**MTN-037**

# A Phase 1 Safety and Pharmacokinetic Study of PC-1005 (MIV-150/Zinc Acetate/Carrageenan Gel) Administered Rectally to HIV-1 Seronegative Adults

**Microbicide Trials Network**

**Funding Agencies:**
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**US *Eunice Kennedy Shriver* National Institute of Child Health and Human Development**
**US National Institute of Mental Health**
**US National Institutes of Health**

**Grant Numbers:**
**UM1AI068633, UM1AI068615, UM1AI106707**

**DAIDS Protocol ID: 35122**

**IND Sponsor:**
**DAIDS**

**IND #TBD**

**Protocol Chair: Craig Hendrix, MD**

**Version 1.0**

**November 9, 2017**

**MTN-037**

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**A Phase 1 Safety and Pharmacokinetic Study of PC-1005 (MIV-150/Zinc Acetate/Carrageenan Gel) Administered Rectally to HIV-1 Seronegative Adults**

## LIST OF ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| AE | adverse event |
| AIDS | Acquired Immunodeficiency Syndrome |
| ALT | alanine transaminase |
| API | active pharmaceutical ingredient |
| ARV | antiretroviral |
| AST | aspartate aminotransferase |
| ASTM | American Society for Testing and Materials |
| AUC | area under the curve |
| $AUC_{inf}$ | area under the curve extrapolated to infinity |
| $AUC_{last}$ | area under the curve up to the last measurable concentration |
| BAT or BAT24 | Dosing Before and After Sex </= Two doses in 24h |
| BID | bis in die (twice a day) |
| BRWG | Behavioral Research Working Group |
| BSWG | Biomedical Science Working Group |
| BV | bacterial vaginosis |
| CAPRISA | Centre for the AIDS Programme of Research in South Africa |
| CASI | computer assisted self-interview |
| CBC | complete blood count |
| CD4 | cluster of differentiation 4 |
| CDC | Centers for Disease Control and Prevention |
| cDNA | complementary DNA |
| CFR | Code of Federal Regulations |
| CG | carrageenan |
| CI | Confidence Interval |
| $C_{max}$ | maximum concentration |
| CMRB | Clinical Microbicide Research Branch |
| CNS | central nervous system |
| CRF | case report form |
| CRMS | Clinical Research Management System |
| CRS | Clinical Research Site |
| CT | *Chlamydia trachomatis,* Chlamydia |
| CTA | Clinical Trial Agreement |
| CV | coefficient of variation |
| CVL | cervicovaginal lavage |
| CWG | Community Working Group |
| CYP1A2 | cytochrome P450 family 1, subfamily A2 genetic locus |
| CYP2C8 | cytochrome P450 family 2, subfamily C8 genetic locus |
| CYP2C9 | cytochrome P450 family 2, subfamily C9 genetic locus |
| CYP2C19 | cytochrome P450 family 2, subfamily C19 genetic locus |
| CYP2D6 | cytochrome P450 family 2, subfamily D6 genetic locus |
| CYP2E1 | cytochrome P450 family 2, subfamily E1 genetic locus |

| | |
|---|---|
| CYP3A | cytochrome P450, family 3, subfamily A genetic locus |
| CYP3A4 | cytochrome P450 family 3, subfamily A4 genetic locus |
| CYP450 | cytochrome P450 |
| DAERS | DAIDS Adverse Experience Reporting System |
| DAIDS | Division of AIDS |
| DAIDS PRO | DAIDS Protocol Registration Office |
| DAPY | di-amino-pyrimidine |
| DLV | delavirdine |
| DNA | deoxyribonucleic acid |
| EAE | expedited adverse event |
| EC | ethics committees |
| $EC_{50}$ | 50% effective concentration |
| EFV | efavirenz |
| EMBRACE | Evaluation of Maternal and Baby Outcome Registry After Chemoprophylactic Exposure |
| ENR | enrollment |
| FDA | (US) Food and Drug Administration |
| FHCRC | Fred Hutchinson Cancer Research Center |
| FMO | flavin-containing monooxygenase |
| g | grams |
| GC | *Neisseria gonorrhoeae,* gonorrhea |
| GCP | Good Clinical Practices |
| GEE | generalized estimating equations |
| GGT | gamma glutamyl transferase |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practices |
| GRAS | Generally Recognized as Safe |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCG | human chorionic gonadotropin |
| HCV | hepatitis C virus |
| HEC | hydroxyethylcellulose |
| HEENT | Head, Eye, Ear, Nose and Throat Examination |
| HHS | (U.S.) Department of Health and Human Services |
| HIV | Human Immunodeficiency Virus |
| HIV-1 | Human Immunodeficiency Virus type 1 |
| HIV-1 IIIB | Human Immunodeficiency Virus type 1, IIIB strain |
| HPTN | HIV Prevention Trials Network |
| HPV | human papillomavirus |
| HSV | herpes simplex virus |
| HSV-1/2 | herpes simplex virus type 1/2 |
| hu-PBL | human peripheral blood lymphocytes |
| hu-SCID | humanized severe combined immunodeficient |
| IATA | International Air Transport Association |
| IB | Investigator's Brochure |
| $IC_{50}$ | half maximal inhibitory concentration |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| IL | Interleukin |

| | |
|---|---|
| IND | Investigational New Drug |
| INR | International normalized ratio |
| IoR | Investigator of Record |
| IRB | Institutional Review Board |
| IUD | intrauterine device |
| IVR | intravaginal ring |
| kg | kilogram |
| LC | Laboratory Center |
| LDMS | Laboratory Data Management System |
| LLOQ | lower limit of quantification |
| LOC | Leadership and Operations Center |
| µg | microgram |
| MAGI | multinuclear activation of a galactosidase indicator |
| MDP | Microbicides Development Programme |
| mg | milligram |
| MIV-150 | Urea, *N*-(5-cyano-2-pyridinyl)-*N*'-[(1*S*,2*S*)-2-[6-fluoro-2-hydroxy-3-(1-oxopropyl)phenyl]cyclopropyl]-; an NNRTI |
| mL | milliliter |
| mM | millimolar |
| MO | Medical Officer |
| mOsm | milliosmole |
| MPA | medroxyprogesterone acetate |
| MPID | Maternal and Pediatric Infectious Diseases |
| MPT | multipurpose prevention technology |
| mRNA | mitochondrial ribonucleic acid |
| MSM | men who have sex with men |
| MT-2 | human melatonin receptor 2 |
| MTN | Microbicide Trials Network |
| MTT | 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a tetrazole |
| MZC | MIV-150, zinc acetate (ZA), and carrageenan (CG) |
| n | number |
| N-9 | nonoxynol-9 |
| NAAT | nucleic acid amplification test |
| NCD | nanocrystal dispersion |
| NF | National Formulary |
| ng | nanogram |
| NHANES | National Health and Nutrition Examination Survey |
| nM | nanomolar |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NICHD | National Institute of Child Health and Human Development |
| NIH | National Institutes of Health |
| NIMH | National Institute of Mental Health |
| NL | network laboratory |
| NNRTI | non-nucleoside reverse transcriptase inhibitor |
| NRTI | nucleotide analogue reverse transcriptase inhibitor |
| NOAEL | no observed adverse effect level |
| NOEL | no observed effect level |
| NSAIDS | non-steroidal anti-inflammatory drugs |
| NVP | nevirapine |

| | |
|---|---|
| OHRP | Office for Human Research Protections |
| P24 | protein 24 |
| PBL | peripheral blood lymphocytes |
| PBMC | peripheral blood mononuclear cell |
| PBS | phosphate-buffered saline |
| PC-1005 | 0.002% MIV-150/0.3% zinc acetate [ZA] in 3.0% carrageenan [CG] gel |
| PCR | polymerase chain reaction |
| PD | pharmacodynamics |
| PEG | polyethylene glycol |
| PEP | post-exposure prophylaxis |
| PFU/pfu | plaque-forming unit |
| pH | potential of hydrogen |
| PID | pelvic inflammatory disease |
| PK | pharmacokinetics |
| PMPA | 9-[(R)-2-(phosphonomethoxy)propyl]adenine monohydrate |
| PoR | Pharmacist of Record |
| PPD | Pharmaceutical Product Development, Inc. |
| PrEP | pre-exposure prophylaxis |
| PRO | Protocol Registration Office |
| PSP | Prevention Sciences Program |
| PSRT | Protocol Safety Review Team |
| PSS | polystyrene sulfonate |
| PsV | pseudovirus |
| PT | prothrombin time |
| PTID | participant identification |
| PVC | polyvinyl chloride |
| PVI | penile-vaginal intercourse |
| RAI | receptive anal intercourse |
| RE | Regulatory Entity |
| RG | reduced-glycerin |
| RNA | ribonucleic acid |
| RSC | Regulatory Support Center |
| RT | reverse transcriptase |
| RTI | reproductive tract infection |
| RT-PCR | real-time polymerase chain reaction |
| Rx | treatment |
| SAE | serious adverse event |
| SCHARP | Statistical Center for HIV/AIDS Research & Prevention |
| SCID | severe combined immunodeficiency |
| SCR | screening |
| SDMC | Statistical Data Management Center |
| SHIV | simian human immunodeficiency virus |
| SMC | Study Monitoring Committee |
| SOP | standard operating procedure |
| SMS | short message service |
| SSP | study specific procedures |
| STI | sexually transmitted infection |
| SUSAR | suspected, unexpected serious adverse reaction |
| TCID | tissue culture infective dose |

| | |
|---|---|
| TEAE | treatment-emergent adverse events |
| TFV | tenofovir |
| TID | ter in die (three times a day) |
| $T_{1/2}$ | half-life |
| $T_{max}$ | Time at which $C_{max}$ is observed |
| TPGS | tocopheryl polyethylene glycol succinate |
| UA | urinalysis |
| ULN | upper limit of normal |
| UNAIDS | Joint United Nations Programme on HIV and AIDS |
| UPMC | University of Pittsburgh Medical Center |
| USA | United States of America |
| USP | United States Pharmacopoeia |
| UTI | urinary tract infection |
| VR | vaginal ring |
| WHO | World Health Organization |
| WSI | web-based self-interviews |
| w/w | weight/weight |
| wt | wild type |
| ZA | zinc acetate |

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**INVESTIGATOR SIGNATURE FORM**

**Version 1.0**
**November 9, 2017**
**A Study of the Microbicide Trials Network**

**Funded by:**
Division of AIDS (DAIDS), US National Institute of Allergy and Infectious Diseases
US Eunice Kennedy Shriver National Institute of
Child Health and Human Development
US National Institute of Mental Health
US National Institutes of Health (NIH)

**IND Sponsors:**
DAIDS (DAIDS Protocol ID: 35122)

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference for Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., NIH, DAIDS) and institutional policies.

