Events

5.1.1 Submitting Follow-Up Information on Adverse Events

For the circumstances listed below, the site is required to submit follow-up information when it becomes available on a new Expedited Adverse Event Form as a Follow-up Report.

- Requests by DAIDS for additional information.
- A change in the relationship between the adverse event and study agent by the study physician.
- Additional significant information that becomes available for a previously reported adverse event. This is particularly important for new information addressing cause of death if the initial assignment was "pending."
- Results of rechallenge with the study agent(s), if performed.

5.1.2 Outcome of Adverse Events

The site **must** follow each reported adverse event and record eventual outcomes in the source documentation. However, report of the outcome of a reported adverse event to the DAIDS Safety Office is not required unless specifically requested by DAIDS.

5.2 Reporting Recurrent Adverse Events

For events that have been previously reported to the DAIDS Safety Office, if the event has fully resolved and then re-occurs to a level requiring expedited reporting, the adverse event must be reported as a New Report to the DAIDS Safety Office.

5.3 Reporting Change in Severity of Adverse Events

Any ongoing event that increases in severity to a higher grade than previously reported must be reported again as a New Report on a new DAIDS Expedited Adverse Event Reporting Form. Ongoing events that improve, but are not resolved and then increase in severity to the same or lower severity grade than previously reported do not have to be reported again to the DAIDS Safety Office. Resolution is the normalization or return to baseline (i.e., prior to study agent exposure) of laboratory values, signs, or symptoms related to the event.

5.4 Study Physician Assessment and Signature

A study physician listed on the Form FDA 1572 for IND studies or the DAIDS Investigator of Record Agreement (IoR) for non-IND studies must review and

verify the data on the DAIDS Expedited Adverse Event Reporting Form for accuracy and completeness. This physician also makes the site's final assessment of the relationship between the study agent and the adverse event. This physician must sign the completed DAIDS Expedited Adverse Event Reporting Form. If necessary to meet timely reporting requirements, sites can submit an expedited adverse event report without a completed signature page. However, the completed signature page, and necessary corrections or additions, must be submitted within the next 3 business days.

6.0 APPENDICES

6.1 Appendix A: Definition of Terms

Adverse Event (AE): An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (ICH E6) (Synonym: Adverse Experience)

DAIDS Safety Office: The Office to which adverse events requiring expedited reporting are submitted. (DAIDS)

Division of AIDS Tables for Grading Adult and Pediatric Adverse Experiences (Toxicity Tables): Lists of common terms and severity (intensity) parameters used to describe adverse events occurring in DAIDS-sponsored clinical studies/trials. (DAIDS)

IND: An investigational new drug application. (21 CFR 312.3)

Investigator's Brochure: A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects. (ICH E6)

Non-IND Study/Trial: A study/trial for which there is no IND filed with the US FDA.

Package Insert: The approved package circular in marketed drug packaging containing the drug description, clinical pharmacology, indications and usage, contraindications, warnings, precautions, adverse reactions, drug abuse and dependence, dosage and administration, how drug is supplied, "clinical studies," and "references." (21 CFR 201.57)

Serious Adverse Event (SAE): Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or

prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. This includes important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. (ICH E6 and E2A)

Study Agent: Drugs, biological products, or combination of drugs and biological products (approved or investigational) defined in the protocol as requiring expedited reporting to DAIDS. (DAIDS)

Study Physician: A physician listed on the Form FDA 1572 for IND studies or on the DAIDS Investigator of Record Agreement (IOR) for non-IND studies. (DAIDS)

Suspected Adverse Drug Reaction (SADR): An adverse event that could potentially have a causal relationship to a study agent (definitely, probably, possibly, probably not related or for deaths, pending). (DAIDS)

Toxicity: An adverse event that has an attribution of possibly, probably, or definitely related to a study agent. (DAIDS) NOTE: This term should not be used for expedited reporting of adverse events to DAIDS.

Unexpected Event: An adverse event, the nature or severity (intensity) of which is not consistent with the applicable product information (Investigator's Brochure, package insert, or summary of product characteristics for a US FDA-approved study agent. (DAIDS)

6.2 Appendix B: Contact Information for DAIDS Safety Office

All completed DAIDS Expedited Adverse Event Forms are submitted to the DAIDS Safety Office. For questions or other communication, please note the following:

Website:	http://rcc.tech-res-intl.com
Office Phone*:	1-800-537-9979 (US only) or +1-301-897-1709
Office Fax*:	1-800-275-7619 (US only) or +1-301-897-1710
Office Email:	RCCSafetyOffice@tech-res.com
Office Hours:	Monday through Friday, 8:30 AM to 5:00 PM (US Eastern Time)
Mailing Address:	DAIDS Safety Office 6500 Rock Spring Drive Suite 650 Bethesda, MD 20817

*Office phone and fax are accessible 24 hours per day.

6.3 Appendix C: Summary Chart for Expedited Reporting of Adverse Events to DAIDS for Protocol-Specified Study Agents

	Standard Level	Intensive Level	Targeted Level
Deaths	All Events	All Events	All Events
Congenital anomalies, birth defects, fetal losses	All Events	All Events	All Events
Disabilities/Incapacities	All Events	All Events	All Events
Hospitalization[1]	All Suspected Adverse Drug Reactions[2]	All Suspected Adverse Drug Reactions[2]	Unexpected Suspected Adverse Drug Reactions [2,3]
Other events	All Grade 4 Suspected Adverse Drug Reactions[2]	All Grades 3 and 4 Suspected Adverse Drug Reactions[2]	Unexpected Life-Threatening Clinical Suspected Adverse Drug Reactions [2,3]

[1]This category includes hospitalization, prolongation of hospitalization or requirement of intervention to prevent permanent disabilities or death.

[2]Suspected adverse drug reactions are adverse events that are assessed as definitely, probably, possibly, probably not related to a study agent (or for deaths, pending).

[3]Unexpected events are adverse events, of a nature or severity (intensity) that is not consistent with the applicable product information (package insert/summary of product characteristics) for a US FDA-approved study agent.

