

**HIV Prevention Trials Network
PROTOCOL CLARIFICATION MEMORANDUM #5**

**HPTN 047: Phase I Safety and Acceptability Study of The Investigational Vaginal
Microbicide PRO 2000/5 Gel (P)
Version 2.0, August 15, 2002**

**05 February 2004
IND # 56,962 (Indevus Pharmaceuticals, Inc.)**

Summary of Revisions

- Study site contact numbers are updated in the PROBLEMS OR QUESTIONS Section of the HPTN 047 Informed Consent Forms (ICFs), Version 2.0, August 16, 2002, to reflect the recently modified telephone dialing system requiring the addition of the number "2" in front of the original 7-digit phone number.

Implementation

The protocol clarification detailed in this memorandum should be implemented immediately. This clarification results in a minor administrative change in the informed consent being used in the study. If The HPTN 047 protocol is amended in the future, these clarifications will be incorporated into the next version.

The HPTU will submit HPTN 047 Protocol Clarification Memorandum # 5 to all responsible Institutional Review Boards (IRBs). Indevus Pharmaceuticals, Inc. will submit this clarification to the Food and Drug Administration for inclusion in their PRO 2000 Investigational New Drug application, IND #56,962 held by Indevus Pharmaceuticals, Inc

IRB approval of HPTN 047 Protocol Clarification Memorandum # 5 is not required.

Rationale

The purpose of HPTN 047 Protocol Clarification Memorandum # 5 is to:

- Recognize that the contact numbers currently listed in the HPTN 047 Informed Consents must have the number "2" added in front of the original 7-digit phone number listed.

- Clarify that all participants who are consented to HPTN 047 are notified of the revision to the local phone numbers listed in the consent form

Implementation

The following protocol modifications, indicated by ~~strike through~~ or under-score text, made to the HPTN 047 Protocol:

PROBLEMS OR QUESTIONS

If you ever have any questions about this study, or in the case of research-related injuries, you should contact Dr. Smita Joshi at [~~24479339/25898759~~], or if you have question about your rights as a research participant, you can call Dr. D.S. Shrotri, Chairman, Ethical Committee, NARI at 25541872.

Please note: This information is verbally given to the participants, as the addition of the number "2" to the telephone dialing system is universal throughout the city of Pune, India.

The following HPTN 047 Informed Consents are affected by the recent modification to the contact numbers:

1. HPTN 047 NARI Informed Consent Women, English, Version 2.0, 16 August 2002
2. HPTN 047 NARI Informed Consent Women, Marathi, Version 2.0, 16 August 2002
3. HPTN 047 NARI Informed Consent Women, English Back-translation, Version 2.0, 16 August 2002.
4. HPTN 047 NARI Informed Consent Men, English, Version 2.0, 16 August 2002, corrected 05 February 2003.
5. HPTN 047 NARI Informed Consent Men, Marathi, Version 2.0, 16 August 2002, corrected 06 January 2004
6. HPTN 047 NARI Informed Consent Men, English Back-translation, Version 2.0, 16 August 2002, corrected 06 January 2004.

The above information is provided to all men and women consented for participation in HPTN 047.

Background

Use of a protocol Clarification Memo to make this minor administrative change to the HPTN 047 Informed Consent Forms was granted on 05 February 2004. Melissa Kin at DAIDS Regulatory Affairs Branch (RAB) confirmed with Deborah Webb, Ph.D., Senior Regulatory Compliance Specialist at the DAIDS Regulatory Compliance Center (RCC).

**HIV Prevention Trials Network
PROTOCOL CLARIFICATION MEMORANDUM #4**

**HPTN 047: Phase I Safety and Acceptability Study of the Investigational Vaginal
Microbicide PRO 2000/5 Gel (P)
Version 2.0, August 15, 2002**

**06 January 2004
IND # 56,962 (Indevus Pharmaceuticals, Inc.)**

Summary of Revisions

- Section 3.2.1, sixth bullet, is revised to add text identifying the specifications for study eligibility for women with a positive urine culture at screening.
- Section 5.6.1, fifth bullet, redundant text is deleted.
- Section 5.6.2, first bullet, directions to document pregnancy test results are deleted. There is no study requirement for pregnancy testing at Day 14.
- The Male Partner Marathi Informed Consent (ICF), Version 2.0, August 16, 2002, RISKS AND/OR DISCOMFORTS and DURING THE STUDY sections are corrected to include omitted text and to provide a more accurate translation of information present in the English Male Partner Informed Consent, Version 2.0, August 16, 2002, corrected 05 February 2003.

Implementation

The protocol clarification detailed in this memorandum should be implemented immediately. This clarification does not result in a change in the informed consent being used in the study. If The HPTN 047 protocol is amended in the future, these clarifications will be incorporated into the next version.

The HPTU will submit HPTN 047 Protocol Clarification Memorandum # 4 to all responsible Institutional Review Boards (IRBs). Indevus Pharmaceuticals, Inc. will submit this clarification to the Food and Drug Administration for inclusion in their PRO 2000 Investigational New Drug application, IND #56,962 held by Indevus Pharmaceuticals, Inc

IRB approval of HPTN 047 Protocol Clarification Memorandum # 4 is not required.

Rationale

The purpose of HPTN 047 Protocol Clarification Memorandum # 4 is to:

- Identify the specifications that would allow women with a positive urine culture at the Screening Visit to be eligible for study participation after treatment of the urinary tract infection.
 - Redundant text regarding the urine dipstick and culture clinical procedure from the Day 14 Follow Up Visit is deleted as it appears twice in Section 5.6.1 (the fifth and seventh bullets).
 - Section 5.6.2 text directing the documentation of a pregnancy test result is deleted as it is not a protocol-required test during or at the Day 14 Follow Up Visit.
 - The Male Partner Marathi Informed Consent is revised to better match the Male Partner English, Version 2.0, August 16, 2002, corrected February 5, 2003..
-

The following protocol modifications, indicated by ~~strike through~~ or under score text, made to the HPTN 047 Protocol:

1. In section 3.2.1, sixth bullet:

- Have a positive urine culture

Note: Women who are symptomatic and have a positive urine culture (urinary tract infection - UTI) at screening will be referred for and/or given treatment. Following completion of treatment for the UTI, women with a negative repeat urine dipstick will be eligible for study participation.

2. In section 5.6.1, fifth bullet:

- ~~Collect urine for leukoesterase screen (if symptomatic) and culture if screen positive for WBC's.~~

3. In section 5.6.2, first bullet:

- ~~Record results of urine pregnancy test.~~

4. The following modifications were made to the Male Partner Marathi Informed Consent, Version 2.0, August 16, 2002:

Note: Male partners of female study participants are not enrolled into HPTN 047. Male partners are consented to inform them of the study risks and benefits for the couple, including the possibility of male exposure to PRO 2000/5 Gel (P) and to obtain consent for HIV testing and STI testing, if indicated.

RISKS AND/OR DISCOMFORTS SECTION:

The following text appeared in the Male Partner English Back-translation, Version 2.0, August 16, 2002 but was not present in the Marathi text:

You may feel slight discomfort while your blood sample is being taken. You may perhaps faint. Swelling may occur at the site where the needle will be pierced in the vein. You may feel embarrassed, uneasy or worried while discussing about sexual intercourse or HIV.

DURING THE STUDY SECTION:

The following text was revised to match the Male Partner English, Version 2.0, August 16, 2002, corrected February 5, 2003:

If you and your partner ~~participate~~ take part in this study ~~then~~ your partner will be ~~supplied~~ provided with tubes of Pro 2000 Gel ~~She will have to be used~~ one tube of Gel ~~per day in two applications for 14 days~~ daily in her vagina ~~for two~~ weeks.

Letter of Amendment #2

DATE: 3 November 2003

RE: LETTER OF AMENDMENT FOR HPTN 047, Version 2.0 August 15, 2002

Phase I Safety and Acceptability Study of the
Investigational Vaginal Microbicide PRO 2000/5 Gel (P)
Version 2.0, August 15, 2002
IND # 56,926, Indevus Pharmaceuticals, Inc

TO: Dr. Smita Joshi, Protocol Chair, NARI

CC: Dr. Steve Reynolds, Protocol Co-Chair, JHU

FROM: JoAnn Kuruc, HPTN CORE Protocol Specialist

THE FOLLOWING INFORMATION IMPACTS THE HPTN 047 STUDY AND MUST BE FORWARDED TO YOUR INSTITUTIONAL REVIEW BOARD (IRB)/ETHICS COMMITTEE (EC) AS SOON AS POSSIBLE FOR THEIR INFORMATION AND REVIEW. THIS MUST BE APPROVED BY YOUR IRB/EC BEFORE IMPLEMENTATION.

THE FOLLOWING INFORMATION MAY ALSO IMPACT THE SAMPLE INFORMED CONSENT. YOUR IRB/EC WILL BE RESPONSIBLE FOR DETERMINING THE PROCESS OF INFORMING SUBJECTS OF THE CONTENTS OF THIS LETTER OF AMENDMENT.

PLEASE FILE THIS LETTER AND ANY IRB/EC CORRESPONDENCE IN YOUR REGULATORY FILE AND OTHER PERTINENT FILES. YOU ARE NOT REQUIRED TO SUBMIT THESE DOCUMENTS TO THE PROTOCOL REGISTRATION OFFICE UNLESS THE CHANGES RESULT IN A CHANGE TO THE INFORMED CONSENT FOR YOUR SITE.

Summary of Revisions

- 1. Section 3.0** is revised to add text to better define the study population.
- 2. Sections 3.1.2, and 3.2.2** are revised to rename and reorder the existing terminology for better clarity and to better define the study population that qualifies as low and high risk for HIV infection. The pelvic findings itemized in Section 3.2.2, 4th bullet, are deleted because they are redundant to Section 3.2.1, 7th bullet.
- 3. Section 3.2.3** is revised to rename the section.

4. **Sections 2.3, 5.2.1 and Appendix I** are revised to delete the requirement of the Initial Acceptability Assessment /Questionnaire at the Enrollment Visit.
5. **Table of Contents** revised to rename Sections 3.1.2, 3.2.2, and 3.2.3
6. **The Protocol Team Roster** is updated.
7. **The incorporation of the following HPTN 047 Protocol Clarification Memorandums** (Date of Clarification Memo indicates effective date of the administrative revisions.)
 - Clarification Memo #3, dated 15 September 2003
 - A definition of a normal Pap Smear was added to section 3.1.1
 - Appendix III: Outcomes, Diagnostics and Follow-up Procedures revised to provide instructions for asymptomatic candida vaginitis at Day 2.
 - Clarification Memo #2, dated 30 January 2003
 - The Male Partner English Informed Consent, Version 2.0, August 16, 2002, RISKS AND/OR DISCOMFORTS section is corrected to include omitted text
 - All Female participants and their male partners are consented using the Marathi (local language), Version 2.0 ICF that presently includes this risk statement.
 - Clarification Memo #1, dated 17 October 2002
 - Section 8.5 is revised to include omitted text

Implementation

This Letter of Amendment does not affect the study design or the informed consents being used in the study. If the HPTN 047 protocol is amended in the future, this Letter of Amendment will be incorporated into the next version.

The following protocol modifications, indicated by ~~strikethrough~~ or under-scored text, are made to the HPTN 047 Protocol.

1. **Section 3.0 Study Population, 3rd sentence**

Participants will be selected for this study according to the inclusion and exclusion criteria in Sections 3.1.1 and 3.2.1. Participants will be designated as low risk or high risk for HIV infection based on the definitions found in sections 3.1.2 and 3.2.2.

2. **Sections 3.1.2 and 3.2.2**

3.1.2 **Definition for Female Participants at Higher Risk for HIV Infection**

- ~~In addition to~~ ~~criteria specified in Section 3.1.1, in order to be eligible for inclusion in the study as~~ To be defined as a female participants at higher risk for HIV infection, women must meet at least one the following ~~criteria~~ (based on participant knowledge and self-report):
 - Have been diagnosed and/or treated for an STD (other than HIV) or pelvic inflammatory disease during the three months prior to screening.
 - Have a current male sexual partner who was diagnosed or treated for an STD (other than HIV) in the three months prior to screening.

Note: Potential participants who are diagnosed with an STD at the time of study screening will be treated for the STD. Participants will be encouraged to refer their male partners for diagnosis and

treatment, however partner notification will not be undertaken. Re-screening will be offered to participant after both partners' complete treatment, if applicable

3.2.2 Definition for Female Participants at Low Risk for HIV Infection

- ~~In addition to the exclusion criteria specified in Section 3.2.1, Female participants women will not be defined excluded from the study as at low risk for HIV infection participants~~ if they meet any of the following criteria (based on participant knowledge and self-report):
 - Have been diagnosed and/or treated for an STD (other than HIV) or pelvic inflammatory disease in the three months prior to screening.
 - Have a current male sexual partner who was diagnosed or treated for an STD (other than HIV) in the three months prior to screening.
 - Have a current male sexual partner who has injected non-therapeutic drugs in the three months prior to screening.
 - Have signs, as seen on a pelvic exam or colposcopy, consistent with an STD, other genital tract infection ~~—other than bacterial vaginosis (BV)—~~ or trauma.
 - ~~Vaginitis~~
 - ~~Cervicitis~~
 - ~~Edema~~
 - ~~Erythema~~
 - ~~Ecchymosis~~
 - ~~Petechial hemorrhage~~
 - ~~Vulvar or cervicovaginal lesions, ulcers, abrasions~~
 - ~~Subepithelial hemorrhage and swelling and~~
 - ~~Laboratory findings indicative of genital tract infection other than asymptomatic BV~~

Note: Signs of a asymptomatic BV include the presence of white to grey homogeneous discharge, positive whiff test (amine odor) with addition of KOH, pH >4.5, presence of clue cells, decrease in lactobacilli morphotypes, and increase in non-lactobacilli morphotypes. Women with clinical or gram stain evidence of BV and symptoms (discharge, odor, itching) at screening should be treated and re-evaluated for inclusion in the low risk participants. Women without symptoms, but with clinical or gram stain evidence of BV, or asymptomatic yeast colonization, are eligible as low risk participants.

3. Section 3.2.3 renamed Exclusion Criteria for Male Partners of Female Participants

4. Sections 2.3, 5.2.1 and Appendix I

- In Section 2.3, sixth paragraph:
The acceptability of PRO 2000/5 Gel (P) will be assessed via questionnaires and focus groups. ~~At their study Enrollment Visits, female participants will complete an Initial Acceptability Questionnaire regarding their willingness to try a vaginal microbicide in the future, concerns about vaginal discharge, perceptions of possible partner reactions, and understanding of potential benefits of product use.~~ At Day 14, female participants will complete a Follow-up Acceptability Questionnaire, regarding their perceptions of PRO 2000/5 Gel (P) – including applicator, vehicle, and use-associated factors – and their perceptions of partner reactions that may have influence use and/or sexual episodes. A question regarding willingness to participate in future Phase III trials also will be included.
- Section 5.2.1, 5th bullet:
 - ~~Complete Initial Acceptability Assessment.~~
- Appendix I. Study Activities/Procedures by Visit – Female, 12th procedure:

Activity/Procedure	Screening	Enrollment (Day 0)	Follow-Up (Day 2)	Follow-Up (Day 7)	Follow-Up (Day 14)
Administer Acceptability Assessment		X			X**

5. Table of Contents:

- 3.1.2 Definition for Female Participants at Higher Risk for HIV Infection
- 3.2.2 Definition for Female Participants at Low Risk for HIV Infection
- 3.2.3 Exclusion Criteria for Male Partners of Female Participants

6. In the Protocol Team Roster

Beverly Bell, MBA/MHA
CORE Protocol Specialist (back-up)

JoAnn Kuruc RN, MSN
CORE Protocol Specialist
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7. Incorporation of the following HPTN Clarification Memorandums:

- **Clarification Memo #3, dated 15 September 2003**

In Section 3.1.1, sixth bullet:

- Have a normal Pap smear at screening, or are able to document a normal Pap smear within 3 months prior to screening.

Note: The Bethesda 2001 System for Pap smear designation of Negative for Intraepithelial Lesion or Malignancy will be presumed normal in the presence of reactive cellular changes associated with inflammation or inflammation caused by non STD organisms.

If an ulcerative or non-ulcerative STD is present at screening but the screening Pap results are reported as normal, re-screening will occur after treatment without repeat of the Pap smear.

If an ulcerative or non-ulcerative STD is present at screening and a Pap smear was not done because of a documented normal Pap result within the three months prior to screening, then the Pap smear will be repeated at the time of re-screening.

Appendix III: Outcomes, Diagnostics and Follow-Up Procedures in the Follow-up and Treatment Action section for Vaginitis as it appears in the footnote:

- For asymptomatic candida vaginitis: If a participant has asymptomatic candida vaginitis at the Day 2 or Day 7 Visit she should continue product use and be re-evaluated at the ~~Day 4~~ next scheduled Study Visit

- **Clarification Memo #2, dated 30 January 2003**

NARI English Male Partner Informed Consent Form, Version 2.0, August 16, 2002 as reflected in the corresponding Marathi and English back-translation of the male Version 2.0, August 16, 2002 informed consent forms should include the following text:

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

All Female participants and their male partners will be consented using the Marathi (local language), Version 2.0 ICF that presently includes this risk statement.

- **Clarification Memo #1, dated 17 October 2002**

8.5 Risks

Using a validated HPLC method with a detection limit of 4×10^{-8} g/ml, PRO 2000/5 was not detected in plasma following 14 intravaginal doses of 4% and 0.5% PRO 2000/5 Gel (nonpreserved formulation) in healthy volunteers.

**HIV Prevention Trials Network
PROTOCOL CLARIFICATION MEMORANDUM #3**

**HPTN 047: Phase I Safety and Acceptability Study of the Investigational Vaginal
Microbicide PRO 2000/5 Gel (P)
Version 2.0, August 15, 2002**

**15 September 2003
IND # 56,962 (Indevus Pharmaceuticals, Inc.)**

Summary of Revisions

- A definition for normal Pap Smear has been added.
- Appendix III: Outcomes, Diagnostics and Follow-up Procedures revised to provide instructions for asymptomatic Candida vaginitis at Day 2

Implementation

The protocol clarifications detailed in this memorandum should be implemented immediately. These clarifications do not result in a change in the informed consent being used in the study. If The HPTN 047 protocol is amended in the future, these clarifications will be incorporated into the next version.