I agree to maintain all study documentation for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. DAIDS will inform the investigator/institution as to when these documents no longer need to be retained.

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

_____
Name of Investigator of Record (print)

_____ _____
Signature of Investigator of Record Date

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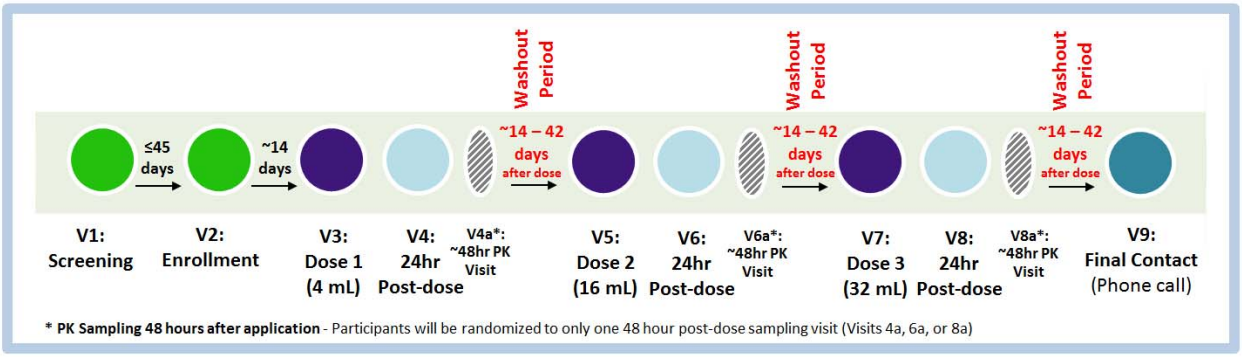
## PROTOCOL SUMMARY

| | |
|---|---|
| **Short Title:** | Safety and PK Study of PC-1005 Applied Rectally |
| **Clinical Phase:** | Phase 1 |
| **IND Sponsor:** | DAIDS |
| **Protocol Chair**: | Craig Hendrix, MD |
| **Sample Size:** | MTN-037 will enroll approximately 12 participants. |
| **Study Population:** | HIV-uninfected men and women (cis or transgender) with a history of consensual RAI who are 18 years or older at Screening |
| **Study Sites:** | Sites selected by MTN Executive Committee |
| **Study Design:** | Phase 1, open label, sequential dose/volume escalation study |
| **Study Duration:** | Approximately 3-5 months of follow-up per participant is planned with a projected accrual period of 6-8 months. The total duration of the study will be approximately 11-13 months. |
| **Study Products:** | PC-1005 (0.002% MIV-150/0.3% zinc acetate [ZA] in 3.0% carrageenan [CG] gel) |
| **Study Regimen:** | Each participant will receive a dose of PC-1005 (4mL, 16mL or 32mL) rectally administered by clinic staff in the clinic. Safety laboratory tests, PK and PD assessments will be performed within 24 hours after each gel administration. Each participant will also be randomized to have a 48 hour post-dosing visit after one of the three doses. After a washout period of two to six weeks (to accommodate scheduling around the menstrual cycles of female participants) following each dosing visit, dosing with the next sequential escalating volume will be administered. A final study contact will occur after the third dosing visit and associated washout period. |

**Figure 1: MTN-037 Study Visit Schedule**




## Primary Objectives:

### Safety

- To evaluate the safety of PC-1005 gel formulation (0.002% MIV-150/0.3% zinc acetate [ZA] in 3.0% carrageenan [CG] gel) when applied rectally

### Pharmacokinetics

- To characterize the systemic and compartmental pharmacokinetics of MIV-150 following rectal gel application

## Primary Endpoints:

### Safety

- Grade 2 or higher AEs as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, and/or Addenda 1, 2 and 3 (Female Genital [Dated November 2007], Male Genital [Dated November 2007] and Rectal [Clarification Dated May 2012] Grading Tables for Use in Microbicide Studies).

### Pharmacokinetics

- MIV-150 concentrations in:
    - Plasma
    - Rectal fluid
    - Rectal mucosal tissue homogenates

## Secondary Objectives:

### Acceptability

- To compare the acceptability of PC-1005 gel formulation across the three doses when administered rectally

### Pharmacokinetics

- To characterize the compartmental pharmacokinetics of MIV-150 in vaginal fluid following rectal gel application

**Secondary Endpoints:**

**Acceptability**

- Participant self-report of comfort with gel application, liking the product across doses, and perceived side-effects

**Pharmacokinetics**

- MIV-150 concentrations in vaginal fluid

**Exploratory Objectives:**

**Biomarkers of Mucosal Safety**

- To evaluate the mucosal toxicity of PC-1005 gel formulation when applied rectally

**Ex Vivo Antiviral Activity**

- To assess the preliminary (ex vivo) antiviral activity of PC-1005 gel formulation after product is applied rectally

**Exploratory Endpoints:**

**Biomarkers of Mucosal Safety**

- Rectal histology
- Tissue archive

**Ex Vivo Antiviral Activity**

- Changes in HIV-1 p24 levels in colorectal explant culture supernatant
- Anti-HIV activity in rectal fluid

# 1 KEY ROLES

## 1.1 Protocol Identification

| | |
|---|---|
| Protocol Title: | A Phase 1 Safety and Pharmacokinetic Study of PC-1005 (MIV-150/Zinc Acetate/Carrageenan Gel) Administered Rectally to HIV-1 Seronegative Adults |
| Protocol Number: | MTN-037 |
| Short Title: | Safety and PK Study of PC-1005 Applied Rectally |
| Date: | November 9, 2017 |

## 1.2 Funding Agencies, Sponsor and Monitor Identification

| | |
|---|---|
| Funding Agencies: | US Division of AIDS (DAIDS)/National Institute of Allergy and Infectious Diseases (NIAID)<br>National Institutes of Health (NIH)<br>5601 Fishers Lane<br>Rockville, MD 20852 USA<br><br>US National Institute of Mental Health (NIMH)<br>6001 Executive Boulevard<br>Rockville, MD 20852 USA<br><br>US *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)<br>Maternal and Pediatric Infectious Diseases (MPID) Branch<br>6100 Executive Boulevard<br>Rockville, MD 20852 USA |
| IND Sponsors: | US Division of AIDS (DAIDS)/National Institute of Allergy and Infectious Diseases (NIAID)<br>National Institutes of Health (NIH)<br>5601 Fishers Lane<br>Rockville, MD 20852 USA |
| Monitor: | Pharmaceutical Product Development (PPD), Inc.<br>929 North Front St.<br>Wilmington, NC 28401-3331 USA |

### 1.3 Medical Officer

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MTN LC Pharmacology Core
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### 1.5 Data Center

MTN Statistical and Data Management Center (SDMC)
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### 1.6 Study Implementation

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# 2 INTRODUCTION

## 2.1 Background of Rectal Microbicide Research and Study Rationale

Microbicides are products that are designed to be applied to the vaginal or rectal mucosa with the intent of preventing the acquisition of sexually transmitted infections (STIs) including the human immunodeficiency virus (HIV),[1] human papillomavirus (HPV), and herpes simplex virus type- 2 (HSV-2). While the original impetus for vaginal microbicide development was to provide women with options for HIV prevention in settings where their partners were unwilling to use condoms for penile-vaginal intercourse, there is recognition that rectal microbicides are needed for men and women who practice receptive anal intercourse (RAI). Similar to lubricants, which are commonly used during anal intercourse (AI), the ideal rectal microbicide would enhance sexual pleasure and potentially result in higher adherence than has been found in most vaginal microbicide trials to date.