Timeframe for Expedited Reporting of Individual Adverse Events:
Adverse events requiring expedited reporting are to be reported to the DAIDS Safety Office **no later than 3 business days** after the site's recognition that the event fulfills the criteria for expedited reporting.

Protocol-Defined Expedited Adverse Event Reporting Period
The protocol-specified reporting level continues throughout the study/trial period (from enrollment of a subject through the end of study follow-up visits for that subject). The protocol may also require the same level of adverse event reporting to be continued beyond the end of study follow-up for each subject.

APPENDIX V: SAMPLE INFORMED CONSENT DOCUMENT (SCREENING)

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

Version 3.0
30 June 2008

PRINCIPAL INVESTIGATOR: **[insert]**
PHONE: **[insert]**
Short Title for the Study: Safety and Acceptability of VivaGel® in Sexually Active Women

Introduction

You are being asked to take part in these screening exams and tests because you are a sexually active woman between the ages of 18 and 24 years, and you may be able to join the research study named above. This study is sponsored by the U.S. National Institutes of Health (NIH). The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. The screening exams and tests include interview questions, urine and blood tests, a physical exam, and an examination of your vagina.

This is a consent form. It gives you information about the screening exams and tests. The study staff will explain the exams and tests to you and what is expected of you. You are free to ask questions about the screening exams and tests at any time. If you agree to have the screening exams and tests, you will be asked to sign this consent form in front of a witness. You will be given a copy of this form to keep.

Why Are These Screening Exams and Tests Being Done?

The main purpose of these screening exams and tests is to find out if you can join a research study. The research study will try to find out if VivaGel® is safe and if there are any bad effects when women apply VivaGel® in the vagina for 2 weeks. About one-third of the women in the research study will place VivaGel® into the vagina twice a day for two weeks. 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 VivaGel®, 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. The other purposes of the study are to see if an ingredient in the gel (SPL7013) goes into the bloodstream, to find out what women think about the study gel, and to see if women use the gel according to the study directions.

VivaGel® study gel is "experimental". This means we do not know all the effects it may have. We do not know if it will be safe and tolerated in all women. This is one of the reasons the study is being done. Because the study gel is experimental, the United States Food and Drug Administration (FDA) and [LOCAL AUTHORITY] [HAS/HAVE] not approved it for use in the general community. The FDA has been informed of this study and has allowed it to happen. The [local authority] has also allowed the study to happen.

Before a large study can be done to find out if VivaGel® stops HIV from getting into the body, we must first make sure it is safe. So far, the safety of the study gel has been tested among 37 women in Australia. 36 of these women applied the gel in the vagina every day for one week, and one woman did not finish the study because of an abnormal test result from the time before she started the gel. In that study, the gel was shown to be safe and women in the study did not have a lot of complaints or problems. The most common complaints were mild abdominal pain. Some women also noticed that the gel leaked out of the vagina. None of these women had any SPL7013 from the VivaGel® in their bloodstream according to the tests that were done.

The United States National Institutes of Health is providing funds for this study to take place. A total of approximately 61 women from Florida and Puerto Rico will join this study (about 30 in Florida and about 30 in Puerto Rico). About 30 women will be in the study here at [INSERT NAME OF SITE]. The whole study will take about ten months to finish. Each woman will be in the study for about eight weeks. It will take about one week to one month to complete the screening exams and tests. Some people may not be able to join the study because of information found during the screening exams and tests. If you can join the study, it will take about three weeks to complete the main study exams and tests. Once enrolled in the study, you will be asked to use the study gel twice a day, everyday, for two weeks. You will have a study visit every week for two weeks, and then a study visit about one week after you finish using the study gel.

What Do I Have To Do If I Take Part in the Screening Exams and Tests?

If you agree to have the screening exams and tests, you will have one or two screening visits here at the study site. The exams and tests will take about one week to one month. Depending on what your screening exams and tests show, more screening visits may be needed. All screening exams and tests will be done within 36 days. If all exams and tests are not done within 36 days, and you still want to find out if you can join the research study, you will have to start the screening exams and tests over from the beginning.

- Answering Questions
  Your first visit will continue today, after you read, discuss, and sign this form. No study exams or tests will be started before the screening exams and tests have been fully explained to you and you have signed this form. The visit will take about one to two hours. To find out if you can join the

study you will be asked some questions. The questions will be about you and where you live. You will be asked questions about your health, the medicines you take, your periods, and your sexual practices. Some people may be embarrassed by questions about their sexual practices.

- Pregnancy Test
  If your answers to the questions show that you may join the study, you will have to give urine for a pregnancy test. You will receive the result of your pregnancy test today. If you are pregnant, you will not be able to join the study. However, site staff will talk to you about options available to you. They will refer you to available sources of medical care and other services you may need. If the study is still open after your pregnancy, you can come back here to find out if you can join the study then.

- Tests for HIV and Sexually Transmitted Infections
  If you are not pregnant, study staff will talk to you about HIV and other sexually transmitted infections or sexually transmitted diseases (commonly known as STIs or STDs). You will have a blood test for HIV, and syphilis, vaginal swabs for bacterial vaginosis, candidiasis, and trichomoniasis and a urine test for gonorrhea and Chlamydia. You will talk about HIV/AIDS and other STIs. You will also talk about ways that HIV and other STIs are spread, and ways to protect against them. You will talk about what it may mean to know the results of these tests. You can discuss whether you are prepared to receive the test results. If you are having health problems that may be due to STIs, the study staff will refer you for treatment.

- Using an Effective Birth Control Method Plus Condoms
  The study gel is not a birth control method. You must agree to use an effective method of birth control such as birth control pills, birth control shots (such as Depo-Provera) or the birth control patch, an intrauterine device (or IUD), be sterilized, or have sex with a partner who is sterilized. You must also be willing to continue to use birth control for one month after you stop applying the study gel. An intrauterine device (IUD) is a small object that is inserted through the cervix and placed in the uterus to prevent pregnancy. If you are using an IUD for birth control and want to join the study, you must have had it put in at least 30 days ago in order to join the study. The study staff will provide male condoms to you free of charge. However, condoms are not considered an adequate means of birth control for the purposes of this study.