The HPTU will submit HPTN 047 Protocol Clarification Memorandum # 3 to all responsible Institutional Review Boards (IRBs). Indevus Pharmaceuticals, Inc. will submit this clarification to the Food and Drug Administration for inclusion in their PRO 2000 Investigational New Drug application, IND #56,962 held by Indevus Pharmaceuticals, Inc

IRB approval of HPTN 047 Protocol Clarification Memorandum # 3 is not required.

Rationale

The purpose of HPTN 047 Protocol Clarification Memorandum # 3 is to:

- Specify the definition of normal Pap smear results
- Add Day 2 follow up and treatment action for asymptomatic Candida vaginitis listed in Appendix III

The following protocol modification, indicated by ~~strike through~~ or under-scored text, is made to the HPTN 047 Protocol:

1. In Section 3.1.1, sixth bullet:

- Have a normal Pap smear at screening, or are able to document a normal Pap smear within 3 months prior to screening.

Note: The Bethesda 2001 System for Pap smear designation of Negative for Intraepithelial Lesion or Malignancy will be presumed normal in the presence of reactive cellular changes associated with inflammation or inflammation caused by non STD organisms.

If an ulcerative or non-ulcerative STD is present at screening but the screening Pap results are reported as normal, re-screening will occur after treatment without repeat of the Pap smear.

If an ulcerative or non-ulcerative STD is present at screening and a Pap smear was not done because of a documented normal Pap result within the three months prior to screening, then the Pap smear will be repeated at the time of re-screening.

2. Appendix III: Outcomes, Diagnostics and Follow-Up Procedures in the Follow-up and Treatment Action section for Vaginitis as it appears in the footnote:

- For asymptomatic Candida vaginitis:
 - If a participant has asymptomatic Candida vaginitis at the Day 2 or Day 7 Visit she should continue product use and be re-evaluated at the ~~Day 14~~ next scheduled Study Visit.

Letter of Amendment #1

DATE: February 24, 2003

RE: LETTER OF AMENDMENT FOR HPTN 047, Version 2.0 August 15, 2002

HPTN 047: Phase I Safety and Acceptability Study of the
Investigational Vaginal Microbicide PRO 2000/5 Gel (P)
Version 2.0, August 15, 2002
IND # 56,926, Indevus Pharmaceuticals, Inc

TO: Dr. Smita Joshi, Protocol Chair, NARI

CC: Dr. Steve Reynolds, Protocol Co-Chair, JHU

FROM: Beverly L. Bell, HPTN CORE Protocol Specialist

THE FOLLOWING INFORMATION IMPACTS THE HPTN 047 STUDY AND MUST BE FORWARDED TO YOUR INSTITUTIONAL REVIEW BOARD (IRB) AS SOON AS POSSIBLE FOR THEIR INFORMATION AND REVIEW. IT MUST BE APPROVED BEFORE IMPLEMENTATION.

THE FOLLOWING INFORMATION MAY ALSO IMPACT THE SAMPLE INFORMED CONSENT. YOUR IRB WILL BE RESPONSIBLE FOR DETERMINING THE PROCESS OF INFORMING SUBJECTS OF THE CONTENTS OF THIS LETTER OF AMENDMENT.

PLEASE FILE THIS LETTER AND ANY IRB CORRESPONDENCE IN YOUR REGULATORY FILE AND OTHER PERTINENT FILES. YOU ARE NOT REQUIRED TO SUBMIT THESE DOCUMENTS TO THE PROTOCOL REGISTRATION OFFICE UNLESS THE CHANGES RESULT IN A CHANGE TO THE INFORMED CONSENT FOR YOUR SITE.

Summary of Revisions

Section 5, Clinical and Laboratory Procedures, Appendices I and II are revised to reflect change to urine PCR assay for *N. gonorrhoeae* and *C. trachomatis* from urine LCR.

The protocol is clarified throughout to specify that chlamydia and gonorrhea testing will be performed using PCR urine (local standard diagnostic methods) rather than by ligase chain reaction (LCR).

Implementation

This clarification does not result in the study design or in the informed consent being used in the study. If the HPTN 047 protocol is amended in the future, this clarification will be incorporated into the next version.

The HPTU will submit this HPTN 047 Protocol Clarification Memorandum to all responsible Institutional Review Boards (IRBs).

IRB approval of this HPTN 047 Protocol Clarification Memorandum is not required. Modifications are indicated by ~~strike through~~ or underscored text

5.1.1 Clinical Procedures (Screening Visit)

- Collect urine for *N. gonorrhoeae* and *C. trachomatis* PCR ~~LCR~~ assay.

5.1.2 Laboratory Procedures (Screening Visit)

- Conduct PRC ~~LCR~~ for *N. gonorrhoeae* and *C. trachomatis*

5.2.1 Clinical Procedures (Enrollment Visit)

- If symptomatic, collect urine for *N. gonorrhoeae* and *C. trachomatis* PCR ~~LCR~~ assay.

In Sections 5.4.1, 5.5.1, 5.6.1. Clinical Procedures (Day 2, Day 7 and Day 14)

- If abnormal vaginal discharge or purulent cervicitis is noted, collect urine for *N. gonorrhoeae* and *C. trachomatis* PCR ~~LCR~~ assay

In Sections 5.2.2, 5.4.2, 5.5.2 and 5.6.2, Laboratory Procedures (Enrollment, Day 2, Day 7 and Day 14)

- Conduct PCR ~~LCR~~ for *N. gonorrhoeae* and *C. trachomatis* if symptomatic.

Appendix I.

Collect urine for *N. gonorrhoeae* and *C. trachomatis* PCR ~~LCR~~***

Appendix II. Laboratory Evaluations

GC/CT PCR ~~LCR~~

HIV Prevention Trials Network

PROTOCOL CLARIFICATION MEMORANDUM #2

**HPTN 047: Phase I Safety and Acceptability Study of the
Investigational Vaginal Microbicide PRO 2000/5 Gel (P)
Version 2.0, August 15, 2002**

January 30, 2003

IND # 56,962 (Indevus Pharmaceuticals, Inc.)

Summary of Revisions

- The Male Partner English Informed Consent Form (ICF), Version 2.0, August 16, 2002, RISKS AND/OR DISCOMFORTS section is corrected by this memo to include the following text:

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

All Female participants and their male partners will be consented using the Marathi (local language) informed consent forms that presently include this risk statement.

Implementation

The protocol clarification detailed in this memorandum should be implemented immediately. This clarification does not result in a change in the informed consent being used in the study to actually consent male partners of female participants. If the HPTN 047 protocol is amended in the future, this clarification will be incorporated into the next version.

The HPTU will submit HPTN 047 Protocol Clarification Memorandum #2 to all responsible Institutional Review Boards (IRBs). Indevus Pharmaceuticals, Inc. will submit this clarification to the Food and Drug Administration for inclusion in their PRO 2000 Investigational New Drug application, IND # 56,962 held by Indevus Pharmaceuticals, Inc.

IRB approval of HPTN 047 Protocol Clarification Memorandum #2 is not required. Informed consent modifications are indicated by ~~striketrough~~ or underscored text.

Rationale

NARI English Male Partner Informed Consent Form, Version 2.0, August 16, 2002 as reflected in the corresponding Marathi and English back-translation of the male Version 2.0, August 16, 2002 informed consent forms should include the following text:

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

This text was inadvertently left out of the NARI English ICF Version 2.0, August 16, 2002.

All Female participants and their male partners will be consented using the Marathi (local language), Version 2.0 ICF that presently include this risk statement.

Background Information

HPTN 047 will be implemented under Protocol Version 2.0, August 15, 2002.

As this omission of this text was the result of an isolated document processing error occurring only in the NARI Male Partner English Version 2.0 ICF, this risk statement does appear in the Male Partner ICF Version 2.0, August 16, 2002, Marathi and English back-translation.

HIV Prevention Trials Network

PROTOCOL CLARIFICATION MEMORANDUM #1

**HPTN 047: Phase I Safety and Acceptability Study of the
Investigational Vaginal Microbicide PRO 2000/5 Gel (P)**

17 October 2002

IND # 56,962

Summary of Revisions

- Section 8.5 is revised to include omitted text. The second paragraph, last sentence should read:

“Using a validated HPLC method with a detection limit of 4×10^{-8} g/mL, PRO 2000/5 was not detected in plasma following 14 intravaginal doses of 4% and 0.5% PRO 2000/5 Gel (nonpreserved formulation) in healthy volunteers.”

The purpose of HPTN 047 Protocol Clarification Memorandum #1 is to revise HPTN 047, Version 2.0, Section 8.5. Previously this sentence did not include the – (negative sign) in the exponent for the number 10.

Implementation

The protocol clarification detailed in this memorandum should be implemented immediately. This clarification does not result in a change in the informed consent. If the HPTN 047 protocol is amended in the future, this clarification will be incorporated into the next version.

The HPTU will submit HPTN 047 Protocol Clarification Memorandum #1 to all responsible Institutional Review Boards (IRBs). Indevus Pharmaceuticals, Inc. will submit this clarification to the Food and Drug Administration for inclusion in their PRO 2000 Investigational New Drug application, IND # 56,962.

IRB approval of HPTN 047 Protocol Clarification Memorandum #1 is not required. Protocol modifications are indicated by ~~striketrough~~ or underscored text.

8.5 Risks

Using a validated HPLC method with a detection limit of 4×10^{-8} g/mL, PRO 2000/5 was not detected in plasma following 14 intravaginal doses of 4% and 0.5% PRO 2000/5 Gel (nonpreserved formulation) in healthy volunteers.

HPTN 047
Phase I Safety and Acceptability Study of the
Investigational Vaginal Microbicide PRO 2000/5 Gel (P)

A Study of the HIV Prevention Trials Network

Sponsored by:

Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institute of Child Health and Human Development
US National Institute on Drug Abuse
US National Institute of Mental Health
US National Institutes of Health

Co-Sponsored by:

Indevus (formerly Interneuron) Pharmaceuticals, Inc.

IND # 56,962

Protocol Chair:

Dr. Smita N. Joshi
National AIDS Research Institute
Pune, India

Protocol Co-Chair:

Dr. Steven J. Reynolds
Johns Hopkins School of Medicine
Baltimore, MD, USA

Final Version 2.0
August 15, 2002

HPTN 047
Phase I Safety and Acceptability Study of the
Investigational Vaginal Microbicide PRO 2000/5 Gel (P)

A Study of the HIV Prevention Trials Network

Sponsored by:

Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institute of Child Health and Human Development
US National Institute on Drug Abuse
US National Institute of Mental Health
US National Institutes of Health

Co-sponsored by:
Indevus Pharmaceuticals, Inc.

HPTN 047 Investigator Agreement:

I, the 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 Declaration of Helsinki and 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 from the date of US FDA marketing approval for the study product for the indication in which it was studied. If no marketing approval is filed, or if the application is not approved, the records must be retained for two years after the FDA is notified that the IND is discontinued. Unless directed otherwise by the HIV Prevention Trials Network (HPTN) Coordinating and Operations Center (CORE). Publication of the results of this study will be governed by HPTN and DAIDS policies. Any presentation, abstract, or manuscript will be made available by the investigators to the HPTN Manuscript Review Committee and DAIDS for review prior to submission.

I have read and understand the information in this protocol and 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.

Signature of Principal Investigator

Date

Signature of Co-Principal Investigator

Date

**Phase I Safety and Acceptability Study of the
Investigational Vaginal Microbicide PRO 2000/5 Gel (P)**

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ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	Acquired immune deficiency syndrome
APTT	activated partial thromboplastin time
BV	bacterial vaginosis
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CL	(HPTN) Central Laboratory
CORE	(HPTN) Coordinating and Operations Center
DAIDS	Division of AIDS
DCGI	Drug Controller General of India
EC	ethics committee
EIA	enzyme immunoassay
FDA	(United States) Food and Drug Administration
FTA-ABS	fluorescent treponemal antibody absorption
HCG	human chorionic gonadotropin
HIV, HIV-1, HIV-2	Human Immunodeficiency Virus, type 1 and type 2
HPTN	HIV Prevention Trials Network
HSV	Herpes simplex virus
HSV-2	herpes simplex virus - type 2
IRB	institutional review board
LL	local laboratory
M _n	number-average molecular weight
M _w	weight-average molecular weight
NIAID	National Institute of Allergy and Infectious Diseases
M-PCR	Multiplex polymerase chain reaction
NIH	National Institutes of Health
PCR	polymerase chain reaction
PT	prothrombin time
RPR	rapid plasma reagin
SAE	serious adverse experience
SDMC	(HPTN) Statistical and Data Management Center
SHIV	Simian/Human Immunodeficiency Virus
STD	sexually transmitted disease
TP/HA	microhemagglutination assay for <i>Treponema pallidum</i>
WBC	White blood cells
w/w	weight/weight

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HPTN 047
Phase I Safety and Acceptability Study of the
Investigational Vaginal Microbicide PRO 2000/5 Gel (P)

SCHEMA

Purpose: To assess the safety of repeated intravaginal doses of 0.5% PRO 2000/5 Gel (P) for 14 consecutive days between menses among sexually active HIV-uninfected women from Pune, India; to assess the acceptability of 0.5% PRO 2000/5 Gel (P) among sexually active HIV-uninfected women and men from Pune, India.

Design: Phase I open-label study with 14 days of twice daily application of 0.5% PRO 2000/5 Gel (P) and follow-up for each female participant. Safety will be assessed via pelvic exam with colposcopy; acceptability will be assessed via standardized questionnaires and focus groups.

Study Population: HIV-uninfected sexually active women from Pune, India at low and higher risk for HIV infection; HIV-uninfected male partners of female participants.

Study Size: 60 HIV-uninfected women (30 low risk and 30 higher risk) and 60 HIV-uninfected male partners.

Treatment Regimen: Twice daily intravaginal application of 0.5% PRO 2000/5 Gel (P) for 14 consecutive days.

Study Duration: Accrual will require four months. Each participant female will be followed for 14 days of product use. Focus groups will be convened within approximately four weeks after the completion of product use and follow-up. Therefore the entire study should be completed within six months.

Primary Objective:

- To assess the safety of 0.5% PRO 2000/5 Gel (P) when administered twice daily for 14 consecutive days on the vulvar and cervicovaginal mucosa of sexually active HIV-uninfected women in Pune, India.

Secondary Objectives:

- To assess the acceptability of, and adherence to, a short-term regimen of 0.5% PRO 2000/5 Gel (P) among HIV-uninfected women in Pune, India.
- To evaluate aspects of product acceptability among HIV-uninfected women and men in Pune, India.
- To assess the feasibility of enrolling HIV-uninfected women at higher risk for HIV infection from Pune, India, into future Phase III vaginal microbicide trials.
- To assess the effect of a twice daily short-term regimen of 0.5% PRO 2000/5 Gel (P) on the vaginal microflora of sexually active HIV-uninfected women in Pune, India.

Study Site:

- Pune, India

1.0 Introduction

1.1 Background

The Joint United Nations Programme on HIV/AIDS recently estimated that 40 million adults and children were living with HIV/AIDS at the end of 2001, and that about 14,000 new infections are occurring each day [1]. The majority of new infections are transmitted through heterosexual contact. As such, there is a clear need for new technologies to prevent the sexual transmission of HIV. Correct and consistent male condom use has been shown to prevent HIV transmission [2], but women often are unable to negotiate the use of condoms by their male partners [3-5]. The female condom has been marketed as an alternative barrier method [4], but this device is relatively costly and requires a certain level of skill and acceptance by the male partner.

Topical microbicides are products designed to prevent the sexual transmission of HIV and other disease pathogens [3-6]. Potentially, they can be applied vaginally to prevent both male-to-female and female-to-male transmission. They also offer a female-controlled option in cases where male condom use cannot be negotiated. Several marketed chemical spermicides, which have shown some activity against HIV and sexually transmitted disease (STD) pathogens in vitro, have been evaluated as topical microbicides. Most notable among these is nonoxynol-9, which has been evaluated in several different doses and formulations. However, no clinical studies have yet demonstrated that these detergent-based products can prevent HIV infection; nonoxynol-9 products have been shown to cause mucosal erosion and ulceration in a dose-dependent manner [7-8]; and preliminary results of a large-scale clinical trial presented at the XIII International AIDS Conference suggested that use of nonoxynol-9 gel afforded no protection against STDs or HIV, and may even be associated with an increased risk of HIV infection [9].

Particularly in light of the most recent findings with respect to the effects of nonoxynol-9 products, increasing attention has been given to developing non-detergent topical microbicides to prevent HIV infection. One such investigational product is PRO 2000/5 Gel (P), which is being developed by Indevus Pharmaceuticals, Inc. The active ingredient, PRO 2000/5, is a naphthalene sulfonic acid-formaldehyde copolymer with an average molecular weight of 5 kD. The compound is straightforward to manufacture, highly stable, and highly water-soluble. PRO 2000/5 Gel (P) is an aqueous gel formulation of PRO 2000/5 containing a synthetic carbomer, a lactic acid/lactate buffer (pH 4.5), and a combination of common preservatives (indicated by the "(P)" suffix).

1.2 Prior Research

1.2.1 Pre-Clinical Research

In vitro, PRO 2000/5 has been shown to suppress infection by a wide range of HIV-1 isolates [10, 11], apparently by inhibiting viral entry into susceptible cells. PRO 2000/5 is also active in vitro against certain other STD pathogens, including herpes viruses, *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Vaginally applied PRO 2000/5 Gel (P) at concentrations as low as 0.5% was shown to inhibit vaginal simian/human immunodeficiency virus (SHIV) infection in macaques and vaginal herpes simplex virus type 2 (HSV-2) infection in mice [12]. Though not spermicidal, PRO 2000/5 Gel (P) has been shown to be contraceptive in rabbits.