HIV

According to UNAIDS, there were approximately 36.7 million people worldwide living with HIV/AIDS at the end of 2015; that year, an estimated 2.1 million individuals worldwide became newly infected with HIV.[2] Unprotected RAI is the sexual behavior with the highest per act risk of HIV acquisition, conferring approximately 10 to 20 times more risk than unprotected receptive vaginal intercourse .[3, 4] Globally, men who have sex with men (MSM) are 19 times more likely to be living with HIV compared with the general population;[5, 6] transgender women are 49 times more likely than the general population to be living with HIV.[7]

HPV

While most genital HPV infections are self-limiting and subclinical, infection is extremely common; estimated lifetime risk is about 75%. Some HPV types cause genital warts and other types are oncogenic. Condoms may not provide full protection.[8] Anal HPV infection prevalence is high among MSM (18-89 years of age) at over 57% as detected using PCR testing in a large US multisite study.[9] Its prevalence in studies among HIV-positive MSM is often double that among HIV-negative men.[10] Infection with HPV increases susceptibility to HIV.[11] HPV infection among MSM is the primary risk factor for developing anal cancer.[10] Many HPV genotypes are associated with anal cancer and an increased risk among females for cervical,[8] vulvar, and vaginal cancers, as well as a significant proportion of head and neck cancers.[8] Two of the most oncogenic genotypes, HPV-16 and 18, are associated with 75% of cervical cancers, 50% of vulvar cancers, 50–75% of vaginal cancers and 80% of anal cancers. While HPV vaccines are now commercially available for males and females, uptake has been low due to cost, dosing regimen, and parental objection. Other challenges are that vaccines are not fully protective against at least 36 other HPV strains associated with anogenital infections, and cold supply chain requirements limit their utility in developing countries.[8, 11, 12] The vaccine is most effective when given prior to exposure to HPV viruses, thus prior to sexual debut.[13] These limitations confirm the need for other preventive modalities such as microbicides with anti-HPV activity.[11]

HSV-2

The seroprevalence of HSV-2 among Americans ages 14-49 is 15.5%.[14] A large population-based survey of US men (part of the NHANES study) revealed that while self-reported same-sex sexual contact (ever) and gay sexual orientation were important markers for high risk of HIV infection, there were no significant differences in HSV-2 prevalence by sexual orientation, when dichotomized as MSM-Ever and non-MSM, at about 18% and 12%, respectively.[15]Infection with HSV-2 increases susceptibility to HIV.[11] There are no FDA-approved topical antiretroviral products for HSV prevention. However, the CAPRISA 004 study, which evaluated the anti-HIV activity of 1% tenofovir gel using a BAT24 (Before and After sex, not to exceed Two doses in 24 hours) dosing strategy in a randomized, placebo-controlled trial among 889 HIV-uninfected South African women, unexpectedly showed a 'bonus' finding of a 51% reduction in HSV-2 incidence in the tenofovir arm, consistent with previous in vitro work demonstrating mucosal concentrations achieved with 1% tenofovir gel have direct antiherpetic activity.[16]

## 2.2 PC-1005 Gel

PC-1005 is a multipurpose prevention technology (MPT) microbicide in development that is active against HIV, HPV, and HSV-2, and has been formulated to be suitable for both vaginal and rectal use.[17] As described below, efficacy results shown in preclinical animal studies suggest the potential of PC-1005 as both an on-demand (coitally dependent) vaginal microbicide and a method of post-exposure prophylaxis (PEP) for preventing HSV-2 and HPV.[11] PC-1005 has been found safe for vaginal use in a Phase 1 trial in which women used the gel once daily for 14 days.[17] MTN-037 will evaluate the safety and pharmacokinetics (PK) of PC-1005 gel administered rectally using an applicator. Demonstrating that PC-1005 is safe in the rectal compartment in men and women will be a critical first study for the development of PC-1005 for rectal use. If proven effective, PC-1005 would be the first MPT of any kind to simultaneously prevent HIV, HSV-2, and HPV.

PC-1005 gel is a translucent gel containing 50 µM MIV-150, a potent NNRTI not used for HIV treatment; 13.7 mM zinc acetate (ZA) dihydrate, a selective antiviral agent generally recognized as safe (GRAS) by the US FDA;[17] and carrageenan (CG), a gelling agent derived from seaweed (also GRAS) (See Table 1 for composition of PC-1005).[18] CG has been used as a thickener in commercially available pre-lubricated condoms and sexual lubricants.[8] PC-1005 gel formulation is iso-osmolar. PC-1005 in its early development was also referred to as MZC (MIV-150, zinc acetate [ZA], and carrageenan [CG]).[11, 17] MIV-150 has been licensed to the Population Council from Medivir.[19]

**Table 1: Composition of PC-1005**

| Composition of PC-1005 | |
|---|---|
| % w/w | 0.002% MIV-150 and 0.3% zinc acetate [ZA] in 3.0% carrageenan [CG] gel |
| Amounts/g of gel | 18.4 µg MIV-150, 0.894 mg zinc ($Zn^{2+}$), and 30 mg of CG |
| Concentrations | 50.0 µM MIV-150 and 13.7 mM ZA (with CG as a vehicle) |

## Description and Mechanism of Action

PC-1005 gel's broad spectrum activity and its excellent safety profile as shown in pre-clinical vaginal and rectal models are due to the unique combination of active pharmaceutical ingredients (APIs). MIV-150 ($C_{19}H_{17}FN_4O_3$) is a potent, HIV-specific NNRTI with CYP450-mediated metabolism[19] that belongs to the group of phenethylthiazolylthiourea derivatives.[11] NNRTIs bind allosterically to the HIV reverse transcriptase (RT) enzyme, preventing viral replication and consequently production of infectious virus. While MIV-150 was originally developed as an oral antiretroviral (ARV) (by Medivir AB; Sweden), its characteristics of rapid systemic clearance and poor systemic absorption rendered it more suitable for use as a topical microbicide.[20]

ZA is a selective antiviral agent that inhibits HIV and HSV-2, appearing to have at least two modes of inhibition against HIV: it inhibits HIV RT at a site not targeted by other RTIs,[21] it has additive effects with MIV-150, and it has immunomodulatory effects that might impart antiviral activity.[11, 21-24] $Zn^{2+}$ is thought to inhibit the synthesis of HIV-RT by forming a highly stable RT-$Zn^{2+}$ (primer-template) complex which ties up RT potentially for hours. Zinc-based products appear to exploit a weakness in HIV and in theory could slow its replication.[21]

Carrageenan is a sulfated polysaccharide extracted from red algae and is a potent infection inhibitor of a variety of sexually transmitted HPVs, acting primarily by inhibiting HPV virion binding to heparan sulfate on the basement membrane.[25] CG resembles heparan sulfate, an HPV attachment factor. It also acts through a post-attachment heparan sulfate-independent effect. While CG demonstrates in vitro activity against HSV and some HIV strains, it is much more potent against genital HPV. Some CG products, even when diluted by a factor of 1 million, block HPV infection.[8]

A first-generation prototype gel (MZC), used in early nonhuman primate and other animal studies, and a modified MZC gel are described by Kizima et al.[11] Modified MZC gel includes a buffer as well as co-solvents and preservatives more suited to clinical testing in humans; its osmolality is 447mOsmol/kg and viscosity (freshly prepared) is 29,900 cP. It is stable for 12 months at 86°F/30°C/65% RH (relative humidity) and for 9 months at 104°F/40°C/75% RH. After 1 month at 122°F/50°C, MZC remained stable. The gel exhibits shear thinning spreading behavior, an important gel property allowing gel to spread evenly throughout the vaginal or rectal compartment.[11, 12]

## Strength of Study Product

The PC-1005 gel strength proposed for use in MTN-037 is 0.002% MIV-150/0.3% ZA in 3.0% CG gel, called PC-1005_D by Population Council. The different formulations of PC-1005 used in preclinical testing are shown in Table 2.

**Table 2: PC-1005 Formulations Tested During Preclinical Evaluation**

| **Attribute** [27] | **PC-1005_A**** | **PC-1005_B**** | **PC-1005_C**** | **PC-1005_C** Protocol: PC-558 | **PC-1005_D** | **PC-1005_D** Protocol: MTN-037 |
|---|---|---|---|---|---|---|
| **Use** | Preclinical | Preclinical | Preclinical | Clinical (vaginal) | Preclinical (rectal) | Clinical (vaginal/rectal) |
| **Carrageenan (λ:κ)** | 95:5 | 60:40 | 90:10 | 90:10 | 82:18 | 82:18 |
| **Lot** | PDR98-15 | RERK-4137 | LamCarr002 or LamCarr 003 | LamCarr003 | LamCarr004 | LamCarr004 |
| **MIV-150 assay** | In spec | In spec | In spec | In spec | In spec | (In spec)* |
| **Zinc assay** | In spec | In spec | In spec | In spec | In spec | (In spec)* |
| **Viscosity (cP)** | In spec | In spec | In spec | In spec | In spec | (In spec)* |
| **Osmolality mOsmol/kg)** | In spec | In spec | In spec | In spec | In spec | (In spec)* |

## 2.3 Non-Clinical Studies of PC-1005 Gel

Anti-HIV-1 Activity

PC-1005 exhibits broad, potent in vitro activity against different HIV clades, tropisms, phenotypes, and drug-resistant mutations (DRMs).[11] MIV-150 is an allosteric inhibitor of HIV RT with an $IC_{50}$ versus pansensitive virus in the 3 nM range in an in vitro MT-4 cell assay in the presence of 50% human serum. This is more potent than other licensed drugs in the NNRTI class tested, including efavirenz (8 nM). MIV-150 also retains activity against some single point mutant strains that become resistant to efavirenz. It loses activity in the presence of virus with 103N+100I. It does retain potency with mutant strains harboring 181C+138K+101E.[26] MIV-150 retains this activity in the presence of semen using in vitro experiments against SHIV.[19] MZC is active against $HIV_{BaL}$ infection in human ectocervical mucosa in a single challenge model as well as under stringent conditions of co-challenge with HSV-2.[27]

While zinc does not directly prevent infection with HIV, it has been shown to enhance peak functioning of the immune system with resulting resistance to infection by bacteria, viruses, and fungi in vitro and in animal and human models.[28] Zinc in the form of nontoxic, free $Zn^{2+}$ within body cells, even in relatively low concentrations, may slow HIV viral replication. $Zn^{2+}$ inhibits HIV-RT (reverse transcriptase) by binding RT in a relatively chemically inactive RT-$Zn^{2+}$ (primer template) complex, potentially for hours.[21]