- Blood and Urine Tests
  If you are willing to have HIV and STI testing, you will give blood (about 30 mL or two tablespoonfuls) [LOCAL EQUIVALENT - SITES TO COMPLETE] and urine for the tests. Your blood will be tested for HIV. You must know what your HIV test result is to join the study. Your blood will also be tested to

check on your general health, including the health of your liver, kidneys and blood. Your urine will also be tested for infections. It takes about [X AMOUNT OF TIME - SITES TO COMPLETE] before your results are ready. We will give you your results as soon as they are available.

- Physical and Pelvic Exams
  You will have a physical exam and a pelvic exam. During the pelvic exam the study doctor or nurse will use a speculum as is usual in collecting a Pap smear. They will check for discharge, or other signs of infection, and other possible problems. The study doctor or nurse will also take some vaginal swabs to test for STIs and other possible problems.

  If a sore (or other problem) is seen during the examination of your vagina, you may need medicine to treat it. You will be asked to see your regular heath care provider for medicine or may be given medicine here. We will ask you to come back here after a few days for another exam. If the sore (or other problem) has cleared up when you come back, you may be able to join the research study.

- Pap Test
  The study staff will also collect samples from your cervix for a "Pap test" or "Pap smear". If the test is abnormal, it could mean you have cervical cancer, or that you should have more tests or treatment to lower your chances of having it turn into cervical cancer. It takes about [X AMOUNT OF TIME – SITES TO INSERT] before Pap test results are ready. If you have a written report confirming a normal Pap smear in the last year you will not need to have a Pap smear taken at this screening visit. The results of your Pap test may affect whether or not you can continue in the study.

- Test Results
  It takes about [X AMOUNT OF TIME – SITES TO INSERT] before HIV, STI, and Pap test results are ready. We will give you the results for all your exams and tests at your next appointment. You will talk with the study staff about the meaning of your test results and how you feel about them.

  If your tests show that you have HIV you will not be able to join the study. The study staff will refer you to available sources of medical care and other services you may need for HIV. They will tell you about other studies that you may be able to join. If your exams and tests show that you have an STI, you will need medicine to treat it. The study staff will refer you to your usual heath care provider for medicine or may give you medicine here to treat the STI. You will not be able to join the research study if your tests show you have an STI. However, if you have had outbreaks of genital herpes in the past, but do not have any on your exam today, you may be able to join the research study.

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE:]
[LOCAL/STATE/NATIONAL] regulations require study staff to report the names of people who test positive for HIV and other infections passed during sex to the [LOCAL HEALTH AUTHORITY]. Outreach workers from the [health authority] may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, the outreach workers will contact them, according to the confidentiality guidelines of the [HEALTH AUTHORITY].

If your exams and tests show no problems, you will be able to enter the research study. You will receive a different Informed Consent Form if you return for the Enrollment Visit. If at any time during the screening it is found that you cannot join the study, the screening process and your visit will end.

Why Would The Doctor Stop the Screening Procedures Early?

The study doctor may need to stop the screening exams and tests early without your permission if:

- The study is cancelled by the U.S. Food and Drug Administration (FDA), U.S. National Institutes of Health (NIH), the drug company supporting this study, the Ethics Committees, the local government or regulatory agency, or the Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research participants).
- Your exams, tests and answers to the questions show you cannot join the study.
- The study staff feels that having the screening exams and tests would be harmful to you.
- You do not want to find out your HIV test result.
- You are not able to come to the visits or complete the screening exams and tests.
- Other reasons that may prevent you from completing the study.

What Are The Risks Of The Screening Visit Tests?

Risk of Blood Draws:

You may feel discomfort or pain when your blood is drawn. You may feel dizzy, faint or lightheaded. You may have a bruise, swelling, or infection where the needle goes into your arm.

Risk of Genital Exams:

You may feel discomfort or pressure during the exam of your genital area and inside your vagina. You may have mild vaginal spotting (bleeding). The mild bleeding will stop shortly after the exam.

Other Possible Risks:

You may become embarrassed, worried, or nervous when discussing how you have sex; ways to protect against HIV and other infections passed during sex, and your test results. You may become worried or nervous while waiting for your

test results. If you have HIV or other infections, knowing this could make you worried or nervous. A trained counselor will help you deal with any feelings or questions you have.

We will make every effort to protect your privacy while you are having the screening exams and tests. Your visits here will take place in private. However, it is possible that others may learn that you are taking part in the study here. Because of this, they may treat you unfairly. For example, you could have problems getting or keeping a job, or being accepted by your family or community.

Are There Benefits To Taking Part In This Study?

You may get no direct benefit from the screening exams and tests. However, you will have a physical exam and a pelvic exam, and counseling and testing for HIV and STIs. You will also have tests to check your general health and the health of your liver, kidneys, and blood. This study cannot provide you with medical care, but study staff will refer you to other available sources of care. If your Pap test result is not normal, you will be referred for treatment at the [INSERT NAME OF PROVIDER/CENTER].

You will get counseling and testing for HIV. You will get free male condoms. If you are infected with HIV, you will be referred for medical care, counseling, and other services available to you. Medical care for HIV infection will not be part of this study. You will need to get medical care for your HIV infection from your own health care provider or we will provide you with a referral to a center where you can receive appropriate care. You will get counseling and testing for STIs and other infections. If you have any of these infections, you will be referred for treatment if needed. You can bring your male partner(s) here so that we can also provide them with referral for diagnosis and treatment for potential STIs.

What Other Choices Do I Have Besides This Study?

You do not have to participate in this study, if you choose not to do so.

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE: There may be other studies going on here or in the community for which you may be eligible. If you wish, we will inform you about other studies that are being conducted locally. There also may be other places where you can go for HIV counseling and testing. We will tell you about those places if you wish.] Please talk to your doctor about these and other choices that may be available to you.