Gels containing up to 4% PRO 2000/5 were well-tolerated in rabbit models for vaginal, penile and ocular irritation. In repeat-dose intravaginal toxicity studies, concentrations up to 4% were reasonably well tolerated for six months in rats and four-and-a-half months in rabbits. No adverse effects were associated with exposure to 0.5% PRO 2000/5 Gel (P) in either species, though the 2% and 4% concentrations were associated with microscopic signs of vaginal irritation in both. Excess mortality was seen in rabbits treated with 4% PRO 2000/5 Gel (P), though some of the deaths were judged to be unrelated to PRO 2000/5 exposure. The relatedness of the others has not yet been determined.

In a small dose-ranging study in dogs, daily intravaginal administration of 2% and 4% PRO 2000/5 Gel (P) for 10 days was associated with microscopic inflammation and ulceration of cervicovaginal (though not uterine) tissue. In pig-tailed macaques, multiple intravaginal doses of 0.5% PRO 2000/5 Gel (P) produced no evidence of genital irritation, whereas cervical and vaginal abnormalities, including epithelial disruption, were observed colposcopically in animals exposed to 2% and 4% PRO 2000/5 Gel (P). The relevance of these findings to human use is unclear. PRO 2000/5 was found to be nonmutagenic in a standard battery of genotoxicity tests, and 4% PRO 2000/5 Gel (P) had no effect on embryo/fetal development in rats or rabbits.

No systemic absorption was detected in two rabbit studies following up to 14 intravaginal doses of 4% PRO 2000/5 Gel (P). Likewise, there was no indication of systemic absorption or toxicity in dogs treated with ten doses of 2% or 4% PRO 2000/5 Gel (P), despite microscopic evidence for cervicovaginal inflammation and ulceration. Low levels of PRO 2000/5 were detected in plasma samples collected from pregnant rats after twelve intravaginal gel applications. PRO 2000/5 at concentrations up to 4% had no effect on the growth of vaginal lactobacilli. Intravenous administration

of PRO 2000/5 to laboratory animals and humans produced toxicological effects typical of polyanions, including reversible coagulopathy, leukocytosis, thrombocytopenia and liver and kidney pathology. 4% PRO 2000/5 Gel (P) was shown not to degrade latex condoms.

1.2.2 Clinical Research

Phase I clinical trials to evaluate the safety and tolerance of intravaginal PRO 2000/5 Gel (P) in healthy, sexually abstinent volunteers were conducted in Antwerp, Belgium and London, England [13]. In these randomized, double-blind, placebo-controlled studies, a total of 73 women were enrolled across both sites and asked to apply placebo (N=25), 0.5% (N=24) or 4% (N=24) PRO 2000/5 Gel (P) intravaginally once per day for two weeks between menses. Sterile, preservative-free gels were used in these trials.

All women enrolled in the placebo and 0.5% groups completed two-weeks of dosing. Three women in the 4% group withdrew because of, respectively: (1) vaginal burning and gastrointestinal symptoms, (2) vulvar ulcers (not evaluated for HSV), genital irritation and gastrointestinal symptoms, and (3) intermenstrual bleeding (28 months after discontinuation, this subject was diagnosed with invasive cervical carcinoma judged unrelated to product use).

No serious adverse events were reported during either trial. Cervical abrasion was observed colposcopically in 3 subjects (2 in the 4% group and 1 in the placebo group) after 14 days of product use, while cervicovaginal ulceration was not seen in any subject during product use. Intermenstrual bleeding (usually "spotting") was reported by participants across all dose groups, and usually resolved with continued dosing. Histological evaluation of vaginal biopsies showed mild or moderate inflammatory cell infiltration in 5/36 baseline and 5/35 post-treatment samples (London cohort only); 4 participants (2 in the 4% group and 2 in the placebo group) showed treatment-emergent increases in these inflammatory signs. Neither laboratory safety tests or nor direct analysis of plasma drug levels showed evidence for systemic absorption of PRO 2000/5. Microscopic evaluation of vaginal swab specimens collected 12 hours after the last gel application indicated that product use had no impact on the normal vaginal ecology (London cohort only). Discharge due to gel expulsion was common across all dose groups. Overall, PRO 2000/5 Gel (P), at both concentrations, was found to be generally well tolerated, with promising local and systemic safety profiles. There were fewer genital adverse events in the placebo and 0.5% groups than in the 4% group.

A subsequent Phase I clinical trial was conducted within the HIV Prevention Trials Network to evaluate the safety, tolerance and acceptability of PRO 2000/5 Gel (P) in healthy, sexually active women at low-risk for HIV/STD infection and asymptomatic, sexually abstinent, HIV-infected women. The study was conducted at two sites in South Africa (Durban and Johannesburg) and two in the United States (Providence, RI and Philadelphia, PA).

In the first part of this open-label study, successive cohorts of about 12 healthy, HIV-uninfected women at low-risk for HIV/STD infection were asked to apply 2% or 4% PRO 2000/5 Gel (P) intravaginally once or twice daily for 14 consecutive days between menses. These participants agreed to engage in vaginal intercourse at least two times per week with a single, monogamous male partner using non-spermicidally lubricated or unlubricated male condoms.

Following interim analysis of the preliminary safety data from these cohorts, a Safety Review Committee determined the highest tolerated dose and dose frequency [4% PRO 2000/5 Gel (P) twice daily], which was then evaluated in a cohort of asymptomatic, HIV-infected women who were sexually abstinent over the two-week dosing period. Subjects underwent baseline pelvic, colposcopic, and laboratory exams, and were re-examined after 7 and 14 days of product use. Acceptability assessments were also performed at baseline and follow-up.

A total of 50 HIV-uninfected and 13 HIV-infected volunteers were enrolled in the study. The product was well tolerated by both populations: no serious adverse events were reported, and 100 percent of the women responding to a post-study questionnaire indicated they would be willing to use the product again if it were shown to protect against HIV.

Four women discontinued product use because of (1) HSV cervicitis, (2) inappropriate enrollment (pregnancy), (3) urinary tract infection, and (4) vulvovaginal erythema and cervicovaginal abrasions. In the course of the study, 73 percent of the women reported adverse events that could have been product-related, with 60 percent of the women reporting only mild events and 13 percent reporting moderate events. Colposcopy was abnormal in 38 percent of the subjects, with abrasion (16 percent), erythema (16 percent), or ulceration (11 percent) being most common findings. These findings were usually mild and resolved during or shortly after discontinuation of product use. Half of the epithelial disruption findings were linked to possible applicator or speculum trauma, sexual activity, or HSV infection; all ulceration findings occurred in the twice daily frequency groups.

Other common, but transient, adverse events included vaginal discharge (27 percent) or bleeding (25 percent), which was usually spotting that stopped while product use continued, burning (16 percent), or irritation (14 percent). One participant showed clinically silent elevations in bilirubin and liver function test values, but no other clinically significant changes in laboratory safety parameters were observed. Differences in PRO 2000/5 concentration, frequency of use, or HIV status, did not appear to be associated with differences in the prevalence of adverse events. Overall, PRO 2000/5 Gel (P) at concentrations up to 4% administered twice daily was judged to be safe and well tolerated in the two study populations.

In a Phase I penile safety study, HIV-uninfected men applied either 4% PRO 2000/5 Gel (P) (n=24) or a gel containing the inactive ingredients of PRO 2000/5 Gel (P) (n=12) to the penis for seven consecutive days. About one in six users of both gels reported mild transient symptoms of genital itching, tingling, irritation, or abrasion. Additional users of both gels reported dryness or flaking of the dried gel. Preliminary findings from a similar Phase I clinical trial in HIV-1 seropositive men were comparable. PRO 2000/5 Gel (P) is not expected to have significant adverse effects on the partners of study participants, should they be exposed to the gels while having sexual intercourse with participants in the absence of a condom.

1.3 Rationale

The International Working Group for Microbicides recommends that candidate vaginal microbicides be evaluated for safety, tolerance and acceptability in populations with different characteristics [6]. This Phase I study serves that purpose, in that it will complement other clinical studies conducted to date by assessing twice daily intravaginal application of 0.5% PRO 2000/5 Gel (P) among sexually active HIV-uninfected women at both low and high risk for HIV infection in Pune, India.

In addition, this study represents a critical step in the clinical development pathway for PRO 2000/5 Gel (P). Given the favorable pre-clinical and clinical profile of PRO 2000/5 Gel (P), the HIV Prevention Trials Network (HPTN) is planning a large-scale Phase II/III trial of PRO 2000/5 Gel (P), to begin in 2003. As currently planned, this Phase II/III study will include thousands of sexually active women at risk for HIV infection in India, Malawi, South Africa, Tanzania, the United States, Zambia and Zimbabwe. Based on the available pre-clinical and clinical safety data, and the results of macaque protection studies, the 0.5% strength has been selected for testing in this study.

In order for Indian women to take part in the Phase II/III study, the Drug Controller General of India (DCGI) and the local Ethics Committee (EC), require that the safety of the investigational product first be established in a Phase I study conducted among Indian women representative of the women who will be included in the Phase II/III study. Since the Phase II/III study will enroll sexually active women who may or may not be characterized by often-cited epidemiologic and/or behavioral risk factors for HIV (e.g., commercial sex work), the Indian regulatory authorities require that a Phase I study be conducted among women at both “low” and “higher” risk for HIV infection. This study meets that regulatory requirement and, in so doing, will extend the safety and acceptability profile of PRO 2000/5 Gel (P) to higher risk women. The study therefore will provide insights for the design and implementation of the Phase II/III study that are not available from prior clinical research studies.

2.0 Study Objectives and Design

2.1 Primary Objective

The primary objective of this study is to assess the safety of 0.5% PRO 2000/5 Gel (P) when administered twice daily for 14 consecutive days on the vulvar and cervicovaginal mucosa of sexually active HIV-uninfected women in Pune, India.

2.2 Secondary Objectives

The secondary objectives of this study are:

- To assess the acceptability of, and adherence to, a short-term regimen of 0.5% PRO 2000/5 (P) Gel among HIV-uninfected women in Pune, India.
- To evaluate aspects of product acceptability among HIV-uninfected women and men in Pune, India.
- To assess the feasibility of enrolling HIV-uninfected women at higher risk for HIV infection from Pune, India, into future Phase III vaginal microbicide trials; and
- To assess the effect of a twice daily short-term regimen of 0.5% PRO 2000/5 Gel (P) on the vaginal microflora of sexually active HIV-uninfected women in Pune, India.

2.3 Study Design

This is an open-label Phase I study of 0.5% PRO 2000/5 Gel (P) to be conducted among 60 HIV-uninfected sexually active women from Pune, India. The male partners of these women also will be enrolled in the study. Half of the female participants will be at low risk for HIV infection; the other half will be at higher risk (see Sections 3.1.2 and 3.2.2 for definitions of low and higher risk). Both low and higher risk participants will apply 0.5% PRO 2000/5 Gel (P) twice daily for 14 consecutive days between menses, and agree to have vaginal intercourse with a single male partner, using study-provided male condoms, at least twice per week during the two weeks of product application.

After providing written informed consent, female participants will undergo eligibility screening, including medical history, pelvic exam, Pap smear (if there is no documented normal Pap in the past three months), urine pregnancy testing, HIV and 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 2-7 days after the participant's next menstrual period, but within 30 days of initial screening. In addition, the participant's male sexual partner will be informed of the study and its requirements of him, asked to

provide written informed consent to take part, and be screened for eligibility. Female participants whose male partners are not willing to provide written informed consent, or are not found to be eligible, will not be eligible to take part in the study. Female participants in a previous microbicide study in Pune indicated that they would not participate without the knowledge of their male partners due to concerns over domestic violence.

At their Enrollment Visits, female participants will be provided their screening test results. Presumptively-eligible participants will undergo a pelvic exam with colposcopy, and urine pregnancy testing to confirm their eligibility. Hematology, coagulation, and liver and renal function testing will be performed, and plasma will be collected and stored for batch testing for PRO 2000/5 drug levels at the end of the study. In addition, participants will be provided with:

- Supplies of 0.5% PRO 2000/5 Gel (P), applicators, panty liners, and male condoms;
- Daily Study Records on which to record the date and time of product applications and episodes of vaginal intercourse, as well as any symptoms experienced;
- instructions for product application and Daily Study Record completion; and
- instructions to contact or return to the study site in the event of discomfort, discolored or malodorous discharge, or other adverse events (AEs; see also Section 6).

After completing two days of product application, participants will complete a study Follow-up Visit (on Day 2) during which their Daily Study Records will be reviewed — to assess adherence to the product use regimen and ascertain whether any adverse events have occurred — and a pelvic exam with colposcopy will be performed. A similar visit will be conducted after five to nine days of twice daily product application, (target Day 7) with the exception that colposcopy will be performed only if abnormalities are observed on speculum exam. Every effort will be made to bring participants back for this visit after day six to ensure adequate exposure to product. Then, after completing 12 to 14 days of twice daily product application, participants will complete a final study follow-up visit (target Day 14) during which their Daily Study Records again will be reviewed and a pelvic exam with colposcopy will be performed. Hematology, coagulation, and liver and renal function testing also will be performed, and plasma will be collected and stored for batch testing for PRO 2000/5 (P) drug levels at the end of the study.

At any of the study follow-up visits, or at any additional ad hoc visits initiated by participants between scheduled visits, abnormalities noted on pelvic exam will be evaluated and followed according to Appendix III; clinical decision-making regarding

continued/discontinued use of PRO 2000/5 Gel (P) also will be guided by Appendix III.

The acceptability of PRO 2000/5 Gel (P) will be assessed via questionnaires and focus groups. At their study Enrollment Visits, female participants will complete an Initial Acceptability Questionnaire regarding their willingness to try a vaginal microbicide in the future, concerns about vaginal discharge, perceptions of possible partner reactions, and understanding of potential benefits of product use. At Day 14, female participants will complete a Follow-up Acceptability Questionnaire, regarding their perceptions of PRO 2000/5 Gel (P) — including applicator, vehicle, and use-associated factors — and their perceptions of partner reactions that may have influenced use and/or sexual episodes. A question regarding willingness to participate in future Phase III trials also will be included.

Focus groups will be conducted among female participants within approximately four weeks after completing product use, to elicit information on product acceptability and considerations for product use that may not emerge through individual questionnaires. Willingness to participate in the focus group discussions is not required, however every effort will be made to obtain feedback from the participants. All participants will be asked individually regarding their interest and any possible concerns they may have with taking part in the groups. Participants may choose to participate in a one-on-one session rather than a group session, discuss their feelings with the interviewer by telephone, or complete a detailed questionnaire.

Approximately concurrent with the female participants' focus groups, the participants' male partners will be invited to take part in focus groups to elicit their perceptions of the study product and considerations for product use. It is assumed that the presence of the study product will not go unnoticed by the male partners, therefore their perceptions of the product will be valuable in future microbicide development.

3.0 Study Population

Sixty HIV-uninfected, sexually active women — 30 at low risk for HIV infection and 30 at higher risk for HIV infection — from Pune, India, will be enrolled in this study. In addition, the single male sexual partner of female participants will be asked to provide informed consent for the study and will be invited to take part in study focus groups. Participants will be selected for this study according to the criteria in Sections 3.1 and 3.2. They will be recruited as described in Section 3.3. Conditions for withdrawal from the study are described in Section 3.4

3.1 Inclusion Criteria

3.1.1 All Female Participants

Women who meet all of the following criteria (by self-report, unless otherwise specified) are eligible for inclusion in this study:

- Age 18-45 years.
- Able and willing to provide written informed consent to take part in the study.
- HIV-uninfected by licensed enzyme immunoassay (EIA).
- Have a regular menstrual cycle with a minimum of 21 days between menses, or are amenorrheic due to long-acting progestin use.
- Have had no change in hormonal contraceptive use in the three months prior to screening and agree to continue use of their preferred contraceptive method while in the study, provided these methods are not listed below as exclusionary methods.
- Have a normal Pap smear at screening, or are able to document a normal Pap smear within three months prior to screening.
- Are sexually active with a single male sexual partner who is eligible for this study per Section 3.1.3 and 3.2.3 below.
- Agree to abstain from sexual intercourse beginning 48 hours prior to the Enrollment Visit.
- Able and willing to complete Daily Study Records.
- Agree for the duration of the study to:
 - apply 0.5% PRO 2000/5 Gel (P) as required per protocol;
 - have vaginal intercourse only with the single male sexual partner who is eligible for this study per Section 3.1.3 and 3.2.3 below;
 - have vaginal intercourse at least two times per week while taking part in the study;
 - use study-provided condoms for each act of vaginal intercourse while taking part in the study;
 - agree for the duration of the study to abstain from:
 - insertion of fingers and other objects into the vagina
 - receiving oral sex
 - receiving anal sex
 - using a female condom, diaphragm, or cervical cap
 - using any vaginal product other than 0.5% PRO 2000/5 Gel (P), including lubricants, desiccants, or feminine hygiene products
 - douching
 - participating in other vaginal microbicide or contraceptive studies while taking part in this study; and
 - using non-therapeutic intravenous drugs.

3.1.2 Female Participants at Higher Risk for HIV Infection

In addition to the criteria specified in Section 3.1.1, in order to be eligible for inclusion in the study as participants at **higher risk** for HIV infection, women must meet at least one the following criteria (based on participant knowledge and self-report):

- Have been diagnosed and/or treated for an STD (other than HIV) during the three months prior to screening.
- Have a current male sexual partner who was diagnosed or treated for an STD (other than HIV) in the three months prior to screening.

Note: Potential participants who are diagnosed with an STD at the time of study screening will be treated for the STD. Participants will be encouraged to refer their male partners for diagnosis and treatment, however partner notification will not be undertaken. Re-screening will be offered to participants after both partners complete treatment, if applicable.