The carrageenan-based vaginal microbicide gel Carraguard® exhibited some anti-infective activity when evaluated in a Phase I safety trial. CVLs (5 mL) collected from participants were tested for carrageenan anti-[HIV] infective activity using an ex vivo titer reduction assay. Ex vivo evaluation revealed that Carraguard® gel retained some ability to reduce HIV infection of target cells from 15 minutes up to 8–24 hours after vaginal application.[29]

Resistance (HIV)

MIV-150 has demonstrated a good resistance profile as displayed in Table 3 and Table 4 below. Additional information for individual studies may be found in the Investigator's Brochure (IB).[19]

**Table 3: Summary of Nonclinical Resistance Development – In vitro Studies**

| Study Type[19] | Assay Type/ Test Model | Outcome |
|---|---|---|
| MIV-150 resistance development (Non-GLP) | MT-4 cells | Resistance development in the presence of MIV-150 was slower than for any other NNRTI studied. There is a significant delay in resistance mutant development after culture with MIV-150 compared to culture with marketed NNRTIs. |
| MIV-150 and ZA resistance development and cross-resistance with other related antiretrovirals (Non-GLP) | MAGI or PBMC assay/MT-4 cells | Triple mutant resistant viruses were isolated in the presence of increasing concentrations of MIV-150 in MT-4 cells resulting in $IC_{50}$ > 10-fold when compared to WT virus for MIV-150, MIV-160, efavirenz, and nevirapine. Combinations of at least 2 − 3 mutations are needed to decrease HIV susceptibility to MIV-150. |

**Table 4: Summary of a Nonclinical Resistance Development In vivo Study (SHIV-RT)**

| Study Type[19] | Species/ Sex | Route/Duration of Dosing | Dose | Outcome |
|---|---|---|---|---|
| In vivo selection of DRMs by MIV-150 in SHIV-RT infected macaques (Non-GLP) | macaques/females (n = 4) | Intramuscularly/ 3 weeks daily/1 week off/3 weeks daily | 0.5 mg/kg/day | Proof-of-concept that MIV-150 can select for viruses expressing DRMs. |
| | macaques/females (n = 6) | MIV-150 IVR/ 8 weeks | 100 mg MIV-150 IVR | Sustained topical delivery of high doses of MIV-150 select for rare DRMs in one-third of the animals. |

In other data from macaques, modified MZC gel applied vaginally did not select for NNRTI-resistant variants; DRMs were not detected in the RT gene of SHIV-RT circulating in 6 infected animals (Kizima et al 2014).[11]

Cross-resistance (HIV)

An in vitro evaluation of development of cross-resistance of HIV-1 using MIV-150 and ZA (separately) with other related antiretrovirals (non-GLP) suggested the absence of cross-resistance between these APIs with a likely different mode of action. No resistant virus was selected, at least during the 9-week in vitro selection, against the combination of 0.2 nM MIV-150/180 µM ZA. MIV-150 resistant viruses were selected in the presence of MIV-

150 only but not in the MIV-150/ZA combined treatment. (see Table 5).[19] A ZA resistant mutant was found to have no cross-resistance with NNRTIs and Lamivudine.[19]

**Table 5: Mutations Selected by MIV-150**

| HIV-1 | Cell system for resistance selection | $EC_{50}$ (95% confidence interval) MIV-150 (nM) | NNRTI mutations |
|---|---|---|---|
| MN WT | N/A | 0.2 (0.18 to 0.25) | WT |
| MN MIV-150-selected | MT-4 | >10 | L100I, K103N, Y181C |
| MN MIV-150-selected | MT-4 | >10 | E138G, Y181C, M230L |
| 92BR014 WT | N/A | 0.7 (0.6 to 0.9) | WT |
| 92BR014 MIV-150-selected | PBMCs | ND* | K103N, E138G, Y181N, M230L |
| 92BR014 MIV-150/ZA-selected | PBMCs | No resistant virus was selected | |

$EC_{50}$ = concentration causing half-maximal inhibition; N/A = Not applicable; ND = Not determined; * virus titer too low to perform the antiviral assay

Mutagenicity

Nonclinical evaluation of the mutagenic potential of MIV-150 (GLP) with Ames Test (bacterial reverse mutation assay, a predictive test of rodent and human carcinogenicity) found no evidence of mutagenic activity in any strain of *Salmonella typhimurium* and *E. Coli*, either with or without metabolic activation.[19]

In vitro cytogenetics evaluation (also GLP) using Chromosome Aberration Assay found that frequencies of cells with structural aberrations were not significantly different from those seen in solvent controls. Frequencies of aberrant cells treated in cultures fell within the historical negative control range. MIV-150 did not induce chromosome aberrations when tested to the limit of solubility in cultured human peripheral blood lymphocytes in the absence and presence of metabolic activation.[19]

Recent reports on the oral administration of undegraded sodium and calcium carrageenan of known quality to pregnant animals reveals fetotoxic effects, with or without frank teratogenic effects, in some species at levels that do not greatly exceed the average daily human rate of intake. These effects appear to be dose-dependent. While carrageenan exhibits no mutagenic effects as measured by the host-mediated and dominant lethal assay procedures, significant abnormalities appear to be induced in the anaphase figures of human embryonic lung cells in tissue culture at dosages that are slightly above average daily human intake. Parenterally administered carrageenan is reported to exert cytotoxic effects on macrophages, suppress delayed hypersensitivity reactions in some tuberculin sensitive animals, activate factors causing procoagulant activity in human blood platelets, increase vascular permeability, and liberate kinin in vitro, all of which point to the possibility of the generation of toxic effects that could cause adverse responses following the oral consumption of carrageenan if, during pregnancy or in the presence of infectious challenge or metabolic disorder, appropriate amounts of carrageenan should be absorbed from the gastrointestinal tract.[30] (Note that MTN-037 includes only topical application.) Additional data regarding the fetotoxicity, teratogenicity,

and mutagenicity of orally or parenterally administered CG is available in two National Technical Reports prepared for the FDA.[31, 32]

Zinc is not mutagenic and has little if any clastogenic properties. Mutagenicity studies strongly suggest that zinc does not represent a mutagenic risk. It is not teratogenic and can, in fact, avert teratogenicity of other agents. Conversely, zinc deficiency may be both harmful to developing organisms and hazardous to human health. In a murine carcinogenicity study, tumors did not develop when zinc compounds including zinc acetate were injected subcutaneously.[33]

In Vitro Metabolism

Clinical drug interaction studies have not been conducted with MIV-150. Using cDNA expressed isoenzymes and hepatic microsomes, CYP3A is involved in the biotransformation of MIV-150, although a role for CYP2C8 and FMO cannot be excluded. MIV-150 was not an inhibitor of CYP1A2, CYP2C9, CYP2D6, and CYP2E1 activity. CYP450-dependent metabolism of MIV-150 appeared to be markedly inhibited by $C_{max}$ or 10x $C_{max}$ concentrations of ritonavir ($C_{max}$), indinavir ($C_{max}$) and efavirenz (10x $C_{max}$). MIV-150, even at 10x $C_{max}$, appeared to have little or no effect on the CYP450-dependent metabolism of the same compounds all of which involve 3A4 metabolism. In hepatic microsome experiments, sulfate conjugates were a major metabolite, but glucuronide conjugates were not identified.

In human supersome studies, MIV-150 was found to be a potent inhibitor in vitro of the isozymes CYP2C9, CYP2C19, and CYP3A4. In studies against specific human hepatic CYP450 isoenzymes in vitro, MIV-150 was a weak inhibitor of CYP2C19 and CYP3A4 activity; $IC_{50}$ values for the isozymes CYP2C9, CYP2C19, and CYP3A4 were 1.55 µg/mL (4.22 µM), 0.094 µg/mL (2.56 µM), and 1.12 µg/mL (3.04 µM), respectively. For reference, median peak plasma concentrations ($C_{max}$) after vaginal dosing of PC-1005 range from 75 to 114 pg/mL or greater than 1,000-fold lower concentration.

Condom Compatibility

A summary of the PC-1005 condom compatibility study is presented in Table 6. A more comprehensive summary follows the table.

**Table 6: Summary of PC-1005 Condom Compatibility Study**

| Study Type | Type of Condoms | Outcome |
|---|---|---|
| Condom compatibility study | 3 brands non-lubricated latex condoms, 1 brand polyisoprene condoms, 1 brand polyurethane condoms, and 1 brand nitrile female condoms treated with: negative control and positive control treated with a degradant (mineral oil for latex and polyisoprene condoms, mineral oil or PEG 200 for polyurethane condoms, and toluene for nitrile condoms), or PC-1005 | • PC-1005 is considered compatible with non-lubricated latex and polyisoprene condoms.<br>• PC-1005 had a plasticizing effect on the polyurethane condoms and nitrile condoms, and increased burst volumes while decreasing burst pressures. |

PEG=polyethylene glycol

This study was conducted to assess the compatibility of PC-1005 with male and female condoms (FHI 360, Durham, NC). Formulation PC-1005_C was used for the study. Although the test method ASTM D7661 and the criteria were specifically for natural rubber latex male condoms, other types of condoms (synthetics) including female condoms were tested as recommended by the draft guidance of vaginal microbicide that FDA published in November 2012. Three brands of non-lubricated latex condoms, 1 brand of polyisoprene condoms, 1 brand of polyurethane condoms, and 1 brand of nitrile female condoms were evaluated for tensile and airburst properties. The tensile and airburst properties of the condoms treated with PC-1005 were compared to those of negative control and positive control treated with a degradant (mineral oil for latex and polyisoprene condoms, mineral oil or PEG200 for polyurethane condoms, and toluene for nitrile condoms).

