

HIV Prevention Trials Network

Protocol 049: Phase I Safety and Acceptability Study of the Vaginal Microbicide 6% Cellulose Sulfate Gel Among HIV-Infected Women

AMENDMENT #1

11 January 2003
IND # 57,833

Summary of Revisions

- An Investigator signature page has been added.
- The duration of the entire study has been extended to 13 months.
- The enrollment visit scheduling has been expanded to 2-6 days after the participant's next menstrual period.
- The inclusion criteria of the protocol have been revised to allow for women up to 50 years to be entered in the study.
- The exclusion criteria of the protocol have been revised to allow antibiotic therapy 14 days prior to enrollment, except antibiotic therapy for gynecological care.
- An abnormal Pap test has been defined.
- The product application regimen has been revised to allow participants in Cohorts 2 and 4 (twice daily dosing) to apply the morning dose if the follow-up pelvic exam is scheduled in the afternoon.
- A section for procedures to follow in the event of a pregnancy has been added.
- Chlamydia and gonorrhea testing by ligase chain reaction has been changed to nucleic acid amplification testing.
- Appendix II has been revised to re-evaluate genital erythema or edema (in a localized area of less than 50 percent) by speculum examination in 48-72 hours only if the erythema or edema is symptomatic.
- The protocol version number, date and table of contents are updated. Other administrative and typographical clarifications and corrections have been incorporated throughout the protocol and sample informed consent forms as needed.

Prior to implementing the procedures described below, the HPTU will submit this amendment, the corresponding protocol version 2.0, and an updated local study informed consent form to its Institutional Review Board (IRB). CONRAD will submit this amendment to the Food and Drug Administration for inclusion in their Investigational New Drug application for Cellulose Sulfate Gel. A copy of this submission will be sent to the Division of AIDS Regulatory Affairs Branch.

Upon receipt of IRB approval, protocol registration with the DAIDS Regulatory Operations Center, and activation by the HPTN CORE, the following protocol modifications, indicated by ~~strike through~~ and **bold** text, will be implemented:

1. Following the title page:

HPTN 049
Phase I Safety and Acceptability Study of
the Vaginal Microbicide 6% Cellulose Sulfate Gel
Among HIV-Infected Women

A Study of the HIV Prevention Trials Network (HPTN)

Sponsored by:

Division of AIDS (DAIDS)
US National Institute of Allergy and Infectious Diseases (NIAID)
US National Institutes of Health (NIH)

I, the Site Principal Investigator, agree to conduct this study in full accordance with the provisions of this protocol and will comply with all requirements regarding the obligations of clinical investigators as fully outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation for a minimum of two years after FDA clearance or until DAIDS/NIAID/NIH and the pharmaceutical co-sponsor advise that it is no longer necessary. Publication of the results of this study will be governed by DAIDS and HPTN policies. Any presentation, abstract, or manuscript will be made available by the investigators to DAIDS, the HPTN Manuscript Review Committee, and the pharmaceutical co-sponsor for review prior to submission.

I have read and understand the information in the Investigator's Brochure, including the potential risks and side effects of the product 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 Site Principal Investigator

Signature of Site Principal Investigator

Date

2. In the List of Abbreviations and Acronyms:

AGC	atypical granular cells
AIS	endocervical adenocarcinoma in situ
ASC	atypical squamous cell
ASC-H	atypical squamous cells, cannot exclude HSIL
ASC-US	atypical squamous cell of undetermined significance
HSIL	high-grade squamous intraepithelial lesions
LCR	ligase chain reaction
LSIL	low-grade squamous intraepithelial lesions
NAT	nucleic acid amplification test

3. In the Protocol Team Roster:

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4. In the protocol Schema:

Study Duration: Accrual will require up to ~~eight~~ **11** months. Each female participant will be followed for 14 days of product use and the entire study should be completed within ~~ten~~ **13** months.

5. In protocol Section 2.4.2:

After providing written informed consent, female participants will undergo eligibility screening, including medical history, symptom-directed physical exam, pelvic exam, urine testing for pregnancy and infection, STD counseling and testing, hematology and coagulation testing, and liver and renal function testing. For participants who are presumptively eligible at this visit, an Enrollment Visit will be scheduled to take place ~~3-5~~ **2-6** days after the participant's next menstrual period, but within 42 days of initial screening.