What About Confidentiality?

Efforts will be made to keep your personal information private. We cannot guarantee absolute confidentiality. If this study is published, your name will not be used and you will not be personally identified.

Your records may be reviewed by:

- The U.S. Food and Drug Administration (FDA)
- U.S. National Institutes of Health (NIH)
- [INSERT NAME OF SITE] IRB
- Study staff
- Study monitors
- Ethics committees
- Drug companies supporting this study

In addition to the efforts of the study staff to help keep your personal information private, a Certificate of Confidentiality has been obtained from the US Federal Government. This Certificate means that study staff cannot be forced to tell people who are not connected with the study, such as the court system, about your taking part in the study. The Certificate of Confidentiality does not prevent you from releasing information about yourself or your participation in the study. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities. You are encouraged but not required to tell sexual partners about your being in this study.

What Are The Costs To Me?

There is no cost to you for the screening exams and tests.

Will I Receive Any Payment?

You will be paid for your time and effort for each screening visit. You will receive [INSERT SITE - SPECIFIC AMOUNT OF MONEY] for each visit. You will also be paid for other costs to you for coming to the screening visits [SUCH AS CHILD CARE, TRAVEL, AND LOSS OF WORK TIME – SITES TO COMPLETE]. There may be one or more screening visits.

What Happens If I Am Injured?

It is unlikely that you will be injured as a result of having the screening exams and tests. If you are injured as a result of having the screening exams and tests, you will be given immediate treatment for your injuries. However, you may have to pay for this care. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the U.S. National Institutes of Health (NIH). You will not be giving up any of your legal rights by signing this consent form.
[SITES TO SPECIFY INSTITUTIONAL POLICY]

What Are My Rights As A Research Participant?

Taking part in the screening exams and tests is completely voluntary. You may choose to not have the screening exams and tests any time. You will be treated the same no matter what you decide. If you choose to not have the screening exams and tests, you will not lose the benefit of services to which you would normally have at this clinic.

We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

What Do I Do If I have Problems or Questions?

For questions about the screening exams and tests or if you have a research-related injury, you should contact:

- [SITE INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

For questions about your rights as a research participant, contact:

- [SITE INSERT NAME OR TITLE OF PERSON ON THE INSTITUTIONAL REVIEW BOARD (IRB) OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

SIGNATURE PAGE

[INSERT SIGNATURE BLOCKS AS REQUIRED BY LOCAL IRB]

If you have read the informed consent (or had it read and explained to you), and all your questions have been answered and you agree to take part in this study, please sign your name below.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness' Name (print) (As appropriate)	Witness's Signature and Date

APPENDIX VI: SAMPLE INFORMED CONSENT DOCUMENT (ENROLLMENT)

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

Version 3.0
30 June 2008

PRINCIPAL INVESTIGATOR:	**[insert]**
PHONE:	**[insert]**
Short Title for the Study:	Safety and Acceptability of VivaGel® in Sexually Active Women

Introduction

You are being asked to take part in this research study because you are a sexually active woman between the ages of 18 and 24 years and have passed the screening tests for this study. This study is sponsored by the U.S. National Institutes of Health (NIH). The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR]. Before you decide if you want to join this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will be given a copy of this form to keep.

Why Is This Study Being Done?

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.

This research study will try to find out if VivaGel® is safe and if there are any bad effects when women apply VivaGel® in the vagina for 2 weeks. About one-third of the women in the research study will place VivaGel® into the vagina twice a day for two weeks. 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 gel called HEC placebo gel into the vagina twice a day for two weeks. Women will be in the group getting VivaGel®, 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. The other purposes of the study are to see if an ingredient in the gel (SPL7013) goes into the bloodstream, to find out what women think about the study gel, and to see if women use the gel according to the study directions.

VivaGel® is "experimental". This means we do not know all the effects it may have. We do not know if it will be safe and tolerated in all women. This is one of the reasons the study is being done. Because the study gel is experimental, the United States Food and Drug Administration (FDA) and [LOCAL AUTHORITY] [HAS/HAVE] not approved it for use in the general community. The FDA has been informed of this study and has allowed it to happen. The [local authority] has also allowed the study to happen.

Before a large study can be done to find out if VivaGel® stops HIV from getting into the body, we must first make sure it is safe. So far, the safety of the study gel has been tested among 37 women in Australia. 36 of these women applied the gel in the vagina every day for one week, and one woman did not finish the study because of an abnormal test result from the time before she started the gel. In that study, the gel was shown to be safe and women in the study did not have a lot of complaints or problems. The most common complaints were mild abdominal pain. Some women also noticed that the gel leaked out of the vagina. None of these women had any SPL7013 from the VivaGel® in their bloodstream according to the tests that were done.

The United States National Institutes of Health is providing funds for this study to take place. A total of 61 women from Florida and Puerto Rico will join this study (about 30 in Florida and about 30 in Puerto Rico). About 30 women will be in the study here at [INSERT NAME OF SITE]. The whole study will take about ten months to finish. Each woman will be in the study for about eight weeks. It will take about three weeks to complete the main study exams and tests. If you can join the study, you will be asked to use the study gel for two weeks. You will have a study visit every week for three weeks, though you or the study staff may request additional visits if they are needed.

What Do I Have To Do If I Am In This Study?

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 three study groups. One group will get VivaGel®, one group will get VivaGel® placebo, and one group will get HEC

placebo gel. All three groups will use the study gel twice daily for 14 days. The study group will be chosen by chance, like flipping a coin, or throwing dice [SITE TO MODIFY TO LOCAL EQUIVALENT]. You cannot choose your group, and the study staff cannot choose your group for you. You have an equal chance of being placed in either of the groups. Neither you nor the study staff will know whether you are in the placebo or VivaGel® groups.

All three groups are important to this study. No matter which study group you are in, you must remember that we do not know if any of the study gels work to protect women from getting HIV. The only known way to protect against getting HIV during sex is to use a male condom every time you have sex.