No condoms leaked or had difficulty with their clamping mechanism. The tensile and airburst properties of the non-lubricated latex condoms and the polyisoprene condoms were within the criteria, adequate to detect less than a 10% change in airburst pressure, airburst volume and percent elongation, as well as a 25% change in break force. Therefore, PC-1005 is considered compatible with these condom types.

The airburst pressure for the polyurethane condoms had a greater than 20% decrease, and the airburst pressure for the nitrile condoms had a greater than 10% decrease. However, it would be difficult to apply the same criteria of the standard ASTM D7661 to the other types since synthetic condoms are much more rigid than latex. The test result suggests that the test articles had a plasticizing effect on the polyurethane condoms and nitrile condoms, and increased burst volumes while decreasing burst pressures. Even though there was a decrease in pressure for the female condoms, the treated burst pressure still met the manufacturer's requirements.[19]

### 2.4 Animal Studies

Anti-SHIV Activity

In studies comparing the preclinical safety and efficacy of TFV 1% gel with that of MZC gel using in vitro, ex vivo, and in vivo assays, MZC showed greater anti-SHIV-RT activity than TFV 1% gel in macaque vaginal explants.[34]

Experiments challenging macaques rectally showed blocking activity of CG gel when applied close to the time of challenge with SHIV-RT, likely due to both a non-specific barrier effect of the gel (coating of epithelium) combined with characteristic polyanion blockade of cell-virus interactions.[11]

Prototype and modified ZA/CG gels were found to significantly reduce SHIV-RT infection in simian models. Macaques repeatedly dosed (daily for 14 days) with ZA/CG gel were protected against vaginal SHIV-RT infection for up to 24 hours. Dosing every other day also offered significant protection after challenge 8 to 24 hours after the last gel dose; a single dose was less effective.[35] MIV-150 in CG administered vaginally in a macaque SHIV model protected against SHIV, with 3 doses of MIV-150 in CG being superior to 3 doses of CG alone.[36] A single dose of MIV-150 in CG administered rectally 30 minutes or 4 hours prior to rectal exposure protected 4/4 macaques challenged with $10^3$ $TCID_{50}$ SHIV

and 2/4 challenged with $10^4$ $TCID_{50}$ SHIV applied 4 hours after the gel.[20] MIV-150 in CG provided partial protection against vaginal SHIV-RT transmission in macaques when the last dose was given 8 hours before challenge.[37]. A single application of MIV-150 in CG provided full protection against vaginal SHIV-RT transmission in macaques for up to 24 hours.[38]

Anti-Herpes Simplex Virus (HSV-2) Activity

MZC applied 10 minutes prior to challenge effectively blocked HSV-2 infection in stringent, high viral dose ($10^6$ pfu) vaginal (1000x 50% lethal dose [$LD_{50}$]) and anorectal (10x $LD_{50}$) mouse models. There was a significant decrease in infection after vaginal challenge (65% uninfected, $p<0.0001$ vs. D-PBS [Dulbecco's phosphate-buffered saline] or CG alone) and anorectal challenge (55% uninfected, $p = 0.0187$ vs. D-PBS). At lower viral doses ($5x10^3$ pfu/mouse), mice dosed with MZC, CG or D-PBS were challenged with HSV-2 to determine the window of protection. Vaginally, a significant decrease in the percentage of mice infected vs. D-PBS was seen when MZC was administered between 8 h before ($p = 0.0038$) and 4 h after ($p = 0.0248$) viral challenge; CG displayed a blocking effect at this lower viral dose. However, the same experiment performed via anorectal challenge showed no significant protection at any time point except when MZC was applied 10 minutes prior to challenge.[11]

In mice, prototype and modified ZA/CG gels were found to significantly increase the number of animals without signs of infection when challenged rectally or vaginally with high-dose HSV-2.[35] ZA and/or CG gels in other murine model studies protected mice (75 to 85% survival; $p < 0.001$) against high-dose ($10^6$-pfu) HSV-2 rectal or vaginal challenge. ZA in HEC was not protective, performing similarly to aqueous ZA solution and the placebo controls.[39]

Anti-Human Papillomavirus (HPV) Activity

HPV infection may be facilitated by trauma to the cervicovaginal epithelium; CG-based gels may show protective potential if developed for use in clinical settings. A study with female macaques simulated a common gynecological procedure (cytology specimen collection via speculum - a Pap smear), followed by an internal digital exam using as lubricant either Surgilube or 1% iota-carrageenan (a known HPV inhibitor). A subgroup underwent speculum and digital exam alone (no cytology specimen collection). Subsequently each animal's cervix was inoculated with HPV16 pseudovirus (PsV); after 3 days cervices were removed and cryosectioned. Significant HPV infection was detected only in cervices of animals subject to both a speculum/digital exam and a cytology specimen collection. In macaques for which the CG gel was used as lubricant, the mean number of infectious events decreased (CG gel vs. Surgilube, mean=3.5 events per section vs. mean=84 infectious events per section, difference=81 events per section, 95% CI=33 to 213 events per section.[40]

The anti-HPV activity of MZC gel is solely due to its carrageenan component.[12] In early in vitro work, carrageenans were shown to inhibit papillomavirus infection.[13] MZC shows greater potency against some HPV strains (e.g., 18 and 45) than others (16). Mice were fully protected against HPV-16 when gel was vaginally applied 8 hours prior to challenge with HPV-16 pseudovirus (PsV).[11] Infection was significantly reduced within a window of

application of 24 hours before to 2 hours after challenge. However, when mice are subject to anorectal challenge the protection window against HPV-16 PsV is much shorter: the gel was protective when applied between 2 hours before and 2 hours after challenge, temporally corresponding to timepoints at which rectal swabs displaying higher CG concentrations were collected. Significant protection continued after 8 hours; these and in vitro data suggest that CG blocks HPV post-challenge.[11]

Toxicology

Summaries of MIV-150 nonclinical toxicology in vivo studies with mice, rats, monkeys, and dogs can be found in the IB.[19] Repeated oral dosing of MIV-150 had little to no effect on hepatic CYP450 activity in the mouse. Other drugs in the NNRTI class are strong inducers and/or inhibitors of CYP3A4 resulting in increases and/or decreases in the concentrations of co-administered 3A4 substrate drugs.[19] In mice receiving very high doses of MIV-150 (>1000 mg/kg) in a behavioral study, an indication of CNS activity was observed.[19]

Zinc acetate (ZA) is an FDA-approved, generally recognized as safe (GRAS) oral drug for Wilson's disease and zinc deficiency. No zinc toxicity was seen in rabbits after daily vaginal dosing with 90 mM ZA for 10 days or after a 10-day treatment with vaginally inserted zinc sulfate-loaded sponges. These doses far exceed doses in the PC-1005 gel (13.7 mM).[19] No zinc toxicity was observed in either the Population Council first-in-human trial (Protocol #558; described below)[17] nor its run-in trial. In the run-in study, zinc blood levels were unchanged from baseline; median $C_{max}$ of zinc was 79 µg/mL (58-94) on Day 3 (three days of daily dosing).[17]

A 14-day rabbit rectal irritation study was conducted for Population Council to assess potential systemic toxicity and toxicokinetics of MIV-150 for varied dose concentrations of PC-1005_D and PC-707_D gels as compared to sham, placebo, and reference controls[41]. (See Table 7 below.) Based on the rectal irritation index, both gels were considered non-irritating at all examined dose concentrations. The no-observable-adverse-effect-level (NOAEL) was considered to be the 5x dose of PC-1005 and PC-707.

**Table 7: Animal Assignment and Dose Concentrations in Rabbit Rectal Irritation Study for PC-1005_D and PC-707_D**

| Group Number | Treatment | Dose Volume (mL/animal/day) | Dose Concentration | Number of Animals | |
|---|---|---|---|---|---|
| | | | | Male | Female |
| | | Main Study | | | |
| 1 | Sham Control | NA | NA | 6 | 6 |
| 2 | PC-525[a] (Vehicle Control/Placebo) | 1 | 0% | 6 | 6 |
| 3 | Conceptrol® (N-9 Reference Control) | 1 | 4% | 6 | 6 |
| 4 | PC-1005 (1x) | 1 | 0.00184% MIV-150, 0.3% Zinc Acetate | 6 | 6 |
| 5 | PC-1005 (3x) | 1 | 0.00553% MIV-150, 0.9% Zinc Acetate | 6 | 6 |
| 6 | PC-1005 (5x) | 1 | 0.00921% MIV-150, 1.5% Zinc Acetate | 6 | 6 |
| 7 | PC-707 (1x) | 1 | 0.3% Zinc Acetate | 6 | 6 |
| 8 | PC-707 (3x) | 1 | 0.9% Zinc Acetate | 6 | 6 |
| 9 | PC-707 (5x) | 1 | 1.5% Zinc Acetate | 6 | 6 |
| | | **Toxicokinetic** | | | |
| 10 | PC-525[a] (Vehicle Control/Placebo) | 1 | 0% | 3 | 3 |
| 11 | PC-1005 (1x) | 1 | 0.00184% MIV-150, 0.3% Zinc Acetate | 4 | 4 |
| 12 | PC-1005 (3x) | 1 | 0.00553% MIV-150, 0.9% Zinc Acetate | 4 | 4 |
| 13 | PC-1005 (5x) | 1 | 0.00921% MIV-150, 1.5% Zinc Acetate | 4 | 4 |
| 14 | PC-707 (1x) | 1 | 0.3% Zinc Acetate | 4 | 4 |
| 15 | PC-707 (3x) | 1 | 0.9% Zinc Acetate | 4 | 4 |
| 16 | PC-707 (5x) | 1 | 1.5% Zinc Acetate | 4 | 4 |

[a]: viscous, carrageenan-based gel
NA - Not applicable; N-9 - Nonoxynol-9

Following daily rectal administration of PC-1005 at 1x, 3x, or 5x formulations, mean $AUC_{0\text{-}24hr}$ and $C_{max}$ values for MIV 150 appeared to increase from PC-1005 (1x) to PC 1005 (3x) with no increase from PC 1005 (3x) to PC-1005 (5x) on Days 1 and 14. On Day 1, a 1 to 3 to 5 fold increase in dose resulted in an approximate 1 to 3.0 to 3.5 fold increase in $AUC_{0\text{-}24hr}$ values and an approximate 1 to 3.2 to 3.4 fold increase in $C_{max}$ values. On Day 14, a 1 to 3 to 5 fold increase in dose resulted in an approximate 1 to 3.6 to 4.6 fold increase in $AUC_{0\text{-}24hr}$ values and an approximate 1 to 4.2 to 4.1 fold increase in $C_{max}$ values.