6. In protocol Section 3.1.1, second bullet:

- Age 18-~~45~~ **50** years, inclusive.

7. In protocol Section 3.2.1, fourth bullet:

- History of prior participation in this study (i.e., in a prior cohort), **as indicated by the study site's screening log and participant identification code list.**

8. In protocol Section 3.2.1, twelfth bullet:

- In the 14 days prior to Enrollment, received a course of antibiotic therapy **for gynecological care.**

9. In Protocol Section 3.2.1, following bullet 9, fourth sub-bullet:

Note: Abnormal Pap smear is defined by the following designations: all atypical squamous cell (ASC) interpretations (atypical squamous cell of undetermined significance (ASC-US), atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesions (HSIL)(ASC-H)), low-grade squamous intraepithelial lesions (LSIL), HSIL, carcinoma in situ and squamous cell carcinoma as well as all atypical glandular cell (AGC) interpretations (atypical endocervical, endometrial, or glandular cells and AGC-favor neoplastic), endocervical adenocarcinoma in situ (AIS), and adenocarcinoma. Reactive Pap smear designations including reactive cellular changes associated with inflammation will be presumed normal in the absence of an ulcerative or non-ulcerative STD (including negative laboratory results for STDs) or deep epithelial disruption on speculum exam or colposcopy.

10. In protocol Section 4.2, second bullet:

- Participants in Cohorts 2 and 4 will apply the assigned product twice daily, in the morning and at bedtime, with an approximate 12-hour interval between applications. On study Day 7, participants in Cohorts 2 and 4 will be instructed to delay their morning application until after completion of their follow-up pelvic exam, **unless the follow-up pelvic exam is scheduled in the afternoon.**

11. In protocol Section 4.0, a new section has been added:

4.7 Procedures to be Followed in the Event of 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 the Protocol Team. The site investigator will counsel the participant and discuss possible risks if the pregnancy is continued. According to procedure included in the SSP Manual, the participant will be followed through the conclusion of her pregnancy, and live births will be followed for one year.

12. In protocol Section 5.1, fourth bullet:

- Collect urine and conduct pregnancy and leukocyte esterase (LE) test; if LE test is positive (greater than trace), perform culture and microscopy at the local laboratory (LL). Ship urine for chlamydia and gonorrhea ~~ligase chain reaction (LCR)~~ **nucleic acid amplification testing (NAT)** at the HPTN Central Laboratory (CL).

13. In protocol Section 5.1, sixth bullet, sixth and seventh sub-bullets:

- ~~• Pap smear (unless medical records document a normal result in the past three months),~~
- ~~• sno-strip and cervicovaginal lavage (CVL) for HIV viral load at the HPTN CL, and~~
- **sno-strip and cervicovaginal lavage (CVL) for HIV viral load at the HPTN CL,**
- **Pap smear (unless medical records document a normal result in the past three months), and**

14. In protocol Section 5.2, second bullet:

- Verify that male sexual partner is eligible for the study and has provided written informed consent for study participation **(cohorts 3 and 4 only)**.

15. In Appendix I, third row following title row:

Collect/update demographic and locator information	X	X	X	X
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16. In Appendix I, eighth row following title row:

Collect urine for: -pregnancy test -leukocyte esterase screen -culture and microscopy <i>(if indicated)</i> -chlamydia and gonorrhea LCR NAT <i>(at Screening; at follow-up only if indicated)</i>	X	X	X	X
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17. In Appendix I, ninth row following title row:

Collect blood for: -complete blood count -CD4+cell count <i>(at Screening only)</i> -syphilis serology <i>(at Screening only; at follow-up only if indicated)</i> -HIV serology <i>(at Screening only, if required)</i> -liver function testing -renal function testing -coagulation testing -plasma HIV viral load -plasma and serum archive <i>(at Enrollment only)</i>	X	X	X	X
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18. In Appendix II, fourth row following title row:

Mild to moderate Localized erythema or edema: localized area of less than 50% of vulvar surface or combined vaginal and cervical surface	Continue.	Naked eye evaluation and/or colposcopy.	If asymptomatic, re-evaluate at next regularly scheduled visit. If symptomatic Re-evaluate by speculum examination in 48-72 hours. If worsened significantly, discontinue product use. Otherwise, continue product use.
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19. In Appendix II

Generalized erythema or severe edema: localized area of more than 50% of vulvar surface or combined vaginal and cervical surface affected by erythema	Discontinue.	Naked eye evaluation and/or colposcopy.	Re-evaluate in 5-7 days.
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20. In Appendix I, ninth row following title row:

Collect blood for: -complete blood count -CD4+cell count (<i>at Screening only</i>) -syphilis serology (<i>at Screening only; at follow-up only if indicated</i>) -HIV serology (<i>at Screening only, if required</i>) -liver function testing -renal function testing -coagulation testing -plasma HIV viral load -plasma and serum archive (<i>at Enrollment only</i>)	X	X	X	X
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21. In the Sexually Abstinent Women and Sexually Active Women Sample Informed Consents, Purpose of Study Section, last paragraph:

The study staff here are conducting this study with funding from the US National Institute of Allergy and Infectious Diseases (NIAID). The Contraceptive Research and Development Program (CONRAD) also is sponsoring this study. About 96 women and 48 men from Birmingham, AL; Providence, RI; Philadelphia, PA, and New York, NY will take part in the study. The study will last about ~~ten~~ **13** months. Your part will last about two months.

22. In the Sexually Abstinent Women and Sexually Active Women Sample Informed Consents, Procedures Section, During the Study sub-section, first paragraph:

You will be given pre-filled applicators of either CS Gel or the approved gel (K-Y Jelly) and instructions on how to use them. A computer program will be used to determine which gel you will use. This will be done “at random,” which means “by chance,” like flipping a coin. You will have a one-out-of-two or “50-50” chance of using each gel. Neither you nor the staff here will be able to choose which gel you use, and neither you nor the staff will know which gel you are given. After all participants finish the study, and we find out the results of the study, if you wish, you will be told which gel you used.

23. In the Sexually Abstinent Women and Sexually Active Women Sample Informed Consents, Risks and/or Discomforts Section, second paragraph:

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

24. In the Sexually Abstinent Women Sample Informed Consent, Pregnancy Section, third paragraph:

If you become pregnant during the study you should tell the study clinician right away. You will stop using the study gel and the study clinician will discuss your choices with you. **The study clinician will contact you every three months during pregnancy, and every three months for one year after the baby is born so that we can find out about your health and your baby's health.**

25. In the Sexually Active Women Sample Informed Consent, Pregnancy Section, second paragraph:

If you become pregnant during the study you should tell the study clinician right away. You will stop using the study gel and the clinician will discuss your choices with you. **The study clinician will contact you every three months during pregnancy, and every three months for one year after the baby is born so that we can find out about your health and your baby's health.**

26. In the Male Partners Sample Informed Consent, Purpose of Study Section, last paragraph:

The study staff here are conducting this study with funding from the US National Institute of Allergy and Infectious Diseases (NIAID). The Contraceptive Research and Development Program (CONRAD) also is sponsoring this study. About 96 women and 48 men from Birmingham, AL; Providence, RI; Philadelphia, PA; and New York, NY will take part in the study. The study will last about ~~ten~~ **13** months. Your part will last about two months.

27. In the Male Partners Sample Informed Consent, Procedures Section, During the Study sub-section, first paragraph:

During the Study: If you and your partner are eligible for the study, and agree to take part, your partner will be given pre-filled applicators of either CS Gel or the approved gel (K-Y Jelly) to apply in her vagina for 14 days. A computer program will be used to determine which gel your partner will be given. This will be done "at random," which means "by chance," like flipping a coin. You and your partner will have a one-out-of-two or "50-50" chance of using each gel. Neither you, your partner, nor the staff here will be able to choose which gel you use, and no one will know which gel you are given. After all participants finish the study, and we find out the results of the study, if you wish, you will be told which gel you and your partner used.