It is not known if the study gel will work to protect against pregnancy, therefore you should not use the study gel as a birth control method. You must agree to use an effective method of birth control such as birth control pills or another hormonal based method (except for vaginal rings), an intrauterine device (or IUD), be sterilized, or have sex with a partner who is sterilized as well as using condoms.

The pharmacy will provide male condoms and panty liners to you free of charge. Each visit is described below. You should continue to use the gel if you get your period. If you have your period at the time of your visit, you will complete all visit exams and tests except for the pelvic exam and associated tests (which may be made up once your period is over). You will insert into the vagina one full applicator, about 3 and a half grams (or about one teaspoonful), of the study gel. You will use the study gel twice a day for 2 weeks, as long as the study staff thinks it is safe for you to keep using the gel after your first week.

Once you join the study, you will return to the site for a follow up visit after one week, two weeks, and three weeks. After two weeks you will stop using the study gel. You will return all of your unused applicators to the study sites at the Week 1 and Week 2 visits in the bags given to you for this purpose. In total, you will have at least four study visits including today's visit.

After all the participants finish the study, and we find out the results of the study, if you wish, you will be told which study gel you received. We will also provide you with a brief summary of the main findings from the study.

Enrollment Visit:

If you decide to take part in this study, your first visit will continue today, after you read, discuss, and sign this form. No study procedures will be started before the visit exams and tests have been fully explained to you and you have signed this form. Today's visit will take about one to one and a half hours.

To find out if you still can join the study you will be asked some questions – the questions will be about you, where you live, and other questions about your health, your periods, alcohol and substance use, the medicine you take, and your sexual practices. Some people may be embarrassed by questions about their sexual history.

If your answers to the questions show that you can join the study, you will:

- Give urine for a pregnancy test if your second screening visit took place on a day other than today. You will be given your result for the pregnancy test today. If you are pregnant, you will not be able to join the study; however site staff will talk to you about options available to you, and will refer you to available sources of medical care and other services you may need. If the study is still open after your pregnancy, you can come back here to find out if you can join the study then.

- Give blood for tests to check on the health of your blood cells, liver, and kidneys and to confirm that there is no SPL7013 already in your blood (about 30 mL or about 2 tablespoons).

- Have a pelvic exam. The study doctor or nurse will use a speculum. The doctor or nurse will check the vagina and cervix for discharge, or other signs of infection, and other possible problems. During the pelvic exam, the study doctor or nurse will look at your genital area and into your vagina through a lens called a colposcope. The lens works like a magnifying glass to help the nurse or doctor see anything that may not be normal. The lens will not be inside your body. They may take digital video pictures of the colposcopy with a camera. You may tell the study staff not to record these images. These images will be kept strictly confidential and used only by study physicians to decide upon the significance of possible changes in the vagina or cervix. The study doctor or nurse may also take some fluids to test for sexually transmitted infections or sexually transmitted diseases (commonly known as STIs or STDs) and other possible problems if they feel this is necessary.

- Have an abdominal exam and vital signs (blood pressure, pulse, and temperature).

- The study doctor or nurse will collect swabs from the vagina and cervix to measure the level of immune activity in the vagina and to check that there is a healthy balance of bacteria in the vagina.

If a sore (or other problem) is seen during the examination of your vagina, you may need medicine to treat it. You will be asked to see your regular heath care provider for medicine or be given medicine here. We may ask you to come back

here after a few days for another exam. If the sore (or other problem) has cleared up when you come back, you may be able to join the research study.

It takes about [X AMOUNT OF TIME – SITES TO INSERT] before these tests are ready. We will give you the results from all the exams and tests after they are ready. You will talk with the study staff about the meaning of your test results and how you feel about them.

If your exams and tests show that you have an STI, you will not be eligible to join the study. The study staff will refer you for treatment of the infections. You will be asked to come back here for a check-up after taking all the medicine.

If you are eligible to join the study, you will be given 20 tubes of either VivaGel® or placebo gel (VivaGel® placebo or HEC placebo) already packaged inside applicators. You will also be given instructions on how to use them. You will receive male condoms, and panty liners and/or menstrual pads. You will insert your first dose of gel while you are in the study clinic.

In addition to your study visits, you will be asked **to do** the following:

- Use an effective method of contraception during the study.
- Contact the study doctor or nurse if you have any discomfort or medical problems.
- Tell the study staff about any medications you take while in the study.
- Agree to use study provided panty liners and/or menstrual pads for your period or in case the study gel leaks out of the vagina. If you need a different kind other than the kind provided to you by the study, let the study staff members know.
- You **must not** use spermicides or male condoms lubricated with spermicides during the study. If you need to use a different kind other than the ones provided to you by the study, let the study staff know.
- It is ok for you to use tampons, take a bath or go swimming while you are using the study gel.

You **must not** do the following during the entire time while in the study:

- Breastfeed
- Use intravenous drugs except for medical use.
- Take part in studies of other vaginal products or any drug or device study. Tell the study staff if you plan to join another study.
- Use other participants' study gel.
- Douche or otherwise clean the vagina, or insert other products into your vagina.
- Practice the following types of sexual activity during the two weeks you are receiving the gel:
    - Oral – vaginal sex (known as cunnilingus)

- Penile – anal intercourse
- Penile – vaginal intercourse **without** your partner using an approved condom

Telephone Call

Two days after you have your Enrollment Visit, you will have a phone call with the study staff to talk about any problems you might have with the gel applicator. You can call the clinic, or the study staff can call you, depending on how you want to arrange it. This call will probably take about 5 minutes or less.