3.1.3 Inclusion Criteria for Male Partners of Female Participants

Male sexual partners of female study participants who meet all of the following criteria (by self-report, unless otherwise specified) are eligible for inclusion in this study:

- Age 18 years or older.
- Able and willing to provide written informed consent, in person, to take part in the study.
- HIV-uninfected by licensed EIA.
- Free of STD symptoms at enrollment.
- Agree to abstain from sexual intercourse beginning 48 hours prior to the Enrollment Visit.
- Able and willing to have vaginal intercourse with their partner who is taking part in the study at least two times per week.
- Agree for the duration of the study (14 days) to:
 - have vaginal intercourse only with the female study participant;
 - have vaginal intercourse with the female study participant at the usual frequency of at least two episodes per week;
 - use study-provided male condoms for each act of vaginal intercourse.

Note: Male partners who report STD symptoms at the time of screening will be offered an exam and clinically appropriate STD work-up. Those who are diagnosed with an STD will be treated, as will their female partners, based on the findings of their own screening and enrollment work-ups. Both the female participant and the male partner will be eligible for re-screening after treatment is completed. If the male partner refuses treatment of an STD, the female partner will not be eligible for participation in the study.

Since each partner will be screened and given his/her test results, no partner notification is required.

3.2 Exclusion Criteria

3.2.1 All Female Participants

Women who meet any of the following criteria by self-report at screening or enrollment, unless otherwise specified, will be excluded from this study:

Note: Women with observed abnormalities as described below will be referred for appropriate clinical follow-up and/or treatment. Since all potential participants are eligible for India's national health service, further clinical care will be provided at no cost to the participant.

- Are menopausal.
- Are currently breastfeeding.
- Are currently using, or within the year prior to screening have used, non-therapeutic intravenous drugs.
- Are pregnant (based on a urine pregnancy test).
- Have one or more grade 3 or higher liver, renal, or hematology abnormalities, as defined by the Division of AIDS (DAIDS) Toxicity Tables at screening.
- Have a positive urine culture.
- Have a clinically detectable genital abnormality (i.e., vulvar, vaginal, cervical and/or perianal ulcer and/or lesion).
- Have a history of adverse reaction to anticoagulant(s).
- Have a history of sensitivity/allergy to latex.
- Have used any spermicide or spermicidally lubricated condom within the past week (prior to enrollment).
- Have participated in any other investigational drug trial within 30 days prior to screening .
- In the three months prior to screening have (any of the following):
 - used an intrauterine contraceptive device,
 - had an abnormal Pap smear,
 - been pregnant,
 - had gynecologic surgery,
 - had breakthrough menstrual bleeding, or
 - had vaginal bleeding during or following sexual intercourse.

3.2.2 Female Participants at Low Risk for HIV Infection

In addition to the exclusion criteria specified in Section 3.2.1, women will be excluded from the study as **low risk** participants if they meet any of the following criteria (based on participant knowledge and self-report):

- Have been diagnosed and/or treated for an STD (other than HIV) or pelvic inflammatory disease in the three months prior to screening.
- Have a current male sexual partner who was diagnosed or treated for an STD (other than HIV) in the three months prior to screening.
- Have a current male sexual partner who has injected non-therapeutic drugs in the three months prior to screening.
- Have signs, as seen on pelvic exam, consistent with an STD, other genital tract infection — other than bacterial vaginosis (BV) — or trauma, including:
 - vaginitis,
 - cervicitis,
 - edema,
 - erythema,
 - ecchymosis,
 - petechial hemorrhage,
 - vulvar or cervicovaginal lesions, ulcers, or abrasions,
 - subepithelial hemorrhage and swelling, and
 - laboratory findings indicative of genital tract infection other than asymptomatic BV.

Note: Signs of asymptomatic BV include the presence of white to grey homogeneous discharge, positive whiff test (amine odor) with addition of KOH, pH>4.5, presence of clue cells, decrease in lactobacilli morphotypes, and increase in non-lactobacilli morphotypes. Women with clinical or gram stain evidence of BV and symptoms (discharge, odor, itching) at screening should be treated and re-evaluated for inclusion as low risk participants. Women without symptoms, but with clinical or gram stain evidence of BV, or asymptomatic yeast colonization, are eligible as low risk participants.

3.2.3 Male Participants

Men who meet any of the following criteria by self-report at screening or enrollment will be excluded from this study:

- Have history of adverse reaction to latex
- Refuse examination and/or treatment for an STD or STD symptoms

3.3 Participant Recruitment

The study will be conducted at Jehangir Hospital and Medical Center. However study participants will be recruited from three other clinical settings affiliated with the HIV Prevention Trials Unit in Pune, India. Specifically, the National AIDS Research Institute (NARI) has established clinical settings to collaborate with the HPTN, as follows:

- the RTI Clinic attached to the Gynecology Outpatient Department of the Sassoon Hospital, attended by female gynecology patients;
- the Skin and Venereal Disease Departments of the Sassoon Hospital, attended by male and female STD patients;
- the Gadikhana Clinic, attended primarily by male and female STD patients.

Note: The Sassoon Hospital is a large referral hospital with an extensive catchment area affiliated with the BJ Medical College.

Men and women attending any of the above clinics routinely are offered HIV and STD screening. Those who provide written informed consent for screening are tested, and those who test positive for treatable STDs are provided treatment according to the US Centers for Disease Control and Prevention (CDC) guidelines. To date, HIV-uninfected persons have been offered enrollment in a long-term follow-up study of HIV incidence. When HPTN 047 opens, HIV-uninfected women also will be invited to screen for this study (co-enrollment in the long-term follow-up study will not be precluded). Low risk participants will be recruited primarily from the RTI Clinic, however eligible low and higher risk participants will be accepted from all locations. For higher risk participants, in addition to direct outreach to female participants, HIV-uninfected males diagnosed with an STD will be informed of the study and invited to refer their female partners for screening.

Although it is expected that recruitment from the three locations listed above will fulfill the study enrollment goals in a timely manner, additional capacity also may be provided through collaboration and recruitment at three other clinics that NARI operates in Pune. Patients are referred to these clinics from all over Pune as well as from other nearby cities.

3.4 Participant Withdrawal

Once a participant has enrolled in the study, the study site will make every reasonable effort to retain her for the 14-day study follow-up period. Given the relatively small study sample size, and the importance of ascertaining all safety outcomes among study participants, 100 percent retention of enrolled participants is targeted. Study site staff are responsible for developing and implementing local standard operating procedures to achieve complete follow-up.

However, participants may withdraw from the study for any reason at any time. The Investigator also may withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures. Participants also may be withdrawn if the study sponsor or US or Indian regulatory authorities terminate the study prior to its planned end date.

Every reasonable effort will be made to complete a final evaluation of participants who terminate from the study prior to Day 14, and study staff will record the reason(s) for all withdrawals from the study in participants' study records.

4.0 Study Product Considerations

4.1 Drug Substance

PRO 2000/5 is a polyanionic polymer consisting of alternating 2-naphthalene sulfonic acid sodium salt and methylene units. The weight-average molecular weight (M_w) is 5 ± 1 kD and the polydispersity (M_w/M_n), a measure of molecular weight distribution, is low (1.2). PRO 2000/5 is synthesized by the acid catalyzed condensation of 2-naphthalene sulfonic acid with formaldehyde, followed by neutralization and molecular weight fractionation.

4.2 Product Preparation and Labeling

PRO 2000/5 Gel (P), 0.5% is a clear, pale yellow aqueous gel formulation containing 0.5% (w/w) PRO 2000/5, Carbomer 1382, lactic acid, trolamine and a combination of common preservatives (methylparaben, propylparaben, and sodium benzoate). It is buffered to pH 4.5. The human dose is 2 g (approximately 2 mL). PRO 2000/5 Gel (P), 0.5% is packaged in single dose, lacquer-lined, aluminum tubes.

Supplies of 0.5% PRO 2000/5 Gel (P) will be provided to study participants in boxes containing 16 tubes and 16 single-use vaginal applicators each. The clinical material is prepared under Good Manufacturing Practice (GMP) conditions for Indevus Pharmaceuticals, Inc. by Dow Pharmaceutical Sciences, Inc. Petaluma, CA, USA. Product will be shipped to the site by the DAIDS Clinical Research Products Management Center (CRPMC).

Supplies of 0.5% PRO 2000/5 Gel (P) are to be stored below 35° C in a secure area. Participants will be instructed to store the product at room temperature. The product has been shown to be stable for 6 months at 40° C/75 percent relative humidity.

The label on each kit will contain the following information:

HPTN 047
Kit No: XXX **Participant ID:** _____
Investigational New Drug: PRO 2000/5 Gel (P), 0.5%
Not for Sale
For Single Use Only. Vaginally insert contents of
one tube with applicator twice each day
for 14 days as instructed.
Store below 35° C
CAUTION: New Drug – Limited by United States
law to investigational use.
Keep out of reach of children.
Manufactured for Indevus Pharmaceuticals, Inc.
Lexington, MA, USA

The label on each tube will contain the following information:

HPTN 047 **Kit No:** XXX
Investigational New Drug: PRO 2000/5 Gel (P), 0.5%
For Single Use Only. Apply Vaginally.
Store below 35° C
CAUTION: New Drug – Limited by United States
law to investigational use.
Keep out of reach of children.
Manufactured for Indevus Pharmaceuticals, Inc.
Lexington, MA, USA

4.3 Dose Regimen

Study participants will be instructed to insert one dose (2 g) of PRO 2000/5 Gel (P) twice daily for 14 consecutive days, beginning on Day 0, the day of the study Enrollment Visit. Participants will be further instructed that, (a) on days when they do not have sexual intercourse, the gel should be applied once in the morning and once in the evening, and (b) on days when they have sexual intercourse, whenever possible, gel application should be timed to coincide (up to one hour before) with intercourse. However, if more than two episodes of intercourse occur on a single day, only two doses should be used. Detailed instructions and practical examples will be provided to study participants at enrollment.

Participants also will be instructed to engage in vaginal intercourse at least twice per week while taking part in the study, preferably within one hour after application of the gel.

Study staff will review instructions for dispensing, administering, and storing PRO 2000/5 Gel (P) with each participant at her Enrollment Visit. Written instructions will be provided to each participant. Instruction will include a demonstration of the proper insertion technique using a pelvic model. In addition, participants will be given the option of inserting their first dose of the product while at the study site, under the supervision of the study clinician.

Assuming adherence to the dosing regimen, administration of doses 1-14 will take place on study Days 0-6. The fifteenth dose will be administered after the Day 7 Follow-up Visit — such that the dose does not interfere with the pelvic exam scheduled to take place on Day 7 — and the last dose will be administered on Day 13 (i.e., the day before the Day 14 Follow-up Visit).

4.4 Product Accountability

The site pharmacist will maintain an accurate inventory and accountability record of study products received and subsequently dispensed. After the study is completed (or otherwise terminated), all unused study product must be returned to Indevus Pharmaceuticals, Inc., or destroyed at the site, in accordance with instructions from Indevus Pharmaceuticals, Inc.

4.5 Adherence Assessment

Participants will record on their Daily Study Records the date and time of each product administration. The records also will collect information on the timing of sexual activity and the emergence/resolution of any symptoms experienced. The investigator or designee will review the Daily Study Records with each participant at her Day 2, Day 7, and Day 14 Follow-up Visits to assess adherence to the study product use and sexual activity requirements.

Twice daily administration of PRO 2000/5 Gel (P) on 14 consecutive study days, beginning with Day 0 is targeted, however lapses of consecutive day use will be accommodated, as follows:

- Participants who miss one or both doses on one day out of 14 will be instructed to complete two applications on one additional day (as soon as possible after Day 13) to achieve a total of 14 days of exposure prior to onset of the next menstrual period.

- Participants who miss one or both doses on two days out of 14 will be instructed to complete two applications on two additional days (as soon as possible after Day 13) to achieve a total of 14 days of exposure prior to onset of the next menstrual period.

Participants who complete twice daily administration of PRO 2000/5 Gel (P) on each study day between the Enrollment Visit (inclusive) and the Day 14 Follow-up Visit, as well as participants who adhere to one of the scenarios described above, will be considered adherent to the product use regimen. In addition, participants who experience an adverse event (AE) that requires product discontinuation (see Appendix III), but complete twice daily administration on the days preceding the AE will be considered “adherent.”

Participants who have fewer than two episodes of vaginal intercourse between study Days 0 and 6 will be encouraged to have at least two episodes between Days 7 and 13. Such participants will not routinely be withdrawn from the study, provided they are willing to try to become compliant for the remainder of the study.

Non-adherent participants (i.e., those who miss one or both doses on three or more days out of 14 in the absence of an AE that requires product discontinuation) will be encouraged to complete twice daily product use on as many days as possible during the 14-day product use period, and will not be replaced. These participants will be asked their reasons for non-adherence, and this information will be recorded on study case report forms.

4.6 Toxicity Management

In response to AEs reported by study participants and/or observed upon exam by study staff, the investigator or designee will recommend either continuation or discontinuation of product use consistent with the criteria in Appendix III. Product use also will be discontinued in the event of pregnancy.

Participants who discontinue product use will not routinely be withdrawn from the study. Rather, every effort will be made to complete the safety evaluations scheduled to take place on study Days 7 and 14.

4.7 Concomitant Medications

Enrolled participants may continue use of all concomitant medications — except exclusionary preparations applied to the external genitalia or inserted into the vagina — during this study. All concomitant medications will be recorded on applicable study case report forms. Medications used for the treatment of AEs that occur during study participation also will be recorded on applicable case report forms.

5.0 Study Procedures

Presented in Sections 5.1-5.5 are the clinical and laboratory procedures to be conducted at individual participant study visits. These procedures also are summarized in Appendices I and II. Focus group procedures are described in Section 5.8.

5.1 Screening Visit for Female Participants (up to Day –30)

Potential participants will be screened for presumptive eligibility for the study according to the procedures described below. All procedures will be completed in a step-wise manner for potential participants who meet the study eligibility criteria. For participants who do not meet the eligibility criteria, screening will be discontinued when ineligibility is determined. For potential participants who are found to be presumptively eligible at this visit, final eligibility will be confirmed at an Enrollment Visit scheduled to take place within 30 days of screening.

5.1.1 Clinical Procedures

- Obtain informed consent.
- Assign Participant ID.
- Collect demographic and locator information.
- Collect medical history and concomitant medication information.
- Provide HIV and STD pre-test and risk reduction counseling.
- Collect urine for HCG pregnancy test; provide participant with result.
- Collect urine for dipstick urinalysis (if symptomatic) and process urine culture if dipstick positive for urinary tract infection (UTI).
- Collect urine for *N. gonorrhoeae* and *C. trachomatis* LCR assay.
- Perform pelvic examination including:
 - speculum examination of vagina and cervix,
 - collect pH sample from the vaginal wall,
 - collect swab from anterior or lateral fornix for:
 - one dried smear (smear specimen on slide and allow to air dry),
 - wet prep (two samples of discharge on slide for saline prep, potassium hydroxide prep and whiff test), and
 - if ulcerative lesions are noted, collect swabs for syphilis dark field microscopy (on-site) and Multiplex PCR (M-PCR) for HSV-2, *H.ducreyi*, and *T. pallidum* (at the HPTN Central Lab),
 - collect ectocervical and endocervical specimen for Pap smear (if no documented normal Pap within the past three months), and
 - bimanual examination for adnexal masses or tenderness.
- Collect blood for HIV, syphilis serology, hematology, liver and renal function, APTT/PT.
- Schedule Enrollment Visit to occur 2-7 days post next menses.

- Instruct participant to abstain from sexual intercourse beginning 48 hours prior to the Enrollment Visit.
- Provide practice Daily Study Records and instructions for completion.
- Complete all required data collection forms.

5.1.2 Laboratory Procedures

- Record results of urine pregnancy test.
- Record results of dipstick urinalysis and process urine culture if dipstick positive for UTI.
- Record vaginal pH measurement.
- Examine wet mount by direct microscopy to detect *T. vaginalis*, *C. albicans* infections, and clue cells for BV.
- Conduct LCR for *N. gonorrhoeae* and *C. trachomatis*.
- Conduct dark field microscopy of swab of ulcerative lesion, if collected.
- Send swab specimen to the HPTN Central Lab for M-PCR, if symptomatic.
- Store unstained dried smear for Gram staining and batch analysis using the Nugent criteria for BV.
- Prepare and read Pap smear if required.
- Conduct EIA test (with confirmation for positives) for HIV.
- Conduct RPR with confirmation by FTA-ABS or TP/HA for *T. pallidum*.
- Conduct complete blood count, APTT/PT, liver and renal function tests.

5.2 Enrollment Visit for Female Participants (Day 0)

Female participants who are found to be presumptively eligible at their Screening Visits will complete Enrollment Visits 2-7 days post-menses, and within 30 days after the Screening Visit. Female participants who do not complete an Enrollment Visit within 30 days of screening must repeat the screening process.

All female participants will receive their screening test results at their Enrollment Visits. For those whose test results meet the study eligibility criteria, the procedures below will be undertaken in a step-wise manner to confirm eligibility. As was the case at the Screening Visit, the procedures will be discontinued if ineligibility is determined at this visit.