Systemic exposure to MIV-150 appeared to increase following repeated administration of PC-1005. Mean $AUC_{0\text{-}24hr}$ accumulation ratios were 1.75, 2.03, and 2.24 at PC-1005 (1x), PC 1005 (3x), and PC 1005 (5x), respectively. Individual $AUC_{0\text{-}24hr}$ accumulation ratios ranged from 1.01 to 2.93 at PC-1005 (1x), from 1.11 to 2.92 at PC-1005 (3x), and from 1.65 to 2.91 at PC 1005 (5x).

The safety of PC-1005_C and PC-525_C on vaginal and rectal mucosal epithelium at the site of product use was evaluated in vivo using *Macaca nemestrina* over 4 consecutive days of daily exposure. Six animals, weighing 5-10 kg and aged 4-13 years (i.e. sexually mature), were in each group; gel was administered at approximately the same time each day at a dose volume of 1.5 mL/animal (vaginal dose) or 2.5mL/animal (rectal dose). Colposcopy was performed to assess CV tissues, vaginal and rectal swabs were taken to test pH and microbiota composition, and rectal lavages were performed to evaluate epithelial sloughing. In the vaginal groups, neither gel caused discernable irriation to CV tissues and pH decreased with gel administration from 7.5 at baseline to closer to 6.5; animals in the rectal groups demonstrated lower pH after product exposure. No profound changes were seen in any of the groups with respect to microbiota. Neither gel resulted in increased shedding of epithelial sheets (defined as at least 3 mm) in rectal lavages conducted 30 minutes after each exposure.

The available information on the oral administration of undegraded carrageenan at levels greatly exceeding the daily human intake reveals evidence of possible adverse effects on the gastrointestinal epithelium. Extensive investigations of carrageenan and the pathogenesis of gastrointestinal changes indicate the susceptibility of the guinea pig to ulcerative colitis when fed relatively high levels of carrageenan in the diet. The work suggests that the occurrence of ulcers in the large bowel of animals is a species-specific phenomenon where feeding of carrageenan can induce ulceration in the cecum and proximal colon of the guinea pig which, to date, does not appear to occur in humans, rats, mice, hamsters, pigs, or squirrel monkeys. Parenterally administered carrageenan has been reported to exert cytotoxic effects on macrophages, suppress delayed hypersensitivity reactions in some tuberculin sensitive animals, activate factors causing procoagulant activity in human blood platelets, increase vascular permeability, and liberate kinin in vitro.[30] PC-1005 gel will be administered topically in MTN-037.

In mice, CG is not damaging to either vaginal or rectal epithelial tissue. In vitro, it is not toxic to the 'healthy' *Lactobacillus* strains *L. jensenii* and *L. crispatus*.[12] MZC and related gel formulations did not induce mucosal toxicity in ex vivo evaluations of safety and anti-

SHIV-RT activity in macaque mucosal explants and in safety evaluations of human ectocervical explants.[42]

Pregnancy, Teratogenic Effects, and Lactation
In animals treated with MIV-150, no fetal malformations have been observed. It is not yet known whether any component of PC-1005 can enter breast milk of a lactating female.[19]

Reproductive Toxicity
The reproductive toxicity profile of PC-1005 gel administered vaginally has not been evaluated; animal reproduction studies have not yet been conducted.[19]

## 2.5 Clinical Studies

MIV-150 Oral Formulation Trials
MIV-150 was studied in 4 Phase 1 clinical trials (see Table 8 below) in men using different oral formulations and dose levels by Chiron Corporation. There were no SAEs reported in association with MIV-150 oral administration. None of these 4 studies achieved the target systemic trough concentration of greater than 120 ng/mL considered necessary for antiviral efficacy.[19] In the Chiron clinical development program, MIV-150 was given to over 60 volunteers in these 4 studies using micronized and nanocrystal dispersion (NCD) formulations. MIV-150 was well-tolerated in 2 single and 2 multiple oral dose studies with doses of 200 to 1600 mg per day. Relative bioavailability was greater for the NCD than the micronized suspension. Treatment-emergent clinical events related to study drug were mild and transitory, and consisted of somnolence, fatigue, and anorexia. After administration of NCD, the absorption of MIV-150 was rapid, with $C_{max}$ occurring within 2 hours. After attaining $C_{max}$, plasma concentrations declined rapidly in an apparent biphasic manner, and 12-hour trough levels were lower than expected. To achieve higher trough levels, 2 controlled-release (CR) formulations of MIV-150 with zero-order (CR01) and first-order (CR02) release kinetics were studied (MIV-102; Table 8). Although there was no significant difference between the 2 formulations, the extent of exposure was up to 17% greater for CR01 than CR02. CR01 was then selected for a multiple dose Phase 1 study (MIV-103, Table 8). Mean trough levels of approximately 48.4 + 29 and 100 + 70 ng/mL were achieved with 800 mg BID and 400 mg TID regimens, respectively. The AUC(0-∞) and Cmax values increased in a less than dose proportional manner over the ascending dose levels in all 4 trials, indicating that absorption is dissolution rate limited. Neither the CR01 nor CR02 formulations provided a superior profile to the parent NCD formulation.

Additional trial details appear below in Table 8 and in the IB.[19]

**Table 8: Summary of Completed Clinical Studies with MIV-150**

| Study | Study Name | Population (N) | (Oral) Dose | Findings: Adverse Events | Findings: PK |
|---|---|---|---|---|---|
| MIV-101 | Bioequivalence of Micronized Suspension and NanoCrystal Dispersion Formulations and a Comparison of the Fed/Fasted Pharmacokinetics in Healthy Male Subjects | MIV-150: (19) Healthy male volunteers aged 18−55<br>Controls: (5) Healthy male volunteers aged 18-55 | 400 mg micronized suspension single dose;<br>200-1600 mg NCD single dose;<br>800 mg NCD single dose fast/ fed (high fat diet) | Total of 31 mild and transient AEs, including 9 drug related: (nausea, insomnia, anorexia, dizziness, dry mouth, cough, headache, and taste perversion. | Systemic exposure of MIV-150 was 2-fold greater in the fed compared to the fasted state. The drug is cleared by non-renal mechanisms (negligible urine drug). $T_{max}$ 0.5-2 hours; half-life 10-13.5 hours; dose-proportionality, but increased variability at 1600 mg dose level. |
| MIV-102 | Bioequivalence and Bioavailability of 2 Different Controlled Release Formulations at 3 Different Dose Levels in Healthy Male Subjects | MIV-150: (14) Healthy male volunteers aged 18−55<br>Controls: (5) Healthy male volunteers aged 18−55 | 400-1600 mg CR01 single dose;<br>400-800 mg CR02 single dose (high fat diet) | Total of 17 mild and transient, 3 considered drug related. Drug-related AEs included: fatigue, somnolence, and anorexia. | $T_{max}$ 2-10 hours; half-life 6-60 hours; sub-proportional kinetics at 800 and 1600 mg dose level. |
| MIV-103 | Safety, Tolerability, and Pharmacokinetics of Multiple Oral Doses in Healthy Male Subjects | MIV-150: (14) Healthy male volunteers aged 18−55 | CRO1 multiple doses 400 mg TID vs 800 mg BID (regular diet) | Total of 19 AEs of which 13 were drug related. NNRTI expected CNS and GI related AEs (disturbance in attention, loose stools, upper abdominal pain). Other drug-related AEs included: fatigue, headache, thirst, weakness, and irritability. All drug-related AEs were reported in the 400 mg TID group. 11 drug-related AEs were mild, 2 were moderate. 1 subject was discontinued for non-drug-related AEs (persistent high fasting blood glucose and glycosuria.) | Systemic exposure to MIV-150 increased 2.5- to 4-fold for the 800 mg BID and 400 mg TID. $T_{max}$ 3-6 hours; half-life 10-27 hours; steady-state achieved 24 hours after start of multiple dosing; sub-proportional between 400 and 800 mg dose levels. Mean plasma levels 71 − 217 ng/mL (400 mg TID) and 42 − 163 ng/mL (800 mg BID). |

| Study | Study Name | Population (N) | (Oral) Dose | Findings: Adverse Events | Findings: PK |
|---|---|---|---|---|---|
| MIV-103b | Ascending Multiple Oral Dose Study of 3 Different Doses of NanoCrystal Dispersion Formulation in Healthy Male Subjects | MIV-150: (16) Healthy male volunteers aged 18 − 55 years | 800 mg NCD BID;<br>1200 mg NCD BID | Total of 47 AEs of which 29 were considered drug related. 4 drug-related AEs in the 800 mg MIV-150 BID cohort included: headache, flatulence, rash, and papular rash. There was a dose-dependent increase at 1200 mg BID in the frequency of drug-related AEs of somnolence, headache, mild GI symptoms. Additional drug-related AEs at 1200 mg BID included: pruritus, fatigue, weakness, and jaundice. A clinically significant AE of cholestatic hepatitis was reported. | Systemic exposure of MIV-150 appeared to increase in a dose-proportional manner between the 800 and 1200 mg dose levels, although variability between subjects was greater at the higher dose level. $T_{max}$ 1-4 hours; biphasic disposition with 3-24 hour half-life; diurnal variation in clearance; dose-proportional but variable between 800 and1200 mg dose levels. |