One-Week Clinic Visit:

This visit will take about an hour. The visits will not be scheduled during your period. You will have the following procedures at your One-Week Clinic Visit:

- Tell the study staff any updated information about your address, telephone number or other contact information.
- Tell the study staff if you had any medical problems or discomfort since your last visit.
- Tell the study staff any new information about your health or your periods.
- Tell the study staff about any medicines you are taking.
- Give urine for a pregnancy test. You will receive the results of your pregnancy test on the day of the visit.
- Complete a computerized questionnaire about your use of the study gel.
- Tell the study staff your thoughts and opinions about the study gel.
- Have an abdominal exam and vital signs (blood pressure, pulse, and temperature).
- Have a pelvic exam with a speculum with collection of swabs from the vagina and cervix.
- Give blood (about 25 mL or a little more than 1 and a half tablespoonfuls) [OR LOCAL EQUIVALENT – SITE TO INSERT]. We will check your blood for the overall health of your blood cells, and the health of your liver and kidneys, the study staff will give you the results of your tests [IN X AMOUNT OF TIME – SITES TO INSERT].
- Receive 10 more tubes of gel (we expect that you may have extra tubes left over at the end of the study that we want you to return to the clinic)

Two-Week Clinic Visit:

This visit will take about an hour and a half. You will stop applying the study gel at this visit. You will complete all of the 1-Week Follow-Up procedures plus:

- Have a pelvic exam with a speculum, and with a colposcopic lens;
- Have a blood test to see if SPL7013 can be measured in your blood;
- Complete a computerized questionnaire about your experiences using the study gel including its use during sex;
- Return all of your unused (if you have any unused) applicators to the clinic.

Three-Week Clinic or Termination Visit:
This visit will take about an hour. At this visit you will:

- Have an abdominal exam and vital signs (blood pressure, pulse, and temperature);
- Have a pelvic exam with a speculum, and have some vaginal and cervical swabs taken;
- Complete a computerized questionnaire about your thoughts and opinions about the study and how easy or difficult it was to be in the study.

The study site staff will give you your test results as soon as they are available. We will ask you to come back to the clinic or, with your permission; we may visit you at your home or a place in your community.

After You Finish Using the Study Gel:
During this study you may have a chance to take part in additional studies. If you choose not to take part in any of our additional studies, your participation in this study remains the same. If you have any problems or concerns regarding your health after using the study gel, let the study staff members know. You can contact the study site staff at any time after you have finished using the study gel. The study site staff will want to let the study sponsor know about any serious problems you tell them about.

Any Time During The Study:
If either you or the study staff members think you may have become pregnant, you will give urine for a pregnancy test. Also, if you are having health problems that may be caused by STIs, you will:

- Have an exam of your genital area and inside your vagina.
- Give blood or urine to test for STIs.
- Get referral for treatment for STIs if you need it.

You are asked to tell the study staff about any medical problems you have, especially genital problems. You can contact the study staff between regular visits to report these problems. The study staff will examine you as necessary. They will refer you for medical care that you may need.

You are also encouraged to tell the study staff if your partner has any genital problems after you have had intercourse during the study. If this kind of problem occurs, your partner or partners may contact the study site staff for a check-up.

If the staff members find that a study gel is causing you problems, they may ask you to stop using the study gel, either for a short time or permanently. The study staff will ask you to stop using the study gel if you become pregnant or if you become infected with HIV. Even if you stop using the study gel, you will be asked

to stay in the study and have your follow up visits. You will also have some or all of the originally planned exams and tests that the study staff would like you to have to check on your health.

If you have an STI that your partner also may have, you can bring him here for counseling and referral for testing and treatment. You can have extra counseling and testing for HIV at any time during the study. If you wish, your partner can have counseling with you. If you become infected with HIV, you can stay in the study but you cannot keep using the study gel and you should return any used and unused applicators to the study clinic. The study staff will give you counseling and refer you to available sources of medical care and other services you may need.

At each study visit, the study staff will update information on where you live and how to keep in contact with you. They will use this information to remind you of scheduled visits. If you miss a visit, the study staff will try to contact you by [SITE-SPECIFIC METHODS]. If you give your permission, they also may visit your home to find you. They will try to reach you through the contact people that you list. If they talk to these people, they will not tell them why they are trying to reach you.

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE:]
[LOCAL/STATE/NATIONAL] regulations require study staff to report the names of people who test positive for HIV and other infections passed during sex to the [LOCAL HEALTH AUTHORITY]. Outreach workers from the [health authority] may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, the outreach workers will contact them, according to the confidentiality guidelines of the [HEALTH AUTHORITY].

How Many Women Will Take Part In This Study?
61 women will take part in this study. About 30 women will be from Florida and about 30 women will be from Puerto Rico.

How Long Will I be In This Study?
You will be in this study about six weeks. You will be asked to apply the study gel for 2 weeks. The total time you will be in the study, including the time to complete the screening exams and tests and the main study is about six weeks.

Why Would The Doctor Take Me Off This Study Early?
The study doctor may need to take you off the study early without your permission if:

- The study is cancelled by the U.S. Food and Drug Administration (FDA), U.S. National Institutes of Health (NIH), the drug company supporting this study, the Ethics Committee, the local government or regulatory agency,

or the Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research participants).
- The Data and Safety Monitoring Board (DSMB) or Study Monitoring Committee (SMC) recommends that the study be stopped early (A DSMB is an outside group of experts who monitor the study; a SMC reviews the progress of the study and the kinds of effects that people report while they are participating in the study).
- You are not able to keep appointments or apply study gel as instructed.
- Other reasons that may prevent you from completing the study successfully.

The study doctor will ask you to stop using the study gel but continue to come in for your follow up visits and procedures if:

- You are pregnant.
- You are breastfeeding.
- You become infected with HIV.
- The study doctor decides that using the study gel would be harmful to you or your partner.
- You require a treatment that you may not take while using the study gel.
- You have a bad reaction to the study gel.

If the study doctor asks you to stop using the study gel, you will still be advised to come in for all of the scheduled follow-up visits that are described above, including things like the abdominal exam, vital signs, pelvic exam, colposcopy, blood tests, and questionnaires. You will stop using the study gel until the study doctor decides it is safe for you to start using the study gel again, if possible.

What are the risks of this study?

Risks of Blood Draws:

You may feel discomfort or pain when your blood is drawn. You may feel dizzy, faint or lightheaded. You may have a bruise, swelling, or infection where the needle goes into your arm.