5.2.1 Clinical Procedures

- Update locator information.
- Provide results of HIV and STD tests and post-test counseling.
- Review practice Daily Study Records for completeness and accuracy.
- Document that the participant's partner has provided informed consent.
- Complete Initial Acceptability Assessment.
- Collect urine for HCG pregnancy test; provide participant with result.
- Collect urine dipstick urinalysis (if symptomatic) and process urine culture if dipstick positive for urinary tract infection (UTI).
- If symptomatic, collect urine for *N. gonorrhoeae* and *C. trachomatis* LCR assay.
- Perform pelvic examination with colposcopy (according to Appendix V) including:
 - speculum examination of vagina and cervix,
 - colposcopic examination of the vulva, vaginal and cervical mucosa,
 - take baseline colposcopic digital image(s) without filter, encompassing the cervix and fornices,
 - collect pH sample from the vaginal wall,
 - collect swab from anterior or lateral fornix for:
 - one dried smear (smear specimen on slide and allow to air dry),
 - wet prep (two samples of discharge on slide for saline prep, potassium hydroxide prep and whiff test), and
 - if ulcerative lesions are noted
 - photograph lesions according to procedures in Appendix V
 - collect swabs for syphilis dark field microscopy (on-site) and M-PCR for HSV-2, *H. ducreyi* and *T. pallidum* (at the HPTN Central Lab)
 - collect blood for syphilis serology
 - bimanual examination for adnexal masses or tenderness.
- Collect blood for hematology, liver and renal function, APTT/PT, PRO 2000/5 analysis and plasma and serum archive.
- Provide instructions for product administration (see Appendix IV).
- Observe first product administration (if desired by participant).
- Provide Daily Study Records and instructions for completion.
- Count and record total number of tubes of study product dispensed to the study participant.
- Distribute study product and applicators (2 kits), condoms and panty liners.
- Instruct participant to return all used and unused tubes and applicators to the clinic at her Day 2 visit.

- Instruct participant on anticipated amount, consistency and color of discharge due to gel expulsion.
- Instruct participant to distinguish between discolored or malodorous discharge and the discharge anticipated with use of study product.
- Instruct participant to contact or return to the study site if she experiences discomfort, discolored or malodorous discharge, or other AEs.
- Administer Behavioral Assessment Questionnaire
- Schedule Day 2 Follow-up Visit.
- Label digital image with location/image number.
- Complete all required data collection forms.

5.2.2 Laboratory Procedures

- Record results of urine pregnancy test.
- Record results of dipstick urinalysis and process urine culture if dipstick positive for UTI.
- Record vaginal pH measurement.
- Examine wet mount by direct microscopy to detect *T. vaginalis*, *C. albicans* infections, and clue cells for BV.
- Conduct LCR for *N. gonorrhoeae* and *C. trachomatis* if symptomatic.
- If ulcerative lesion was observed, conduct dark field microscopy of swab and serology (RPR with confirmation by FTA-Abs or TP/HA) for *T. pallidum* and prepare and ship swabs to the HPTN Central Lab for M-PCR.
- Store unstained dried smear for Gram staining and batch analysis using the Nugent criteria for BV.
- Conduct complete blood count, APTT/PT, liver and renal function tests.
- Prepare plasma samples for determination of study drug levels for batch shipping at the end of the study.
- Archive plasma and serum.

5.3 Screening/Enrollment Visit for Male Participants Only (Day –30 to Day 0)

- Obtain written informed consent.
- Collect demographic and locator information.
- Collect information on STD history during the past three months and current STD symptoms. If current symptoms are reported, offer exam and clinically appropriate STD work-up.
- Provide HIV pre-test counseling.
- Collect blood for HIV serology, and
- Deliver test results and post-test counseling when results are available.

- Provide the participant with:
 - instructions regarding the study behavioral requirements, and
 - instructions to contact study staff to ask questions and/or report AEs.

5.4 Day 2 Follow-Up Visit for Female Participants

This visit is scheduled to take place on study Day 2. As described below, the baseline evaluations completed at the study Screening and Enrollment Visits are repeated at this visit. Diagnosis and follow-up of any observed abnormalities will proceed according to Appendix III.

5.4.1 Clinical Procedures

- Update locator information.
- Review Daily Study Records and note the time of last product application; review instructions for completion of Daily Study Records if needed.
- Count used and unused product tubes and conduct adherence interview. Store used tubes until end of study. If space does not allow storage, then document the count and disposal.
- Perform pelvic examination with colposcopy (according to Appendix V) including:
 - speculum examination of vagina and cervix
 - colposcopic examination of the vulva, vaginal and cervical mucosa
 - take colposcopic digital image(s) encompassing the cervix and fornices
 - collect pH sample from the vaginal wall
 - collect swab from anterior or lateral fornix for:
 - one dried smear (smear specimen on slide and allow to air dry)
 - wet prep (two samples of discharge on slide for saline prep potassium hydroxide prep and whiff test) and
 - bimanual examination for adnexal masses or tenderness
 - if abnormal vaginal discharge or purulent cervicitis is noted, collect urine for *N. gonorrhoeae* and *C. trachomatis* LCR assay.
 - if ulcerative lesions are noted:
 - Photograph lesions according to procedures in Appendix V.
 - collect swabs for syphilis dark field microscopy (on-site) and M-PCR for HSV-2, *H. ducreyi* and *T. pallidum* (at the HPTN Central Lab)
- If symptomatic, collect urine for dipstick urinalysis.
- Provide instruction for follow-up care and product use, or not, as appropriate .

- Instruct participant to contact or return to the study site if she experiences discomfort, discolored or malodorous discharge or other AEs.
- Distribute additional study supplies (e.g., condoms, panty liners) if needed.
- Schedule Day 7 Follow-up Visit.
- Label digital image with location/image number.
- Complete all required data collection forms.

5.4.2 Laboratory Procedures

- Record results of dipstick urinalysis and process urine culture if dipstick positive for UTI.
- Record vaginal pH measurement.
- Examine wet mount by direct microscopy to detect *T. vaginalis*, *C. albicans* infections, and clue cells for BV.
- Conduct LCR for *N. gonorrhoeae* and *C. trachomatis* if symptomatic.
- If ulcerative lesion was observed, conduct dark field microscopy of swab and serology (RPR with confirmation by FTA-ABS or TP/HA) for *T. pallidum* and prepare and ship swabs to the HPTN Central Lab for M-PCR.
- Store unstained dried smear for Gram staining and batch analysis using the Nugent criteria for BV.

5.5 Day 7 Follow-up Visit for Female Participants (Target Day 7, allowable Day 5-9)

This visit is scheduled to take place on study Day 7. Every effort should be made to complete this visit on Day 7, however the visit may take place — if necessary — between Days 5 and 9. As described below, the baseline evaluations completed at the study Screening and Enrollment Visits are repeated at this visit, with the exception that colposcopy is performed only if abnormalities are observed on speculum exam. Diagnosis and follow-up of any observed abnormalities will proceed according to Appendix III.

5.5.1 Clinical Procedures

- Update locator information.
- Review Daily Study Records and note the time of last product application; review instructions for completion of Daily Study Records if needed.
- Count used and unused product tubes and conduct adherence interview. Store used tubes until end of study. If space does not allow storage, then document the count and disposal.

- Perform pelvic examination including:
 - speculum examination of vagina and cervix,
 - collect pH sample from the vaginal wall,
 - collect swab from anterior or lateral fornix for:
 - one dried smear (smear specimen on slide and allow to air dry),
 - wet prep (two samples of discharge on slide for saline prep, potassium hydroxide prep and whiff test),
 - bimanual examination for adnexal masses or tenderness.
 - if abnormal vaginal discharge or purulent cervicitis is noted, collect urine for *N. gonorrhoeae* and *C. trachomatis* LCR assay.
 - if ulcerative lesions are noted:
 - photograph lesions according to procedures in Appendix V.
 - collect swabs for syphilis dark field microscopy (on-site) and M-PCR for HSV-2, *H. ducreyi* and *T. pallidum*. (at the HPTN Central Lab)
 - label digital image with location/image number.
- If symptomatic, collect urine for dipstick urinalysis.
- Provide instruction for follow-up care and product use, or not, as appropriate.
- Instruct participant to contact or return to the study site if she experiences discomfort, discolored or malodorous discharge, or other AEs.
- Provide Daily Study Records and review instructions for completion.
- Distribute additional study supplies if needed.
- Schedule Day 14 Follow-up Visit.
- Complete all required data collection forms.

5.5.2 Laboratory Procedures

- Record results of dipstick urinalysis and process urine culture if dipstick positive for UTI.
- Record vaginal pH measurement.
- Examine wet mount by direct microscopy to detect *T. vaginalis*, *C. albicans* infections, and clue cells for BV.
- Conduct LCR for *N. gonorrhoeae* and *C. trachomatis* if symptomatic.
- If ulcerative lesion was observed, conduct dark field microscopy of swab and serology (RPR with confirmation by FTA-ABS or TP/HA) for *T. pallidum* and prepare and ship swabs to the HPTN Central Lab for M-PCR.
- Store unstained dried smear for Gram staining and batch analysis using the Nugent criteria for BV.

5.6 Day 14 Follow-up Visit for Female Participants (Target Day 14, allowable Day 12-16)

This visit is scheduled to take place on study Day 14. Every effort should be made to complete this visit on Day 14, however the visit may take place — if necessary — between Days 12 and 16. As described below, the baseline evaluations completed at the study Screening and Enrollment Visits, including routine colposcopy, are repeated at this visit. Diagnosis and follow-up of any observed abnormalities will proceed according to Appendix III.

5.6.1 Clinical Procedures

- Update locator information.
- Administer Follow Up Acceptability Assessment.
- Review Daily Study Records and note the time of last product application.
- Count the number of used and unused product tubes and conduct adherence interview. Store used tubes until end of study. If space does not allow storage then document the count and disposal.
- Collect urine for leukoesterase screen (if symptomatic) and culture if screen positive for WBCs.
- Perform pelvic examination with colposcopy (according to Appendix V) including:
 - speculum examination of vagina and cervix,
 - colposcopic examination of the vaginal and cervical mucosa for lesions,
 - take colposcopic digital image(s) without filter, encompassing the cervix and fornices,
 - collect pH sample from vaginal wall,
 - collect swab from anterior or lateral fornix for:
 - one dried smear (smear specimen on slide and allow to air dry),
 - wet prep (two samples of discharge on slide for saline prep, potassium hydroxide prep and whiff test),
 - bimanual examination for adnexal masses or tenderness.
 - if abnormal vaginal discharge or purulent cervicitis is noted, collect urine for *N. gonorrhoeae* and *C. trachomatis* LCR assay.
 - if ulcerative lesions are noted:
 - photograph lesions according to procedures in Appendix V.
 - collect swabs for syphilis dark field microscopy (on-site) and M-PCR for HSV-2, *H. ducreyi* and *T. pallidum*.
(at the HPTN Central Lab)
- If symptomatic, collect urine for dipstick urinalysis.
- Provide instruction for follow-up care as appropriate.
- Collect blood specimens for hematology, liver and renal function, APTT/PT and PRO 2000/5 analysis.

- Instruct participant to contact or return to the study site if she experiences discomfort, discolored or malodorous discharge, or other AEs within the next week.
- Schedule focus group visit.
- Label digital image with location/image number.
- Complete all required data collection forms.

5.6.2 Laboratory Procedures

- Record results of urine pregnancy test.
- Record results of dipstick urinalysis and process urine culture if dipstick positive for UTI.
- Record vaginal pH measurement.
- Examine wet mount by direct microscopy to detect *T. vaginalis*, *C. albicans* infections, and clue cells for BV.
- Conduct LCR for *N. gonorrhoeae* and *C. trachomatis* if symptomatic.
- If ulcerative lesion was observed, conduct dark field microscopy of swab and serology (RPR with confirmation by FTA-ABS or TP/HA) for *T. pallidum* and prepare and ship swabs to the HPTN Central Lab for M-PCR.
- Store unstained dried smear for Gram staining and batch analysis using the Nugent criteria for BV.
- Conduct complete blood count, APTT/PT, liver and renal function tests.
- Prepare plasma samples for determination of study drug levels for batch shipping at the end of the study.
- Archive plasma and serum.

5.7 Interim Contacts and Visits (ad hoc)

Interim contacts and visits may be performed at participant request at any time during the study. All interim contacts and visits will be documented in participants' study records and on applicable case report forms.

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 — with colposcopy — procedures described for the Day 2 and 14 Follow-up Visits, and diagnosis and follow-up of any observed abnormalities will proceed according to Appendix III.

5.8 Focus Groups

Female study participants will take part in focus groups within approximately four weeks after completing product use, to elicit information on product acceptability and considerations for product use that may not emerge through individual questionnaires. Willingness to participate in the focus group discussions is not required. However, every effort will be made to obtain feedback from the participants. All participants will be asked individually regarding their interest and any possible concerns they may have with taking part in the groups. Participants may choose to participate in a one-on-one session rather than a group session, discuss their feelings with the interviewer by telephone, or complete a detailed questionnaire. Male sexual partners also will be invited to take part in roughly concurrent — but separate — focus groups. Each focus group will include approximately 3-7 participants. Dyads will be held at the wish of the participants. Each group will be conducted according to the following established principles:

- A trained facilitator will lead each group according to an interview guide based on a standard set of relevant questions.
- The facilitator will permit broad and equitable discussion among group participants.
- Each session will be audio-taped and transcribed for qualitative content analysis.

No personal identifying information will be collected during focus groups.

6.0 Adverse Event Reporting Requirements

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.

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. Depending on the severity of the event, the clinician will instruct the participant to present to the study site (for more mild events) or to an emergency room (for more serious events) for immediate evaluation. 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, 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.

Study site staff will document on study case report forms all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. All AEs will be defined as described in the DAIDS HPTN SAE Reporting Manual (dated June 1, 2001). All AEs will be graded using the DAIDS Table for Grading Severity of Adverse Experiences (also referred to as the “Toxicity Table”). Both the DAIDS SAE Reporting Manual and the Toxicity Table are provided in the study-specific procedures manual. The investigator or designee will assess the relationship of all AEs to the study product based on the DAIDS HPTN SAE Reporting Manual, the Investigator’s Brochure, and his/her clinical judgment.

Site staff also will report all AEs that meet serious adverse event (SAE) reporting requirements according to the procedures set forth in the Study-Specific Procedures Manual and the time frames set forth in the DAIDS HPTN SAE Reporting Manual. Specifically, DAIDS-defined “intensive” reporting requirements will be followed for this study. Information on all AEs will be included in reports to the US Food and Drug Administration (FDA), and other applicable government and regulatory authorities, such as the DCGI. Site staff will report information on all AEs and SAEs to their EC in accordance with all applicable regulations and local EC requirements.

Note: The above-stated reporting requirements apply to enrolled female study participants. Participants and their male partners will be instructed to report AEs experienced by male partners to the study clinician, who will evaluate and document the event, as well as provide follow-up care or refer the partner for such care. In the event that a male partner experiences an AE that meets SAE reporting requirements, the event will be reported as an SAE according to the procedures set forth in the Study-Specific Procedures Manual and the time frames set forth in the DAIDS SAE Reporting Manual.

7.0 Statistical Considerations

7.1 General Design

This is a Phase I open-label study with 14 days of twice daily application of 0.5% PRO 2000/5 Gel (P) and follow-up for each study participant. Safety will be assessed after 7 and 14 days of product use. Acceptability measures will be assessed at baseline and after 14 days of product use via standardized questionnaire; additional acceptability information will be collected through focus groups with female study participants and their male sexual partners conducted approximately 2-3 weeks after completing the product use regimen.

7.1.1 Primary Endpoints

Consistent with the primary study objective to assess the safety of 0.5% PRO 2000/5 Gel (P) when administered twice daily for 14 consecutive days on the vulvar and cervicovaginal mucosa, the following primary endpoints — that warrant discontinuation of product use — will be assessed:

- Macroscopic evidence of damage (determined not to be due to pathogen or mechanical trauma) to the vulvar and/or vaginal epithelium including ulceration and other lesions, abrasion, severe erythema, and/or severe edema.
- Macroscopic evidence of damage (determined not to be due to pathogen or mechanical trauma) to the cervical mucosa including ulceration and other lesions, abrasion, severe erythema, and/or severe edema.
- Laboratory evidence of grade 3 or higher toxicity for hematology, liver or renal function (as defined by the DAIDS Toxicity Tables) which cannot be directly attributed to another cause after consultation with the protocol chairs, the study site clinician, the medical officer, statistician, and the protocol specialist.

7.1.2 Secondary Endpoints

Consistent with the secondary study objective to assess the acceptability of, and adherence to, a short term regimen of 0.5% PRO 2000/5 Gel (P), the following endpoints will be assessed:

- The proportion of participants who were “adherent” to the product use regimen, as defined in Section 4.5.

- The proportion of participants who at their Day 14 Follow-up Visits report via questionnaire that they would be "completely unwilling" to use 0.5% PRO 2000/5 Gel (P) during sexual intercourse in the future.

Consistent with the secondary study objective to evaluate aspects of product acceptability, the following endpoints will be assessed (via questionnaire and focus group discussions):

- Reported positive aspects of using PRO 2000/5 Gel (P).
- Reported negative aspects of using PRO 2000/5 Gel (P).

Consistent with the secondary study objective to assess the feasibility of this population for enrollment in future Phase II/III vaginal microbicide studies, the following endpoint will be assessed:

- The proportion of participants who at their Day 14 Follow-up Visit report via questionnaire they would be willing to participate in future phase II/III vaginal microbicide trials.

Consistent with the secondary study objective to assess the effect of a twice daily short-term regimen of 0.5% PRO 2000/5 Gel (P) on the vaginal microflora of sexually active HIV-uninfected women in Pune, India, the following endpoint will be assessed:

- The Gram stain scores at enrollment, and follow-up (Days 2, 7 and 14).

7.2 Sample Size and Accrual

A minimum of 60 sexually active women — 30 at low risk for HIV infection and 30 at higher risk for HIV infection - will be included in this study. Both low and higher risk participants will be recruited for the study concurrently, and it is expected that accrual will be completed within four months. As described in Section 7.3 below, accrual will be suspended for a safety data review if any two women enrolled in the study experience a grade 3 or higher AE judged by the investigator or designee to be possibly, probably or definitely related to product use.

This Phase I study is designed to rule out high toxicity rates in a sample of women that is representative of the population from Pune, India, who will be eligible to take part in the planned Phase II/III study of PRO 2000/5 Gel (P). Because the Phase II/III study may include women who meet the definitions of low and higher risk for HIV infection as defined for this study, toxicity rates will be assessed among all 60 participants combined. The table below presents the probability of observing two or more toxicity outcomes among the 60 study participants given various “true” event rates.