BID = twice daily; CR = controlled release; CR01=Zero-order controlled release; CR02=first-order controlled release; NCD = NanoCrystal Dispersion; TID = three times daily

MIV 150 Gel Formulation Trial

Prior to a Phase 1, first-in-human PC-1005 trial (the Population Council Protocol #558; described below),[17] an open-label, safety and PK run-in trial was conducted at one US site with 5 healthy adult women aged 19-49. Women self-administered 4 mL PC-1005 gel vaginally once daily for 3 consecutive days (clinician-supervised dosing). Blood was collected at multiple time points from 30 minutes to 24 hours after doses 1 and 3, and 48 and 72 hours after dose 3. MIV-150 was detectable in all participants' blood; accumulation was not noted, suggesting low systemic absorption. On Day 3, the median (and CV%) of MIV-150 PK parameters were: half-life ($T_{1/2}$) of 4.82 (25.2) hours; $C_{max}$ of 84.7 (48.1) pg/mL; $T_{max}$ of 3.92 hours (range 1.97–6.00 hours); and $AUC_{last}$ of 834 (25.0) pg h/mL). Blood zinc levels were unchanged from baseline.[17]

The Population Council Protocol #558 proceeded upon satisfactory safety and PK assessments from the run-in trial.[17] In this Phase 1, double-blind, parallel, placebo-controlled, randomized trial with 20 HIV-seronegative women at a US site, participants were randomized (4:1) to apply vaginally 4 mL PC-1005_C (the same formulation, based on the PC-1005 specifications for Phase 1 study product, to be used in MTN-037) or placebo once a day for 14 days.[17] Safety, PK, pharmacodynamics, and acceptability were evaluated. All PK sampling followed directly observed dose administration. Participants were randomized (1:1) to a final PK/PD assessment that included collection of CVL for antiviral activity, at either 4 or 24 hours after the Day 14 dose. All 7 CVLs collected 4 hours after the Day 14 dose showed measurable anti-HPV activity in cell-based assays.[17] Participants (n=20) ranged from 19-44 years old; 52% were Black or African American. A total of 23 treatment emergent adverse events (TEAEs) occurred during the trial. Adverse events were primarily mild and/or unrelated and were comparable between groups; the majority of AEs were DAIDS Grade 1 (11, PC-1005; 2, placebo) or Grade 2 (4, PC-1005, 1, placebo). There were no Grade 3 or 4 AEs and no participant discontinued product because of AEs. AEs designated as related by the study investigator included metrorrhagia, vaginal discharge, vulvovaginal pruritus, abdominal discomfort, constipation, and urinary tract infection in the PC-1005 group; and uterine spasm (cramps) in both groups. No significant histopathologic changes in cervical or vaginal biopsies were observed in any of the 17 women who completed the randomized period. Median peak ($C_{max}$) MIV-150 concentrations ranged from 75 to 114 pg/mL and no accumulation of drug concentration with time was seen. Median time to peak concentration ($T_{max}$) ranged from 3-5 hours at different periods of the study (overall range 2-12 hours). Median half-life ranged from 3.9-5.5 hours. Plasma zinc levels were unchanged from baseline and were within the normal range (60-130 µg/dL).[17] All (7/7) CVLs collected 4h post-dose demonstrated antiviral (HIV, HPV) activity. High baseline CVL anti-HSV-2 activity precluded assessment of post-dose activity. Among those completing the trial (13/17, PC-1005; 3/3, placebo), 11/17 reported liking the gel overall; 7 recommended reducing the volume.

Plasma concentrations achieved through oral dosing (400 mg TID or 800 mg BID) ranged from 42-217 ng.mL; plasma MIV-150 concentrations in the vaginal dosing gel formulation study described above ranged from 75-114 pg/mL, approximately 1,000-fold lower than the concentrations achieved with oral dosing. There have been no rectal dosing studies of MIV-150.

Safety: Vaginal Administration

Data suggest carrageenan alone is active against other infections such as HPV, show it to be generally recognized as safe (GRAS), safe and acceptable for topical use, and show it displays intrinsic antiviral activity.[11] Phase 1, 2, and 3 studies have shown 3% CG gel to be safe and acceptable when applied vaginally.[12] A large (N=6,202 South African women) Phase 3 clinical trial for CG-based Carraguard® gel showed that the gel was safe, with no side effects or increased risks. [11, 43] However, results also showed that it had no statistical effect on HIV infection (in the context of only 41.1% adherence, measured by applicator testing). Among adherent users of the Carraguard® gel, the prevalence of high-risk HPV infection was significantly lower than among adherent users of placebo gel.[8, 11] The Carraguard® study results were the first published showing a protective effect against HPV infection with use of a vaginal microbicide. The CG lambda-kappa ratios cited for the various test products referenced throughout the protocol and Investigator's Brochure fall within the target specifications set for the proposed product by the manufacturer. Please note that Carraguard® has a carrageenan lambda-kappa percentage ratio of 95:5; the CG to be used in MTN-037 has a carrageenan lambda-kappa percentage ratio of 82:18.

## 2.6 Study Hypotheses and Rationale for Study Design

### Study Primary Hypotheses

It is hypothesized that PC-1005 gel (0.002% MIV-150/0.3% ZA in 3.0% CG gel) will be safe when applied to the rectum and well-tolerated among healthy men and women (cis or transgender) who have a history of receptive anal intercourse (RAI).

### Rationale for Study Design

Rectal microbicides are needed for individuals at risk of acquiring a variety of infections including HIV, HPV, and HSV-2 through unprotected RAI. It is important to expand the rectal microbicide pipeline though the addition of products such as PC-1005 (a non-nucleoside reverse transcriptase inhibitor [NNRTI], MIV-150, combined with ZA in a CG gel). As most RAI is facilitated by the use of a lubricant (such as digital application to the perianal area, penis, and/or the rectal area prior to intercourse, or the use of pre-lubricated condoms), the use of a rectal gel microbicide has the potential advantage of both familiarity and context. There is considerable community desire to use rectal microbicides as lubricants.[44]

Rationale for the Dosing and PK Sampling Schedule

MTN-037 is the first study to assess the safety and PK of PC-1005 gel applied rectally. A single dose exposure for all participants at each dose (4 mL, 16 mL, and 32 mL) will allow for the identification of any safety concerns. Such application may be representative of episodic, intermittent or coital dosing. Intermittent dosing of rectal gel associated with sexual activity may be a more feasible strategy for long-term use. Experiments with nonhuman primates (macaques) and mice suggest a much broader time window of

protection against the three viruses when applied vaginally, as opposed to rectally.[11] However, potential use of rectal microbicide gels as coital lubricants would require gel application close to the time of potential viral exposure.[11] This dose/volume escalation study design will allow for the identification of any safety concerns and provide critical PK and PD data. Safety assessments for each participant including a review of AEs will be performed prior to proceeding to the next higher dose/volume.

The ideal coital-dosing regimen for PC-1005 gel applied rectally is not yet known. The selection of the proposed dosing range (from 4 mL up to 32 mL) is consistent with a growing literature regarding lubricant use practices among MSM in the US and elsewhere, findings that contribute toward a profile of 'typical' lubricant use in RAI. One study[45] conducted from 2007-2010 recruited 168 HIV seronegative, racially and ethnically diverse, low-income MSM (mean age 35.5 years; range not provided) residing in Los Angeles, California, USA who practice RAI. At baseline and follow-up visits, participants who reported using lubricant were queried via computer assisted self-interview (CASI) about their last sexual event with up to 3 recent partners, including the amount of commercial lubricant used and number of re-applications. Nearly all (94.9%) reported using 30 mL (6 teaspoons) or less in their most recent RAI encounter (see Table 9 below).

**Table 9: Lubricant Practices**

| **Los Angeles, CA, USA N=289 Sexual Events** | |
|---|---|
| *How much lubricant was used?* | |
| 5 mL or less (1 teaspoon) | 26% |
| About 10 mL (2 tsp) | 36.8% |
| About 15 mL (3 tsp) | 21.7% |
| About 30 mL (6 tsp) | 10.4% |
| About 50 mL (10 tsp) | 5.2% |
| *How many times was lubricant reapplied?* | |
| Never | 26% |
| Once | 27.3% |
| Twice | 29.4% |
| Three or more times | 17.3% |

Another study[46] assessed rectal lubricant use in 1995-1996 among 307 HIV seropositive and -negative Latino MSM residing in New York City (mean age 31; range 18-55). Of those reporting lubricant use (N=273) who provided responses, 94% used at least 5 mL (1 tsp) per encounter, about a third (35%) used ≤10mL, and nearly two thirds (60%) used ≤15mL.

Additionally, a 2008 study[47] that recruited 843 HIV seropositive and –negative Peruvian MSM aged 18 and older (61% aged 18-29) assessed lubricant use via CASI. While not queried about the amount of lubricant used, 85% of participants who reported having used lubricant during RAI with their most recent partner reported applying it 1-2 times (82% applied it prior to sexual contact).