Risk of Genital Exams:

You may feel discomfort or pressure during the exam of your genital area and inside your vagina. You may have mild vaginal spotting (bleeding). The mild bleeding will stop shortly after the exam.

Other Possible Risks:

You may become embarrassed, worried, or nervous when discussing sexual behaviors and HIV. You may become worried or nervous while waiting for your STI and HIV test results. If you have HIV, knowing your HIV status could make you worried or nervous. You will talk with a trained staff member who will help you deal with any feelings or questions you have.

Risks of VivaGel®

It is very important to use the study gel as instructed by staff. The study gel used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship to the study gel. If you have questions concerning additional study drug side effects please ask the study staff at your site.

Some of the effects of VivaGel® are still unknown. Some possible effects are dryness, itching, burning, redness, a sore or pain in the genital area. You may also have discharge if the study gel comes out of the vagina. The study staff will give you panty liners and/or menstrual pads in case you need them.

Your male sexual partners will be protected from potential risks associated with exposure to VivaGel® through:

- Consistent use of approved condoms during penile-vaginal sex
- Avoidance of oral-vaginal sex

Possible Risks to Your Privacy

We will make every effort to protect your privacy while you are in this study. However, it is possible that you could have problems if people learn that you are in this study. They might think that you are infected with HIV or at risk of HIV because of sexual behavior or illegal drug use. Because of this, others may treat you unfairly. For example, you could have problems getting or keeping a job. You also could have problems being accepted by your family or community. There also is a risk to your privacy if someone else taking part in this study knows you.

Are There Risks Related To Pregnancy?

Because there is no information on VivaGel® in pregnant women, VivaGel® should not be used during pregnancy. You must agree to try to not become pregnant during the study. It is not known if the study gel used in this study harms unborn babies. You and your partner must be willing to use an effective method of birth control such as birth control pills or another hormonal based method (except for vaginal rings), an intrauterine device or IUD, be sterilized, or have sex with a partner who is sterilized. You should discuss this with the study staff. You must be willing to continue to use birth control for one month after you stop applying the study gel.

The study staff will provide male condoms to you free of charge. If you can become pregnant, you must have a pregnancy test before you enter this study. The test must show that you are not pregnant.

What If I Have A Positive Pregnancy Test During The Study?

If you think you may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you about your choices. If you have a

positive pregnancy test while using the study gel, we will ask you to stop using the study gel and return all used and unused applicators, but will ask you to continue to be in the study and to come in for your follow up visits. There are no anticipated additional risks to you if you choose to continue to take part in this study.

If you are pregnant and choose to continue the pregnancy, this study will not provide care related to your pregnancy, the delivery of your baby, or the care of the baby. Your baby may have been exposed to SPL7013 if you received VivaGel®, and if it was absorbed from the vagina into your blood, and we do not know if this will affect unborn babies. The study staff will contact you to ask you a few questions about the outcome of your pregnancy. You must arrange for your care and your baby's care outside of this study. This study cannot provide care related to termination of pregnancy, though study staff can provide you with information regarding your access to termination of pregnancy as part of counseling you about your pregnancy test results.

Breastfeeding

It is unknown if there are any effects of VivaGel® on breast milk. It is unlikely that the study gel will pass through breast milk but absorbing the study gel from the vagina into the blood may affect breast milk and may cause harm to your infant. You must agree to not breastfeed during this study. Women who are currently breastfeeding are advised to not enroll in this study.

Are There Benefits To Taking Part In This Study?

There is no direct benefit to you because no one knows if the study gel will prevent HIV infection. Also, you may be in the study group that receives the placebo gel, which will not help in preventing HIV. Information learned from this study may help in the development of ways to prevent the spread of HIV in the future. You will receive pelvic exams and counseling and testing for HIV and STIs. You will also have tests to check the overall health of your liver, kidneys, and blood cells. This study cannot provide you with medical care, but study staff will refer you to other available sources of care. If your Pap test result shows anything that is not normal, you will be referred for advice and/or treatment.

You will get counseling and testing for HIV. You will get free male condoms. If you are infected with HIV, you will be referred for medical care, counseling, and other services available to you. Medical care for HIV infection will not be part of this study. You will need to get medical care for your HIV infection from your own health care provider or we will provide you with referral to a Center that can provide you with appropriate care. You will get counseling and testing for STIs. If you have an STI diagnosed, you will get medicine to treat them, if needed. You can bring your partner here for counseling and referral for testing and treatment for STIs if this is needed.

What Other Choices Do I Have Besides This Study?
You do not have to participate in this study, if you choose not to.

[SITES TO INCLUDE/AMEND THE FOLLOWING IF APPLICABLE: There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about. There also may be other places where you can go for HIV counseling and testing. We will tell you about those places if you wish.] Please talk to your doctor about these and other choices that may be available to you.

What About Confidentiality?
Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by:

- The U.S. Food and Drug Administration (FDA)
- U.S. National Institutes of Health (NIH)
- [INSERT NAME OF SITE] IRB
- Study staff
- Study monitors
- Ethics committees
- Drug companies supporting this study

In addition to the efforts of the study staff to help keep your personal information private, a Certificate of Confidentiality has been obtained from the US Federal Government. This Certificate means that study staff cannot be forced to tell people who are not connected with the study, such as the court system, about your taking part in the study. The Certificate of Confidentiality does not prevent you from releasing information about yourself or your participation in the study. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities. You are encouraged but not required to tell your sexual partners about your being in this study.

What Are The Costs To Me?
There is no cost to you for study related visits, study products, physical examinations, laboratory tests or other procedures.

Will I Receive Any Payment?
You will receive payment for your time and effort in this study. You will receive [INSERT SITE-SPECIFIC AMOUNT OF MONEY] per visit. You will also receive payment for activities affected by your participation in this study [SUCH AS CHILD CARE, TRAVEL, LOSS OF WORK TIME – SITES TO COMPLETE].