True Event Rate	Pr(2+ events observed)
1%	.12
5%	.81
7%	.93
10%	.99
15%	>.99
20%	>.99

Based on the above, with a total of 60 study participants, if any toxicity outcome occurs at a rate of five percent, then the probability of observing at least two such events is 81 percent. Alternatively, 60 participants provide greater than 90 percent power to detect rates of at least seven percent, and near certainty of detecting rates of at least 10 percent. The power provided with this sample size is robust to possible non-adherence to the study treatment regimen. Specifically, if up to 10 percent of participants were non-adherent to the regimen, a subgroup analysis of toxicity rates among adherent participants also would provide 90 percent power to detect rates of at least seven percent. In the event that up to 20 percent of participants were non-adherent, a subgroup analysis of toxicity rates among adherent participants would provide 90 percent power to detect rates of at least 8 percent.

7.3 Data Monitoring

Close collaboration among protocol team members will be necessary to evaluate study progress and respond to occurrences of toxicity in a timely manner. Rates of accrual, adherence, follow-up, and AE incidence will be monitored closely by the protocol team on a regular basis. The team will meet via conference call every two weeks during the period of study implementation, and additional ad hoc calls will be convened if required.

The Site Investigator is responsible for continuous close monitoring of all AEs that occur among study participants, and for alerting the rest of the protocol team if unexpected concerns arise. All concerns then will be addressed according to DAIDS and HPTN standard operating procedures. In particular, for this study, accrual will be suspended if two or more study participants experience a grade 3 or higher AE (as defined by the DAIDS Standard Toxicity Tables) judged possibly, probably, or definitely related to product use. The protocol team then will review all pertinent safety data and determine whether to continue accrual and product use. A decision to stop the study may be made by the protocol team at this time, or at any such time that the team agrees that an unacceptable type and/or frequency of AEs has been observed.

7.4 Data Analysis

Statistical analyses, described in Sections 7.4.1 and 7.4.2, will be performed using the SAS® and StatXact statistical software packages. As noted above, all analyses will include available data on all 60 study participants. When the use of descriptive statistics is required, the following methods will be used: for categorical variables, the number and percent in each category, with exact confidence intervals for the proportions; for continuous variables, the mean, median, standard deviation, quartiles, and range (minimum, maximum). Changes from baseline to follow-up will be analyzed using McNemar's test (for categorical response variables) or the paired t-test (for continuous response variables). A summary of the analysis tables that will be created is provided in Appendix VIII.

7.4.1 Primary Analyses

Primary data analyses will tabulate the number of primary endpoints — listed in Section 7.1.1 — observed during the study. All participants who enroll in the study will be included in each tabulation. Individual participants will contribute once to the calculation of event rates. Additional safety analyses will tabulate the number and type of AEs observed overall and by severity and relationship to product. AEs that lead to discontinuation of product use and/or study participation will be tabulated separately. The temporal relationship of product application and AE onset, and the duration of symptoms, also will be evaluated. Finally, baseline and Day 14 laboratory measures will be summarized and the change in function, defined as the difference between the baseline and Day 14 measurements, will be described.

7.4.2 Secondary Analyses

Secondary data analyses will tabulate endpoints listed in Section 7.1.2. Factors relating to acceptability will be tabulated separately for applicator associated factors (e.g., discomfort, design/packaging, disposal), vehicle-associated factors (e.g., consistency/texture, color, odor), and use-associated factors (e.g., ease of use, partner perceptions/considerations, discharge of product, embarrassment, other social costs), based on participants' questionnaire responses. In addition, transcripts from all focus group discussions will be prepared and analyzed qualitatively. Finally, to determine the effects of this short-term regimen of PRO 2000/5 Gel (P) on vaginal microflora, Gram stain scores at the Day 2, Day 7, and Day 14 follow-up visits will be compared with Gram stain scores at enrollment.

8.0 Human Subjects Considerations

8.1 Ethical Review

This protocol and the template informed consent forms contained in Appendices VI and VII — and any subsequent modifications — will be reviewed and approved by the HPTN Protocol Review Committee and DAIDS Prevention Science Review Committee with respect to scientific content and compliance with all applicable research and human subjects regulations.

The protocol, site-specific informed consent forms, participant education, outreach, and recruitment materials, and other requested documents — and any subsequent modifications — also will be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at the study site. This includes the IRB(s) of the participating US institution as well as the local EC(s) in Pune.

Subsequent to initial review and approval, the IRB and EC(s) will review the protocol at least annually. The Investigator will make safety and progress reports to the IRB and EC(s) at least annually, and within three months of study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others.

8.2 Informed Consent

Written informed consent will be obtained from each female study participant before she is screened for and/or enrolled in the study. Written informed consent also will be obtained from female participants' male partners. All participants also must verbally affirm their understanding of the investigational nature of the study, its risks and benefits, other treatment alternatives, their rights to terminate participation in the study without affecting her/his health care at the study site, whom to contact with questions regarding the study, and that she/he freely has given informed consent to participate in the study. Participants will be provided with a copy of their informed consent forms if they are willing to receive them. Study staff will document the informed consent process as described in the Study-Specific Procedures Manual.

The study site is responsible for developing study informed consent forms for local use, based on the templates in Appendices VI and VII, in accordance with all applicable US and Indian regulations and local guidelines. The study site also is responsible for translating the template form into local language — Marathi — and verifying the accuracy of the translation by performing an independent back-translation. The HPTN Coordinating and Operations Center (CORE) will review

all site-specific informed consent forms and back-translations and forward them to the DAIDS Regulatory Operations Center (ROC) for approval according to DAIDS policies; study site staff may not begin obtaining informed consent from study participants until after receiving HPTN CORE confirmation of "site registration" to begin study operations. Detailed site registration procedures are included in the Study-Specific Procedures Manual.

8.3 Confidentiality

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to study staff. All laboratory specimens, colposcopic photographs, reports, study data collection, process, and administrative forms will be identified by coded number only to maintain participant confidentiality. All computer entry and networking programs also will be done by coded number only, and all local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

Participants' study information will not be released without the written permission of the participant, except as necessary for monitoring by NIAID and/or its contractors (e.g., the DAIDS monitoring contractor), Indevus Pharmaceuticals, Inc., representatives of the HPTN CORE and/or Statistical and Data Management Center (SDMC), and the FDA, DCGI, and other regulatory authorities.

Note: Among other documentation, the DCGI requires that the name and address of all study participants be reported to DCGI after completion of the study. This requirement will be communicated to study participants during the informed consent process. Study participants will be informed that every effort will be made to ensure their confidentiality throughout this process.

8.4 Benefits

There may be no direct benefits to participants in this study. However, participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to the development of a safe and effective microbicide that prevents sexual transmission of HIV.

In addition, participants will receive HIV counseling and testing as part of the study screening process as well as pelvic exams and Pap smears. Participants also will be screened for a number of STDs, and provided STD treatment if applicable. (See also Section 8.8.)

8.5 Risks

Based on initial toxicology results obtained with intravaginal PRO 2000/5 Gel (P) and the AEs observed in clinical studies of intravaginal administration, potential risks include vulval ulceration, abrasion, erythema, burning, itching, and soreness; vaginal ulceration, abrasion, erythema, bleeding, irritation, inflammation, burning, itching, soreness, and dryness; increased vaginal discharge; cervical ulceration, abrasion, ecchymosis, erythema, subepithelial and/or petechial hemorrhage, inflammation, and soreness; dysuria; dyspareunia; pelvic pain; abdominal pain; nausea; and diarrhea.

Based on the toxicology results obtained with parenteral PRO 2000/5 and the events observed in clinical studies of parenteral administration, potential risks and side effects consequent to systemic absorption may include coagulopathy, thrombocytopenia, leukocytosis, hepatocellular alterations with elevated hepatic transaminases, nephrotoxicity, splenomegaly and changes in the distribution of lipoproteins. Using a validated HPLC method with a detection limit of 4×10^8 g/mL, PRO 2000/5 was not detected in plasma following 14 intravaginal doses of 4% and 0.5% PRO 2000/5 Gel (nonpreserved formulation) in healthy volunteers.

PRO 2000/5 Gel (P) may be wholly or partially contraceptive in humans. This will pose no risk to the study population; women of childbearing potential must have a negative pregnancy test prior to enrollment and agree to use appropriate contraceptive methods for the duration of the study.

Although the study site will make every effort to protect the privacy and confidentiality of all study participants, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as HIV-infected or at "high risk" for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

Male and female study participants may experience discomfort when having pelvic exams and/or undergoing phlebotomy for this study. During phlebotomy, they also may feel dizzy or faint, or develop a bruise, swelling or infection where the needle is inserted. Female participants may become embarrassed, worried, or anxious when receiving HIV and STD counseling. They may become worried or anxious while waiting for their HIV and STD test results. Trained counselors will be available to help participants deal with these feelings.

8.6 Incentives

Pending IRB/EC approval, participants will be provided with financial compensation for travel to study visits and time away from work while enrolled in this study. The amount of compensation will be specified in the study informed consent forms.

8.7 Communicable Disease Reporting Requirements

Neither STDs nor HIV are notifiable to either the local health authority in Pune (the Pune Municipal Corporation Health Department) or the state health authority (the Government of Maharashtra Ministry of Health).

8.8 Access to HIV-Related Care

HIV pre-test, risk reduction, 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. Counseling will be provided accordance with the guidelines formulated by India's National AIDS Control Organization. The study site will document its counseling policies and procedures prior to study implementation for purposes of staff training and study monitoring.

As part of the eligibility screening process, this study will identify persons who have become infected with HIV. Each of the clinics from which potential study participants will be recruited (see Section 3.3) provide medical care to HIV-infected persons according to guidelines formulated by India's National AIDS Control Organization and Technical Resource Group for chemoprophylaxis. Study staff will provide participants with their HIV test results in the context of post-test counseling and refer all persons found to be HIV-infected to these sources of care.

8.9 Study Discontinuation

As noted in Section 7.3, accrual into this study will be suspended if two or more participants experience grade 3 or higher AEs (as defined by the DAIDS Standard Toxicity Tables) judged possibly, probably, or definitely related to product use. The protocol team then will review all pertinent data and determine whether to continue accrual and product use. The protocol team may decide to stop the study 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 study also may be discontinued at any time by NIAID, the HPTN, the manufacturer of the study product, and/or the FDA, DCGI, or other regulatory authorities.

9.0 Laboratory Specimens and Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the U.S. Centers for Disease Control and Prevention (CDC).

10.0 Administrative Procedures

10.1 Study Coordination

Implementation of this study will be directed by the protocol as well as a Study-Specific Procedures Manual. This manual will outline procedures for conducting study visits; data and forms processing; AE assessment, management and reporting; dispensing study products and documenting product accountability; and other study operations. Study case report forms will be developed by the protocol team and HPTN SDMC. Data will be transferred to the HPTN SDMC, entered, and cleaned using the SDMC DataFax data management system. Quality control reports and queries will be routinely sent back to the site for verification and resolution.

Close cooperation between the study Investigator, NIAID Medical Officer, Protocol Specialist, Biostatistician, Data Managers, and other protocol team members will be necessary in order to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. Rates of accrual, adherence, follow-up, and AE incidence will be monitored closely by the team, and discussed routinely during conference calls scheduled to take place at least every two weeks during the study implementation period.

Indevus will hold the Investigational New Drug (IND) application for this study under IND 56,962. Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement executed between Indevus and NIAID.

10.2 Study Monitoring

On-site study monitoring will be performed in accordance with DAIDS policies. Study monitors will visit the site to verify compliance with human subjects and other research regulations and guidelines, assess adherence to the study protocol and study-specific procedures manual, and confirm the quality and accuracy of information collected at the study site and entered into the study database. The Investigator 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, product accountability forms), as well as observe

the performance of study procedures. The Investigator also will allow inspection of all study-related documentation by authorized representatives of the HPTN CORE, SDMC, NIAID, Indevus Pharmaceuticals, Inc., FDA, DCGI, and other regulatory authorities. A site visit log will be maintained at the study site to document all visits.

10.3 Protocol Compliance

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, Protocol Co-Chair, and NIAID Medical Officer. All protocol amendments will be submitted to and approved by the appropriate IRBs/ECs, and documentation of approval will be forwarded to the HPTN CORE for submission to the DAIDS ROC for approval prior to implementing the amendment.

10.4 Investigator's Records

The Investigator will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. In accordance with US regulations, the Investigator will retain all study records for at least two years following the date of marketing approval for the study product for the indication in which it was studied. If no marketing application is filed, or if the application is not approved, the records must be retained for two years after the FDA is notified that the IND is discontinued. Study records include administrative documentation — including site registration documents and all reports and correspondence relating to the study — as well as documentation related to each participant screened and/or enrolled in the study — including informed consent forms, locator forms, case report forms, notations of all contacts with the participant, and all other source documents. All records must be retained on-site throughout the study's period of performance. The HPTN CORE will provide the study site with written instructions for long-term record storage at the completion of the period of performance.

10.5 Use of Information and Publications

Publication of the results of this study will be governed by HPTN policies. Any presentation, abstract, or manuscript will be made available by the Investigator to the HPTN Manuscript Review Committee, DAIDS, and Indevus Pharmaceuticals, Inc. for review prior to submission.

11.0 References

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Appendix I. Study Activities/Procedures by Visit – Females

Activity/Procedure	Screening	Enrollment (Day 0)	Follow-Up (Day 2)	Follow-Up (Day 7)	Follow-Up (Day 14)
Obtain informed consent	x				
Obtain informed consent from male partner (prior to enrollment)*	x				
Collect/update demographic and locator information	x	x	x	x	x
Assign participant ID	x				
Collect medical history	x				
Provide HIV/STD pre-test counseling	x				
Provide HIV/STD test results and post-test counseling		x			
Distribute study instructions/supplies	x	x	x	x	
If participant willing, observe product application		x			
Review Daily Study Records		x	x	x	x
Administer Behavioral Assessment		x			
Administer Acceptability Assessment		x			x**
Collect urine for pregnancy test***	x	x			
Collect urine for UTI dipstick	if indicated	if indicated	if indicated	if indicated	if indicated
Collect urine for and <i>N. gonorrhoeae</i> , <i>C. trachomatis</i> LCR ***	x	if indicated	if indicated	if indicated	if indicated
Perform pelvic examination	x	x	x	x	x
Perform Pap smear****	x				
Perform colposcopy		x	x	if indicated	x
Collect blood for laboratory evaluations***	x	x		if indicated	x
Dispense Study Product		x			
Count returned product tubes			x	x	x
Schedule next visit	x	x	x	x	x
Complete and submit data collection forms	x	x	x	x	x

*Male partner must provide informed consent and STD history information prior to enrollment of the female participant.

**Participants will also be offered participation in a focus group or quantitative interview within 4 weeks after completing product use.

***Refer to Appendix II: Laboratory Evaluations for visit-specific detail.

Appendix IA. Study Activities/Procedures by Visit – Males

Activity/Procedure	Screening/ Enrollment (Day-30-0)	Enrollment (Day 0)	Follow-Up (Day 2)	Follow-Up (Day 7)	Follow-Up (Day 14)
Obtain informed consent	x*				
Provide HIV/STD pre-test counseling	x				
Collect blood for HIV serology	x				
Provide HIV/STD test results and post-test counseling		x			
Collect STD history (and offer genital exam if indicated)*	x				
Collect/update demographic and locator information	x				
Distribute study instructions/supplies	x				
Schedule next visit	x	x			
Complete and submit data collection forms		x			

*Male partner must provide informed consent and STD history information prior to enrollment of the female participant.

Appendix II: Laboratory Evaluations

Evaluation					Visit			
Test	Purpose	Specimen	Volume	Laboratory	Screening	Enrollment Day 0	Follow-up Day 2 and Day 7	Follow-up Day 14
HCG	Pregnancy	Urine	10 ml	on site	x	x		
dipstick urinalysis if indicated, urine culture	Urinary tract infection	Urine	10 ml	on site LL (culture)	if indicated	if indicated	if indicated	if indicated
Wet mount	<i>T. vaginalis</i> , <i>C. albicans</i> , vaginal pH, bacterial vaginosis	Swab/slide	n/a	on site	x	x	x	x
pH		pH stick	n/a	n/a	x	x	x	x
Gram stain	Vaginal flora pattern	Swab/slide	n/a	on-site	x	x	x	x
Pap smear	Cervical atypia	Spatula/slide	n/a	LL	x			
GC/CT LCR	<i>N. gonorrhoeae</i> , <i>C. trachomatis</i>	Urine	n/a	LL	x	if indicated	if indicated	if indicated
M-PCR for HSV-2, <i>H. ducreyi</i> , <i>T. pallidum</i>	HSV-2, <i>H. ducreyi</i> , <i>T. pallidum</i>	Swab of ulcer	n/a	HPTN CL	if indicated	if indicated	if indicated	if indicated
EIA with confirmation	HIV	Red top	10 ml	LL	x			
Blood chemistries	Liver/renal function tests	Red top	10 ml	LL	x	x		x
RPR with confirmation	<i>T. pallidum</i>	Red top	10ml	LL	x	if indicated	if indicated	if indicated

Appendix II (Continued)

Evaluation					Visit			
Test	Purpose	Specimen	Volume	Laboratory	Screening	Enrollment Day 0	Follow-up Day 7	Follow-up Day 14
APTT/PT	Assess anti-coagulant effect	Blue Top	2 ml	LL	x	x		x
PRO 2000/5 assay	Measure plasma drug levels	Green top	6 ml	TBA		x		x
CBC	Hematology	Purple top	8 ml	LL	x	x		x
Plasma archive	Archive	Yellow top	10 ml	LL		x		
Serum archive	Archive	Red top	10 ml	LL		x		

LL: Local Laboratory

CL: Central Laboratory

Appendix III. Outcomes, Diagnostics, and Follow-Up Procedures

Condition	Product Use	Evaluation	Enrollment Action	Follow-up and Treatment Action
Deep Epithelial Disruption (Ulceration)	Discontinue	Swab for HSV-2 M-PCR and syphilis dark field and collect serology specimen.	If laboratory results confirm pathogen, recruit an additional participant.	Re-evaluate in 5 to 7 days. If the ulcer has become worse or not healed in 5 to 7 days, perform a biopsy. Ask the participant to return in 7 to 10 days for a follow-up syphilis serology.
Superficial Epithelial Disruption (Abrasion/Peeling)	Continue	Naked eye evaluation and/or colposcopy		Re-evaluate by speculum examination in 48 hours. If the condition is significantly worse, discontinue product use. If the condition is the same, continue product use.
Mild to moderate 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		Re-evaluate by speculum examination in 48-72 hours. If worsened significantly, discontinue product use. Otherwise, continue product use.
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.