What Happens If I Am Injured?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. However, you or your insurance company may have to pay for this care. This institution or the U.S. National Institutes of Health (NIH) does not have a program to provide money for your injuries. You will not be giving up any of your legal rights by signing this consent form.
[SITES TO SPECIFY INSTITUTIONAL POLICY]

What Are My Rights As A Research Participant/Volunteer?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. You will be treated the same no matter what you decide. If you choose not to participate or to leave the study, you will not lose the benefit of services to which you would otherwise be entitled at this clinic. We will tell you about new information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

What Do I Do If I have Problems or Questions?

For questions about this study or a research-related injury, contact:

- [SITE INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

For questions about your rights as a research participant, contact:

- [SITE INSERT NAME OR TITLE OF PERSON ON THE INSTITUTIONAL REVIEW BOARD (IRB) OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE]
- [SITE INSERT TELEPHONE NUMBER AND PHYSICAL ADDRESS OF ABOVE]

SIGNATURE PAGE
[INSERT SIGNATURE BLOCKS AS REQUIRED BY LOCAL IRB]

If you have read the informed consent (or had it read and explained to you), and all your questions have been answered and you agree to take part in this study, please sign your name below.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness' Name (print) (As appropriate)	Witness's Signature and Date

APPENDIX VII: SAMPLE INFORMED CONSENT (STORAGE AND FUTURE TESTING OF SPECIMENS)

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

Version 3.0
30 June 2008

PRINCIPAL INVESTIGATOR: **[insert]**
PHONE: **[insert]**
Short Title for the Study: Safety and Acceptability of VivaGel® in Sexually Active Women

INTRODUCTION

You have decided to take part in a Division of AIDS research study. While you are in this research study there may be some samples of blood and/or fluid from your cervix taken from you that might be useful for future research. You are being asked to agree to the storage of these samples. This consent form gives you information about the collection, storage and use of your samples. The study staff will talk with you about this information. Please ask any questions, if you have some. If you agree to the storage of your samples, you will be asked to sign this consent form. You will be given a copy of this form copy to keep.

HOW WILL YOU GET THE SAMPLES FROM ME?

The research doctors want to save any extra blood and cervical fluid leftover from your tests during the study. This leftover blood and cervical fluid will be kept and used for future research.

HOW WILL YOU USE MY SAMPLES?

Your samples will be used to look for evidence of your body's response to infection (such as examining cells, proteins, and other chemicals in your body) while you were using the study gel and after you stopped using the study gel. Tests may also include examining your genes (DNA), since they might affect your response to disease in important ways. Your genes might make you more or less likely to becoming infected, affect your responses to infection, or make your responses to treatment stronger or weaker. No other kinds of genetic test will be done by anyone on your stored specimens without first explaining the test to you and getting your permission. The researchers do not plan to contact you or your regular doctor with any results from tests done on your stored samples. This is because research tests are often done with experimental procedures, so the results from one research study are generally not useful for making decisions on managing your health. Should a rare situation come up where the researchers decide that one of the test results would provide important information for your health, the researchers will notify your study doctor and your study doctor will try to contact you. If you wish to be contacted with this type of test result, you must

give the study doctor or nurse any change to your address and/or phone number. If you want your regular doctor to be told about this type of test result, you must provide the study doctor or nurse with your regular doctor's name, address and phone number. Your samples will not be sold or used directly to produce products that can be sold for profit.

Research studies using your samples will be reviewed by the National Institutes of Health, and Ethics Committee, and a special committee at the researcher's institution (an Institutional Review Board) whose purpose is to protect you as a research participant.

HOW LONG WILL YOU KEEP MY SAMPLES?
There is no time limit on how long your samples will be stored.

HOW WILL MY SAMPLES BE STORED?
Your samples will be stored at special facilities that are designed to store samples safely and securely. The storage facilities are designed so that only approved researchers will have access to the samples. Some employees of the storage facilities will need to have some access to your samples in order to store them and to keep track of where they are, but these people will not have information that directly identifies you. An Institutional Review Board will oversee the storage facilities to protect you and other research volunteers from harm.

DOES STORAGE OF MY SAMPLES BENEFIT ME?
There are no direct benefits to you.

WHAT ARE THE RISKS?
There are few risks related to storing your samples. When tests are done on the stored samples there is a small but possible risk to your privacy. It is possible that if others found out information about you that is learned from tests (such as information about your genes) it could cause you problems with your family (having a family member learn about a disease that may be passed on in families or learning who is the biological parent of a child) or problems getting a job or insurance.

WHAT ABOUT CONFIDENTIALITY?
In order to keep your information private, your samples will be labeled with a code that can only be traced back to your research clinic. Your personal information (name, address, phone number) will be protected by the research clinic. When researchers are given your stored samples to study they will not be given your personal information. The results of future tests will not be included in your health records.

We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This certificate

means that researchers cannot be forced to tell people who are not connected with the research, such as the court system, about your participation. Also, any publication of the research will not use your name or identify you personally.

People who may review your records include: [INSERT NAME OF SITE] IRB, National Institutes of Health (NIH), study staff, study monitors, and their designees. Having a Certificate of Confidentiality does not prevent you from giving information about yourself and your participation in the study. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.

WHAT ARE MY RIGHTS?

Allowing your samples to be stored is completely voluntary. You may decide not to have any samples stored other than what is needed to complete this study and still be in this research study or any future study. If you decide now that your samples can be stored for future research, you may change your mind at any time. You must contact your study doctor or nurse and let them know that you do not want your samples used for future research. Your samples will then not be used and will be destroyed.

WHAT DO I DO IF I HAVE QUESTIONS?

For questions about the storage of your samples, contact (*insert the name of the investigator*) at *(insert telephone number)*.

For questions about your rights related to the storage of your samples for research, contact (*insert the name or title of person on the Institutional Review Board) at (insert telephone number)*.

SIGNATURE PAGE
[INSERT SIGNATURE BLOCKS AS REQUIRED BY LOCAL IRB]

If you have read the informed consent (or had it read and explained to you), and all your questions have been answered and you agree to take part in this study, please sign your name below.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness' Name (print) (As appropriate)	Witness's Signature and Date

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