Appendix III. (Continued)

Vaginitis (findings on exam such as vaginal discharge)	Temporarily discontinue except for asymptomatic candida vaginitis	Perform wet mount for <i>candida vaginitis</i> , <i>trichomoniasis</i> , and bacterial vaginosis.	If laboratory results confirm pathogen, recruit an additional participant.	See below
Bleeding/Spotting	Temporarily discontinue (until evaluated)	Naked eye evaluation and/or colposcopy		If determined to be endometrial bleeding with no other source, continue product use. Re-evaluate in 72 hours if the participant reports the bleeding/spotting has not resolved.
Suspected cervicitis (findings on exam such as discharge from cervical os)	Provisionally continue	Evaluate for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> .	If laboratory results confirm pathogen, discontinue treatment and recruit an additional participant.	Treat with oral medication and re-evaluate in 48-72 hours. If condition is worse, discontinue product use.
Petechial hemorrhage	Continue	Naked eye evaluation and/or colposcopy		Re-evaluate by speculum examination in 48 to 72 hours. If the condition is significantly worse, discontinue product use. Otherwise, continue product use.
Ecchymosis	Continue	Naked eye evaluation and/or colposcopy		Re-evaluate by speculum examination in 48 to 72 hours. If the condition is significantly worse, discontinue product use. Otherwise, continue product use.

Vaginitis:

- For trichomonas or symptomatic BV, treat or refer for treatment. Do not resume product use.
- For symptomatic Candida vaginitis: manage with oral medication and re-evaluate in 3-5 days. If resolved, restart product use. If observed at Day 14, treat and follow up to document resolution.
- For asymptomatic Candida vaginitis :
 - If a participant has asymptomatic Candida vaginitis at the Day 7 Visit she should continue product use and be re-evaluated at the Day 14 Visit
 - If at the Day 14 Visit there are signs and symptoms compatible with vaginitis, treat and follow-up to document resolution.

Appendix IV: Participant Instructions for Using PRO 2000/5 Gel (P)

The study kit provided to you contains tubes of the study gel and applicators to insert the gel into the vagina. Before using the gel and applicators, please read the following instructions carefully. The study nurse will answer any questions you may have.

1. Remove one applicator and one tube of study gel from the study kit.
2. Remove applicator from the sealed wrapper. Before filling the applicator, push plunger completely down inside barrel.
3. To open the tube, unscrew the plastic cap. Turn the cap upside down and puncture the foil seal on the opening of the tube.
4. Holding the tube upright, attach the applicator barrel to the neck of the tube and turn the applicator clockwise until it is firmly seated.
5. Hold the applicator firmly on the tube neck. Squeeze the tube from the bottom filling the applicator to the single line indicated.
6. Unscrew the study gel tube from the applicator.
7. With one hand, hold the filled applicator by placing your thumb and middle finger **HALF-WAY** along the barrel.
8. Choose a comfortable position, for example, standing with one leg raised, squatting with your feet apart, or lying on your back with your knees apart. With the other hand, gently spread the vaginal opening.
9. Gently slide the applicator into the vagina until your fingers touch your body.
BE CAREFUL NOT TO INSERT THE APPLICATOR TOO FAR.
10. Hold the applicator firmly in place and push the plunger into the barrel (the gel-filled half of the applicator). With the plunger still depressed, withdraw the applicator from the vagina.
11. Replace plastic cap on study gel tube and store the used tube in the study kit. Bring the study kit with you on your next visit.

Appendix V: Colposcopy Procedures

GENERAL GUIDELINES

Procedures will be performed by experienced and certified clinicians.

Lavage and Removal of Visual Obstruction

Throughout the colposcopy procedures, if necessary, remove any obstruction caused by residual PRO 2000/5 Gel (P) only by sterile, isotonic, non-bacteriostatic saline lavage. Then, only if lavage does not adequately remove the gel, use large saline-moistened swabs (scopettes) in a gentle dabbing fashion. Avoid twisting or rolling the swab over the surface of epithelium. At no time should a dry swab be used during examination of either the cervix or the vagina, as this may traumatize the epithelium of either surface. Do not lavage **prior** to collection of pH, wet prep, and slide for gram stain.

Specimen collection

Specimen collection required by protocol should be performed only after all colposcopic viewing and photography is completed.

External Genitalia

- Inspect the genital area for abnormalities.
- Examine the external genitalia including the perineum, peri-anal area and the mucosal lining of the introitus.

Cervix

- Gently insert a speculum of appropriate size moistened with warm saline into the vagina, so as to enable the cervix to be seen clearly.
- Carefully open the speculum blades to prevent trauma and bring the cervix into view.
- Perform naked eye examination, noting the general state of the cervix.
- Note and describe presence and degree of ectopy, presence of edema or erythema, areas of thickened epithelium and other surface irregularities or abnormalities.
- Examine for vascular or mucosal disruption of the cervix.

Use of Magnification

For each area examined, external genitalia, cervix, and vagina, the following procedures are to be followed:

- Perform naked eye observation, noting the general state of tissues.
- Using low power (x4-10 magnification) and no filter examine tissues for abnormalities.

Photography/Imaging

Colposcopic digital images will be produced using 35mm or digital imaging for a multi-magnification colposcope.

Enrollment Visit - Baseline Images

- Use the appropriate low power (x4-10 magnification) to take one colposcopic image, encompassing as much of the cervical face and fornices as can be seen without manipulation. Note the magnification used.
- Additional images of the cervix, vagina or vulva may be recorded at the discretion of the study staff at any study visit.

Day 14 Follow-up Visit Images

- Use the **same** low power magnification noted (x4-10 magnification) **for baseline photo** to take one colposcopic photograph, encompassing as much of the cervix and fornices as can be seen without manipulation.
- Day 14 visit or AE visits - Images of Findings
- Use the appropriate magnification to ensure that all margins of a finding are captured in an image.
- Take multiple images if needed to capture all findings.

COLSPOSCOPY PROCEDURES

Positioning of the Participant

For colposcopic examination, the participant should lie on a soft examination table with leg stirrups in the lithotomy position so as to enable the perineum and vulva to be inspected. At all times, the comfort and privacy of the woman should be ensured.

External Genitalia

(Colposcopic examination of the external genitalia precedes insertion of the speculum)

- Perform naked eye examination of the external genitalia including the perineum, peri-anal area and the epithelial lining of the introitus.
- Use appropriate magnification (usually 4-10X) for colposcopic examination of the same areas. Note findings.

Cervix

- Use a speculum of appropriate size (moistened with warm saline, if necessary) to permit adequate visualization of the vagina and cervix.
- Gently insert and open the speculum so as to prevent trauma and enable the cervix and upper vagina to be seen clearly.
- Perform naked eye examination without manipulation, noting the general state of the cervix.
- Note presence and degree of ectopy. Note general shape and size of os.

At this time, collect the appropriate specimens (away from any apparent abnormal areas), according to protocol. The area from which the wet preparation is taken should be excluded from the subsequent examination, or findings should be noted as "probably iatrogenic - wet preparation site."

- pH - Place a Baxter S/P pH indicator strip against the lateral vaginal wall;
- Gram Stain - Collect swab specimen from lateral vaginal wall or anterior fornixanterior fornix for one dried smear (smear specimen on slide and allow to air dry) to be archived for Gram Stain;
- Wet Prep - Collect a swab specimen from the vaginal pool for saline preps, potassium hydroxide preps and whiff test).

COLPOSCOPIC EXAMINATION OF CERVIX:

Inspect the cervix under appropriate magnification (usually 4-10X) and note findings.

COLPOSCOPIC EXAMINATION OF FORNICES:

Under appropriate magnification (usually 4-10X), examine the anterior, right lateral, left lateral, and posterior fornices and adjacent cervical trunk and note findings. If necessary, slightly manipulate the speculum so that the fornices may be adequately visualized. The lateral fornices are best exposed by placing a saline-moistened large swab (scopette) into the contralateral fornix and pressing toward the head and laterally. For example, to view the right lateral fornix, place the moistened swab into the left lateral fornix and press gently toward the woman's head and left side. A dry swab should never be used.

Vagina

COLPOSCOPIC EXAMINATION OF VAGINA:

To examine the rest of the vagina, slowly withdraw the speculum with the blades moderately open, refocusing as needed. Alternately, the speculum can be rotated ninety degrees to allow visualization of the anterior and posterior vaginal walls. Note findings.

NOTES:

(A) It may be helpful to record the length and axis of the vagina, position of the uterus, and least traumatizing type/size of speculum on the source document during the first examination for reference at later examinations. This information should be reviewed prior to subsequent examinations to reduce the chance of causing iatrogenic injury.

(B) At no time should a dry swab be used during examination of either the cervix or the vagina, as this may traumatize the epithelium of either surface. Large swabs moistened with sterile, isotonic, non-bacteriostatic saline should be used.

DESCRIPTION OF FINDINGS

GENERAL GUIDELINES

The results of the colposcopic examination should be documented by recording the state of the epithelium and blood vessels for each numbered finding, as outlined below.

Epithelium

Integrity:

- Intact
- Disrupted
 - superficial
 - deep: Complete disruption is now called “deep” and exposes stroma and possibly blood vessels. A bleeding area should be considered “deep”.

Color: normal, slightly red, red, white, other (including pale)

Blood vessels

Integrity:

- Intact
- Disrupted

Any probable infectious area should be described in the participant's Case Report Form (CRF).

Table I gives the terms for possible findings observed during colposcopy used in previous studies and summarizes the characteristics of these findings. The terms in italics in Table 1 are from the original WHO procedure. They have been replaced with the descriptors in bold.

Table 1

	Blood vessels intact	Blood vessels disrupted
Epithelium intact	<i>Erythema (color red or slightly red)</i> <i>Edema (color pale)</i>	<i>Ecchymosis</i> <i>Petechiae</i> <i>Petechial hemorrhage</i>
Epithelium disrupted – superficial	<i>Abrasion</i> <i>Ulcer</i>	<i>Abrasion</i> <i>Ulcer</i>
Epithelium disrupted – deep	<i>Abrasion</i> <i>Ulcer</i>	<i>Abrasion</i> <i>Ulcer</i>

The CRF may require that terms used in the original WHO procedure be recorded. The correct term is determined by assessing the following factors and referring to Table 2. Any finding that is not adequately represented by these descriptors should be noted as "Other" on the participant's Case Report Form with the clinician's impression.

1. Demarcation

The suspicious area can be either sharply demarcated or diffuse.

2. Peripheral reaction

The existence of a reaction surrounding the finding should be noted. It generally appears as a hyperemic reaction or as an inflammatory reaction with erythema and/ or edema. The presence of erythema (red or slightly red epithelium) and/or edema (accumulation of fluid in interstitial area manifested as swelling and pallor) associated with other findings.

3. Slough

Existence of a necrotic component in the base of the finding in the process of separating from the viable layers. (Macroscopic epithelial disruption of multiple layers with a liquefaction process such as necrosis)

4. Size, site and number

The size of the finding should be measured where practical with a scale. The site(s) and the number of findings should be noted on the diagram of the Case Report Form and will serve to monitor the resolution of findings at subsequent visits.

5. The following Note and define any additional abnormalities may be recorded on the source document observed such as:

- a) Hyperemia and/or abnormal discharge which might indicate a vaginitis or reaction to microbicide
- b) Mucopurulent Presence of an abnormal amount, color and/or odor of vaginal discharge or a mucopurulent discharge from the cervix which might indicate endocervical infection
- c) Abnormal amount, color and/or odor of vaginal discharge
- d) Bleeding and its source which might make further examination impossible
- e) Macroscopic condylomata (HPV)
- f) Cervical or vaginal ulceration (HSV, syphilis, chancroid infection) or reaction to microbicide)
- g) Signs of chronic or acute trauma
- h) Foreign bodies
- i) Hyperkeratosis
- j) Other, explain

6. The following should be considered Normal findings:

- a) Anatomic variants
- b) Mucus retention cysts
- c) Atrophic changes
- d) Nabothian cysts
- e) Gland openings
- f) Gartner's) Gartner's duct cyst
- g) Skin tag
- h) Ectopy

Appendix V (continued)

Table 2
Colposcopic Characteristics of Lesions

	Ulcer	Abrasion	Ecchymosis	Petechial Hemorrhage	Subepithelial Hemorrhage + Swelling	Erythema	Edema
Epithelium	disrupted	partially disrupted	Intact	intact	intact + swelling	intact	intact + swelling
Blood Vessels	intact or disrupted	intact or disrupted	disrupted	disrupted	disrupted	intact	intact
Demarcation	sharp	diffuse	sharp or diffuse	sharp	sharp or diffuse	sharp or diffuse	sharp or diffuse
Peripheral Reaction	+/-	+/-	+/-	+/-	+/-	no	+/-
Slough	yes	no	no	no	no	no	no
Size	any	any	0.5cm or more	less than 0.5cm	any	any	any

Appendix VI. Sample Informed Consent Form for Female Participants

Sample Informed Consent Form
DIVISION OF AIDS, NIAID, NIH

HPTN 047
Phase I Safety and Acceptability Study of the
Investigational Vaginal Microbicide PRO 2000/5 Gel (P)
Version 1.0 [date]

WOMEN

Principal Investigator: [name]
Telephone Number: [number]

INFORMED CONSENT

You are being asked to take part in the research study named above. This is a study of an experimental gel called PRO 2000/5 Gel (P), or "PRO 2000 Gel" for short. Before you can decide whether or not to take part in this study, we would like to explain the purpose of the study, any risks and benefits to you, and what is expected of you.

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives you information about the study that will be discussed with you. Once you understand the study, and if you agree to take part, you will be asked to sign this consent form. You will be given a copy to keep.

- Before you learn about the study, it is important that you know the following:
- Your participation is entirely voluntary.
- You may decide not to take part or to withdraw from the study at any time without losing the benefits of your routine medical care.
- You cannot take part in the study unless your male sexual partner also agrees to take part.

PURPOSE OF THE STUDY

PRO 2000 Gel is being developed as a "vaginal microbicide." It is designed to be inserted into the vagina to protect women from getting HIV during sex. HIV is the virus that causes AIDS. PRO 2000 Gel is "experimental." This means we do not yet know all the effects of the gel, and we do not know if it works to protect against HIV. Because of this, the Drug Controller General of India (DCGI) and the United States Food and Drug Administration (FDA) have not approved the gel for use in the general population. The DCGI and the FDA have approved this study.

Before research can be done to find out if PRO 2000 Gel protects against HIV, we must first make sure it is safe. So far, PRO 2000 Gel has been tested for safety in 136 women from Europe and the United States. Among these women, the gel was found to be safe and generally well tolerated. The main purpose of this study is to find out if there are any bad effects when PRO 2000 Gel is used by Indian women. Another purpose is to find out what Indian women and men think about using PRO 2000 Gel when having sex.

The study staff here are conducting this study with funding from the US National Institute of Allergy and Infectious Diseases (NIAID). About 60 women will take part in the study. If you agree to take part in the study, your part will last for about two months.

PROCEDURES

Screening Visit: If you decide to take part in the study, your first visit will continue today, after you read, discuss, and sign this form. The visit will take about 1 hour. To find out if you are eligible for the study, you will answer some questions, have a pelvic exam, and give urine and blood (40ml or 2 and a half tablespoons) for testing. The questions will be about you, your health, your male sexual partner, and your sexual practices. If your answers to the questions show that you are not eligible for the study, your visit will end after answering the questions.

If your answers to the questions show that you may be eligible for the study, you will have counseling about HIV and other sexually transmitted diseases (STDs). You will talk about HIV/AIDS and other STDs, HIV and STD tests, what it may mean to know your HIV and STD status, and whether you are prepared to receive your HIV and STD test results. You also will talk about ways that HIV and other STDs are spread, and ways to protect against them.

If you agree to undergo HIV and STD testing, you will give blood and urine for the tests. Your urine also will be tested for pregnancy. If you are pregnant, you will not be eligible for the study. Your blood also will be tested to check on your overall health, liver, and kidneys. Then you will have a pelvic exam. The study clinician will look in your vagina and take some fluids to test for STDs and other possible problems. If your exam shown no problems, you will continue to be eligible for the study.

Enrollment Visit: This visit will take place 2-7 days after your next menstrual period. By the time of this visit, your partner must come to the study site to give his informed consent to take part in the study, and to answer some questions to confirm his eligibility.

This visit will take about 1 hour. We will tell you all your test results, including your STD and HIV test results. We will talk with you about the meaning of the results and how you feel about them. You must receive your HIV test results to be in this study.

If the tests show that you are infected with HIV, you will not be eligible for the study. However, we will tell you about other studies you may be eligible for. We also will refer you for medical care and other services you may need. If the tests show that you are infected with another STD, you will not be able to join the study at that time. You will be given treatment for the STD and, after you finish the treatment, you can come back to find out if you are eligible for study at that time.

If the test show that you are eligible for the study, you will fill out a questionnaire on your opinions about vaginal products. You will give urine and blood (46ml or 3 tablespoons) for testing as at the Screening Visit, and have a pelvic exam. Some of your blood will be saved for testing if you have medical problems later in the study, but all of your blood will be discarded after the study is finished. During the pelvic exam, the clinician will look into your vagina through a lens. The lens is attached to a camera, and a picture will be taken of the inside of your vagina. If your exam shows no problems, you will be entered into the study.

During the Study: You will be given tubes of PRO 2000 Gel, applicators, and instructions on how to use them. You will insert one tube of PRO 2000 Gel into your vagina 2 times per day for 14 days. You are asked to have vaginal sex with your partner at least 2 times per week. You and your partner must use condoms given to you by study staff each time you have sex.

You will be given a study diary to use every day. In the diary, you will record when you used the gel, when you had sex, and if you had any medical discomfort or problems. You are asked to contact the study nurse or doctor if you feel itching or burning, or notice a change in your vaginal discharge like a bad smell, different color, or any blood. You will bring your study diary and tubes of PRO 2000 Gel to your follow-up visits.

Day 2 Follow-Up Visit: You will insert PRO 2000 Gel two times per day for 2 days, and then return here for a follow-up visit. This visit will take about 1 hour. You will review your diary with the study staff and answer questions about your use of the gel, your sexual activity, and whether you had any medical problems or discomfort. You also will have a pelvic exam with the lens.

Day 7 Follow-Up Visit: You will insert PRO 2000 Gel two times per day for 7 days, and then return here for a follow-up visit. This visit will take about 1 hour. You will review your diary with the study staff and answer questions about your use of the gel, your sexual activity, and whether you had any medical problems or discomfort. You also will have a pelvic exam. Unless a problem is seen on this exam, the lens will not be used at this visit.

Day 14 Follow-Up Visit: You will insert PRO 2000 Gel two times per day for another 7 days, and then return here for a follow-up visit. You will review your diary with the study staff and answer questions about your use of the gel, your sexual activity, and whether you had any medical problems or discomfort. You will fill out a questionnaire on your opinions of PRO 2000 Gel. You will give urine and blood (26ml or about one and a half tablespoons) for tests like at the Enrollment Visit. Your blood also will be tested to see if your body absorbed any PRO 2000 Gel. You will have a pelvic exam with the lens. A picture will be taken of the inside of your vagina.

Group Discussion: Within 4 weeks after you finish your study visits, you will take part in a group discussion with other women who were in the study, to talk about what it was like to use PRO 2000 Gel. There will be about 3-7 other women in the group, and the group will meet once for 1-2 hours. Everyone will be addressed only by a first name of their choosing during the discussion. If you are concerned about taking part in a group you may choose to discuss your feelings in a one-on-one interview or by telephone with an interviewer, or complete a more detailed questionnaire.

Contact Procedures: Once you join the study and start using the gel, it is very important for us to stay in touch with you and find out how you are doing. We will ask for your name, address, phone number, and other contact information at your first study visit. We also will ask for the names and contact information of people we can contact if we cannot reach you. We will ask you to update this information at each study visit. We will use your contact information to remind you of scheduled study visits. If you miss a visit, we may call or send letters or visit your home to find you. We also will try to reach you through the contact people that you list for us. If we talk to these people, we will not tell them why we are trying to reach you.

Other Requirements: While in this study, you are asked not to insert any objects or products other than PRO 2000 Gel into your vagina. This includes diaphragms, cervical caps, and female condoms, or your own or your partner's fingers. You are asked to have sex only with the male partner who has given informed consent to be in this study with you. You are asked to have vaginal sex with this partner at least 2 times per week, and to use the male condoms that we will give you every time you have sex. You are asked to not receive oral or anal sex.

You are asked to tell the study staff about any medications you take while you are in the study. You are asked to not take part in studies of other vaginal products, and to tell the study staff if you plan to join another study.

If you have any medical problems or discomforts from the gel, study staff may ask you to come in for an extra study visit to check on these problems. If a problem like a sore is found during a pelvic exam, the clinician may take a picture of it with the lens. The clinician also will use a swab to take a sample to test for STD. After 5-7 days, you will be asked to come back for another exam with the lens. If the sore has not healed, the clinician will remove small samples of the skin (about the size of the pencil tip) for more testing.

If you drop out of the study before using the gel for 14 days, study staff may ask you to complete a final study visit with a pelvic exam.

You must return all tubes of PRO 2000 Gel (P) to the study site.

RISKS AND/OR DISCOMFORTS

You may experience some discomfort when having pelvic exams for this study. You may feel discomfort when your blood is drawn. You may feel dizzy or faint. You may have a bruise, swelling or infection where the needle goes into your arm.

You may become embarrassed, worried, or anxious when discussing sexual behaviors and HIV. You may become worried or anxious while waiting for your STD and HIV test results. If you have HIV, knowing your HIV status 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.

Some women who used PRO 2000 Gel in other studies experienced vaginal irritation, vaginal burning, mild vaginal bleeding, genital sores, pain when urinating, abdominal pain, nausea and diarrhea. You also may experience these or other symptoms we do not know about yet. There is a possibility that vaginal sores may increase the risk of getting HIV and other STDs.

There is a possibility that PRO 2000 Gel could be absorbed from the vagina into the blood. It is not known whether this causes any bad effects. There also a possibility that you could be allergic to the material (latex) used to make condoms. “Allergic” means that you have itching, swelling or skin irritation where the condom touches your skin.

We will make every effort to protect your privacy and confidentiality while you are in this study. However, it is possible that others may learn of your participation here, and think that you are infected with HIV, or at “high risk” for HIV. Because of this, others may treat you unfairly or discriminate against you. 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 you are known by someone else in taking part in the group discussion.

PREGNANCY

It is not known if PRO 2000 Gel has any effect on pregnancy in humans, or whether it has any effect on the fetus. Because of the unknown effects and safety concerns of the gel, pregnant women may not join this study. You must have a negative pregnancy test before you join this study. You also must use study-provided condoms each time you have sex while in the study. If you become pregnant during the study, you should tell the clinician right away. You will stop using PRO 2000 Gel and the clinician will talk with you about your choices.

Because it is not known whether PRO 2000 Gel passes through breast-milk and produces undesirable effects in infants, women who are breastfeeding may not be in the study.

BENEFITS

This study may be of no direct benefit to you. However, you or others may benefit in the future from information learned from this study.

You will receive pelvic exams, counseling and testing for HIV and STDs, and STD treatment if needed. This study cannot provide you with other medical care, but study staff will refer you to other available sources of care. If we find that you are infected with HIV, we will refer you for medical care and other services you may need, and tell you about other research studies that you may be eligible for (if any).

NEW FINDINGS

You will be told any new information learned during the course of the study that might cause you to change your mind about staying in the study. At the end of the study, you will be told when the study results may be available and how to learn about them.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT

You may be removed from the study without your consent for the following reasons:

- The investigator decides that continuing in the study would be harmful to you;
- You are unable to use Pro 2000 Gel as instructed, or to keep study appointments;
- You have a bad effect from Pro 2000 Gel;
- You become pregnant;
- You need a treatment not allowed on this study;
- The study is cancelled by the US Food and Drug Administration, NIAID, DCGI, or the company that makes Pro 2000 Gel; and/or
- Other administrative reasons.

ALTERNATIVES TO PARTICIPATION

There are no gels known to prevent HIV infection. The only known way to prevent HIV infection during sex is to use a condom every time you have sex.

COSTS TO YOU

There is no cost to you for being in the study.

You will be reimbursed for your time and effort at scheduled study visits. [*Insert local amount.*]

CONFIDENTIALITY

Your research records, including the photographs of your vagina, will be confidential to the extent permitted by law. You will be identified by a code, and personal information from your records will not be released without your written permission. You will not be personally identified in any publication about this study. However, your records may be reviewed, under guidelines of the Federal Privacy Act, by the United States Food and Drug Administration, NIAID, DCGI, study monitors, and the company that makes PRO 2000 Gel. In addition, your name and address will be provided to the Drug Controller General of India after the study is completed. Every effort will be made to ensure that once your information is transferred to the DCGI it is maintained by them in a confidential manner.

RESEARCH-RELATED INJURY

[*Sites to specify institutional policy:*] Based on what we know now, it is unlikely that you will be injured as a result of being in this study. If you are injured as a result of being in this study, the [institution] will give you immediate necessary treatment for your injuries. The cost of this treatment [will/will not] be charged to you [or your insurance company]. You will be told where you may receive additional treatment for your injuries. There is no program for monetary compensation or other forms of compensation for such injuries.

PROBLEMS OR QUESTIONS

If you ever have any questions about this study, or in case of research-related injuries, you should contact [name of investigator] at [number], or if you have questions about your rights as a research participant, you can call [name and title of IRB/EC member] at [number].

SIGNATURE PAGE:

If you have read the informed consent (or if you have had it read to you) and understand the information, and you voluntarily agree to join this study, please sign your name below.

Volunteer's name (print)

Volunteer's signature

Date

Name of staff member who administered consent (print)

Staff member's signature

Date

Witness' name (print)

Witness' signature

Date

If the volunteer cannot read, this form must be read to the volunteer exactly as written, in the volunteer's native language, and a witness must sign this form to confirm that the correct information was given to the volunteer and that the volunteer freely consents to be in this study.

Appendix VII. Sample Informed Consent Form for Male Partners

Sample Informed Consent Form
DIVISION OF AIDS, NIAID, NIH

HPTN 047
Phase I Safety and Acceptability Study of the
Investigational Vaginal Microbicide PRO 2000/5 Gel (P)
Version 1.0 [date]

MEN

Principal Investigator: [name]
Telephone Number: [number]

INFORMED CONSENT

You and your partner are being asked to take part in the research study named above. This is a study of an experimental gel called PRO 2000/5 Gel (P), or "PRO 2000 Gel" for short. Before you can decide whether or not to take part in this study, we would like to explain the purpose of the study, any risks and benefits to you, and what is expected of you.

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives you information about the study that will be discussed with you. Once you understand the study, and if you agree to take part, you will be asked to sign this consent form. You will be given a copy to keep.

Before you learn about the study, it is important that you know the following:

- Your participation is entirely voluntary.
- You may decide not to take part or to withdraw from the study at any time without losing the benefits of your routine medical care.
- If you decide not to take part in the study, your partner will not be able to take part.
- You cannot take part in the study unless your female sexual partner also agrees to take part.

PURPOSE OF THE STUDY

PRO 2000 Gel is being developed as a "vaginal microbicide." It is designed to be inserted into the vagina to protect women from getting HIV during sex. HIV is the virus that causes AIDS. PRO 2000 Gel is "experimental." This means we do not yet know all the effects of the gel, and we do not know if it works to protect against HIV. Because of this, the Drug Controller General of India (DCGI) and the United States Food and Drug Administration (FDA) have not approved the gel for use in the general population. The DCGI and the FDA have approved this study.

Before research can be done to find out if PRO 2000 Gel protects against HIV, we must first make sure it is safe. So far, PRO 2000 Gel has been tested for safety in 136 women from Europe and the United States. Among these women, the gel was found to be safe and generally well tolerated. The main purpose of this study is to find out if there are any bad effects when PRO 2000 Gel is used by Indian women. Another purpose is to find out what Indian women and men think about using PRO 2000 Gel when having sex.

The study staff here are conducting this study will funding from the US National Institute of Allergy and Infectious Diseases (NIAID). About 60 women and their male partners will take part in the study. If you agree to take part in the study, your part will last for about one month.

PROCEDURES

Enrollment Visit: If you agree to take part in this study, study staff will ask you some questions to find out if you are eligible for the study. If your answers to the questions show that you may be eligible, you will have counseling about HIV and other sexually transmitted diseases (STDs). You will talk about HIV/AIDS and other STDs, the test, what it may mean to know your HIV and STD status, and whether you are prepared to receive HIV and STD test results. You also will talk about ways that HIV and other STDs are spread, and ways to protect against them.

If you are having any health problems that may be due to an STD, you will be offered an exam and STD testing. If you have an STD, you and your partner will not be able to join the study at that time. You will be given treatment and, after you finish the treatment, you can come back to find out if you are eligible for the study at that time.

If you agree to undergo HIV testing, and STD testing if necessary, you will give blood (up to 40 ml or 2½ tablespoons) for the tests. Your test results will be available in about [x days/weeks (site to specify)]. You must receive your HIV test result to be in the study.

During the Study: If you and your partner join the study, your partner will be given tubes of PRO 2000 Gel to insert in her vagina every day for two weeks. You are asked to have vaginal sex together at least two times per week during these weeks. You must use condoms given to you by the study staff every time you have sex together. You are asked not to have oral or anal sex with your partner, and not to insert your fingers or other objects into her vagina. You are asked to have sex only with this partner during these two weeks.

You also are asked tell the study staff if your skin comes into contact with PRO 2000 Gel. If this happens, study staff will ask you if you had any reactions to the gel. They also may ask you to come to the clinic for an exam.

After you and your partner use PRO 2000 Gel for two weeks, you will be asked to take part in a group discussion with other men who took part in the study, to talk about your experiences with the gel. Everyone will only be addressed by a first name of their choosing during the discussion. [If you are concerned about taking part in a group you may choose to discuss your feelings in a one-on-one interview or by telephone with an interviewer, or complete a more detailed questionnaire.] You may choose not to come to the group and still be in the study.

RISKS AND/OR DISCOMFORTS

Because you will have sex with your partner after she has put PRO 2000 Gel in her vagina, it is possible that some of the gel will come into contact with your skin. It is not known whether PRO 2000 Gel causes side effects when it comes into contact with the penis or the skin around the penis. Therefore, it is important to use the gel only as instructed, and to use condoms every time you have sex with your partner.

There is a possibility you may be allergic to the material (latex) used to make condoms. "Allergic" means you have itching, swelling or skin irritation where the condom touches your skin.

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

You may become embarrassed, worried, or anxious when discussing sexual behaviors and HIV. You may become worried or anxious while waiting for your STD and HIV test results. If you have HIV, knowing your HIV status 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.

We will make every effort to protect your privacy and confidentiality while you are in this study. However, it is possible that others may learn of your participation, and think that you are infected with HIV, or at "high risk" for HIV. Because of this, others may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job. You also could have problems being accepted by your family or community. Also, if you take part in the group discussion, there is a risk to your privacy if you are known by someone else in the group.

BENEFITS

This study may be of no direct benefit to you. However, you or others may benefit in the future from information learned from this study. You will receive counseling and testing for HIV and STDs, and STD treatment if needed. If you have health problems that may be due to an STD, you will receive an exam, tests, and treatment if needed. This study cannot provide you with other medical care, but study staff will refer you to other available sources of care if we find that you are infected with HIV.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT

You may be removed from the study without your consent for the following reasons:

- Your partner stops taking part in the study;
- The investigator decides that continuing in the study would be harmful to you or your partner;
- The study is cancelled by the FDA, NIAID, DCGI, or the company that makes PRO 2000 Gel; and/or
- Other administrative reasons.

ALTERNATIVES TO PARTICIPATION

There are no gels known to prevent HIV infection. The only known way to prevent HIV infection during sex is to use a condom every time you have sex.

COSTS TO YOU

There is no cost to you for being in the study.

CONFIDENTIALITY

Your research records will be confidential to the extent permitted by law. You will be identified by a code, and personal information from your records will not be released without your written permission. You will not be personally identified in any publication about this study. However, your records may be reviewed, under guidelines of the Federal Privacy Act, by the United States Food and Drug Administration, NIAID, DCGI, study monitors, and the company that makes PRO 2000 Gel. In addition, your name and address will be provided to the Drug Controller General of India after the study is completed. Every effort will be made to ensure that once your information is transferred to the DCGI it is maintained by them in a confidential manner.

PROBLEMS OR QUESTIONS

If you ever have any questions about this study, or in case of research-related injuries, you should contact [name of investigator] at [number], or if you have questions about your rights as a research participant, you can call [name and title of IRB/EC member] at [number].

SIGNATURE PAGE

If you have read this informed consent form (or if you have it explained to you) and understand the information, and you voluntarily agree to join this study, please sign your name or make your mark below.

_____ Participant Name (printed)	_____ Participant Signature	_____ Date
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_____ Name of staff member who Administered consent (printed)	_____ Participant Signature	_____ Date
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_____ Witness Name (printed)	_____ Witness Signature	_____ Date
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If the participant cannot read, this form must be read to the participant exactly as written, in the participant native language, and a witness must sign this form to confirm that the correct information was given to the participant and that the participant freely consented to join the study.

Appendix VIII: Analysis Tables

1. Study completion - number and percentage of subjects completing the study. Day of discontinuation.
2. Baseline demographics - descriptive summaries of demographic characteristics.
3. Pelvic exam at baseline - descriptive summaries of pelvic exam variables at baseline.
4. Colposcopic exam at baseline - descriptive summaries of colposcopic exam at baseline.
5. Laboratory measurements at baseline - descriptive summaries of laboratory measurements.
6. Acceptability at baseline - descriptive summaries of acceptability variables at baseline.
7. Adherence - descriptive summaries of adherence.
8. Protocol deviations - descriptive summaries of protocol deviations.
9. Pelvic exam at Day 2, Day 7, and Day 14 - descriptive summaries of pelvic exam variables at Day 2, Day 7, and Day 14.
10. Change in selected pelvic exam variables from baseline to Day 2, Day 7 or Day 14 - change from baseline to Day 2, Day 7, and Day 14 pelvic exam variables.
11. Colposcopic exam at Day 2 and Day 14 - descriptive summaries of colposcopic exam at Day 2 and Day 14.
12. Change in selected colposcopic exam variables from baseline to Day 2 and Day 14 - baseline, Day 2, and Day 14 colposcopic exam variables.
13. Treatment emergent adverse events - number of subjects experiencing adverse events while on treatment by MeDRA SOC and preferred term. Summaries will be given by severity and by relationship to study treatment.
14. Change in selected AEs from baseline to Day 2, Day 7, and Day 14 - number and percentage of subjects experiencing AEs at baseline and at Day 2, Day 7, and Day 14 follow-up visits.
15. Laboratory data at Day 14 - descriptive summaries of laboratory measurements.

16. Change in laboratory data - descriptive summaries of the change in laboratory measurements from baseline to Day 14.
17. Acceptability at Day 14 - descriptive summaries of acceptability variables at and Day 14.
18. Change in acceptability variables from baseline to Day 14 - baseline and Day 14 acceptability variables.
19. Concomitant medications - descriptive summaries of concomitant medications at baseline, Day 2, Day 7, and Day 14.