A rectal gel volume escalation study was performed with an iso-osmolar polyoxyethylene and carbomer gel approved for vaginal use (FemGlide; Trumbuill, CT). Participants

applied sequential single doses of 5, 20, 35, and 50 mL after which acceptability was assessed. Participants then were given 3 take-home doses of the highest volume they deemed "somewhat acceptable" or "completely acceptable" and applied the gels 2 hours prior to anticipated receptive anal intercourse. Up to 35 mL of the gel was acceptable to the majority of participants. For some participants, volumes classified as acceptable when applied without sex were not acceptable when used prior to and during sex. In general, participants stated their highly likely intentions to use microbicides when available.[48]

# 3 OBJECTIVES

## 3.1 Primary Objectives

**Safety**

- To evaluate the safety of PC-1005 gel formulation (0.002% MIV-150/0.3% ZA in 3.0% CG gel) when applied rectally

**Pharmacokinetics**

- To characterize the systemic and compartmental pharmacokinetics of MIV-150 following rectal gel application

## 3.2 Secondary Objectives

**Acceptability**

- To compare the acceptability of PC-1005 gel formulation across the three doses when administered rectally

**Pharmacokinetics**

- To characterize the compartmental pharmacokinetics of MIV-150 in vaginal fluid following rectal gel application

## 3.3 Exploratory Objectives

**Biomarkers of Mucosal Safety**

- To evaluate the mucosal toxicity of PC-1005 gel formulation when applied rectally

**Ex Vivo Antiviral Activity**

- To assess the preliminary (ex vivo) antiviral activity of PC-1005 gel formulation after product is applied rectally

# 4 STUDY DESIGN

## 4.1 Identification of Study Design

MTN-037 is a Phase 1, open label, sequential dose/volume escalation study

## 4.2 Summary of Major Endpoints

**Primary Endpoints:**

**Safety**

- Grade 2 or higher AEs as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, and/or Addenda 1, 2 and 3 (Female Genital [Dated November 2007], Male Genital [Dated November 2007] and Rectal [Clarification Dated May 2012] Grading Tables for Use in Microbicide Studies).

**Pharmacokinetics**

- MIV-150 concentrations in:
    - Plasma
    - Rectal fluid
    - Rectal mucosal tissue homogenates

**Secondary Endpoints:**

**Acceptability**

- Participant self-report of comfort with gel application, liking the product across doses, and perceived side-effects

**Pharmacokinetics**

- MIV-150 concentrations in vaginal fluid

**Exploratory Endpoints:**

**Biomarkers of Mucosal Safety**

- Rectal histology
- Tissue archive

**Ex Vivo Antiviral Activity**

- Changes in HIV-1 p24 levels in colorectal explant culture supernatant
- Anti-HIV activity in rectal fluid

### 4.3 Description of Study Population

The study population will consist of HIV-uninfected men and women (cis or transgender) with a history of consensual RAI who are aged 18 years or older and meet the criteria outlined in Section 5.2 and Section 5.3.

### 4.4 Time to Complete Accrual

The time to complete accrual is anticipated to be approximately 6-8 months.

### 4.5 Study Groups

MTN-037 will enroll approximately 12 evaluable participants – approximately 6 men and 6 women.

### 4.6 Expected Duration of Participation

Each participant will be on study for approximately 3-5 months. The total duration of the study will be approximately 11-13 months.

### 4.7 Sites

Sites selected by the MTN Executive Committee.

# 5 STUDY POPULATION

### 5.1 Selection of the Study Population

The inclusion and exclusion criteria in Section 5.2 and Section 5.3 will be used to ensure the appropriate selection of study participants.

#### 5.1.1 Recruitment

Participants will be recruited from a variety of sources, including outpatient clinics, universities and community-based locations. Recruitment materials will be approved by site Institutional Review Boards (IRBs) prior to use.

#### 5.1.2 Retention

Once a participant is enrolled in MTN-037, study sites will make every effort to retain the participant in follow-up to minimize possible bias associated with loss-to-follow-up. Sites will be responsible for developing and implementing local Standard Operating Procedures (SOPs) to target and ensure high rates of retention.

## 5.2 Inclusion Criteria

Individuals who meet the following criteria are eligible for study inclusion:

1. Men and women (cis or transgender) who are 18 years or older at Screening, verified per site SOP

2. Able and willing to provide written informed consent

3. HIV-1/2 uninfected at Screening and Enrollment, per applicable algorithm in Appendix II and willing to receive HIV test results

4. Able and willing to provide adequate locator information, as defined in site SOP

5. Available to return for all study visits and willing to comply with study participation requirements

6. In general good health at Screening and Enrollment, as determined by the site IoR or designee

7. At Screening, history of consensual RAI at least once in their lifetime per participant report

8. Willing to not take part in other research studies involving drugs, medical devices, genital or rectal products, or vaccines for the duration of study participation (including the time between Screening and Enrollment)

9. Willing to follow abstinence requirements for the duration of study participation (See Section 6.8 for additional information)

10. For participants of childbearing potential: a negative pregnancy test at Screening and Enrollment

11. For participants of childbearing potential: Per participant report at Enrollment, using an effective method of contraception and intending to use an effective method for the duration of study participation; these include:
    a) Hormonal methods, excluding vaginal rings
    b) Intrauterine device (IUD) inserted at least 42 days prior to Enrollment (but not past the maximum length of recommended usage according to package instructions)
    c) Sterilization of participant or partner at least 42 days prior to Enrollment
    d) Self-identifies as having sex with women exclusively

## 5.3 Exclusion Criteria

Individuals who meet any of the following criteria will be excluded from the study**:**

1. At Screening:
    a) Hemoglobin Grade 1 or higher*
    b) Platelet count Grade 1 or higher*
    c) White blood count Grade 2 or higher*

d) Aspartate aminotransferase (AST) or alanine transaminase (ALT) Grade 1 or higher*
e) Serum creatinine >1.3× the site laboratory upper limit of normal (ULN)
f) International normalized ratio (INR) >1.5× the site laboratory ULN
g) History of inflammatory bowel disease by participant report

**As per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1, July 2017*

*Note: Otherwise eligible participants with an exclusionary test result can be re-tested during the screening process. If a participant is re-tested and a non-exclusionary result is documented within 45 days of providing informed consent for screening, the participant may be enrolled.*

2. Known adverse reaction to latex or polyurethane (ever)

3. Anticipated use of and/or unwillingness to abstain from the following medications during study participation:
   a) Anticoagulant medications
   b) Rectally-administered medications

4. Known adverse reaction to any of the components of the study product

5. Use of pre-exposure prophylaxis (PrEP) for HIV prevention within 1 month prior to Enrollment, and/or anticipated use and/or unwillingness to abstain from PrEP during trial participation

6. Use of post-exposure prophylaxis (PEP) for potential HIV exposure within the 3 months prior to Enrollment

7. Condomless RAI and/or penile-vaginal intercourse with a partner who is known to be HIV-positive or whose status is unknown in the 6 months prior to Enrollment

8. Non-therapeutic injection drug use in the 12 months prior to Enrollment

9. Participation in research studies involving drugs, medical devices, genital or rectal products, or vaccines within 30 days of the Enrollment Visit

10. Gynecologic, genital, or rectal procedure (e.g., tubal ligation, dilation and curettage, piercing, hemorrhoidal resection, polyp removal) 60 days or less prior to Enrollment, or rectal biopsy, 7 days or less prior to Enrollment

    *Note: Colposcopy and cervical biopsies for evaluation of an abnormal Pap test as well as IUD insertion/removal are not exclusionary. Anoscopy and endoscopy without rectal biopsies are not exclusionary*

11. Per participant report, medical records, clinical diagnosis and/or diagnostic testing at either Screening or Enrollment:
    a) Diagnosis or treatment of any anogenital STI in the past 3 months (including window between Screening and Enrollment)

b) Symptoms, clinical or laboratory diagnosis of active pharyngeal, anorectal infection or RTI requiring treatment per current CDC guidelines (http://www.cdc.gov/std/treatment)
c) Current symptomatic UTI

Infections requiring treatment include Neisseria gonorrhea (GC), Chlamydia trachomatis (CT) infection, syphilis, active herpes simplex virus (HSV) lesions, anogenital sores or ulcers, or symptomatic genital warts, chancroid, pelvic inflammatory disease (PID), symptomatic bacterial vaginosis (BV), symptomatic vaginal candidiasis, other vaginitis, and trichomoniasis.

*Note: Otherwise eligible participants with an exclusionary UTI, BV and/or candida finding may be re-tested during the screening process.*

*Note: HSV-1 or HSV-2 seropositive diagnosis with no active lesions is permitted since treatment is not required.*

12. Participants who meet any of the following additional criteria will be excluded from the study:
    a) Pregnant or breastfeeding at either Screening or Enrollment or planning to become pregnant or begin breastfeeding during study participation

    *Note: A documented negative pregnancy test performed by study staff is required for inclusion; however, a self-reported pregnancy is adequate for exclusion from screening/enrollment into the study.*

    b) Last pregnancy outcome 90 days or less prior to Screening

13. Has any other condition that, in the opinion of the IoR/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving study objectives.

### 5.4 Co-enrollment Guidelines

As indicated in Section 5.2 and Section 5.3, participants must not take part in other research studies involving drugs, medical devices, genital products, rectal products or vaccines after the Screening Visit and while taking part in MTN-037 unless approved by the Protocol Safety Review Team (PSRT). Participation in the following types of studies may be allowed at the discretion of the IoR/designee:

- Participants may take part in ancillary studies if approved by MTN-037 PSRT
- Participants who become infected with HIV may take part in observational and/or interventional studies for HIV-positive persons
- Participants who become pregnant while on study product will be offered enrollment in MTN-016

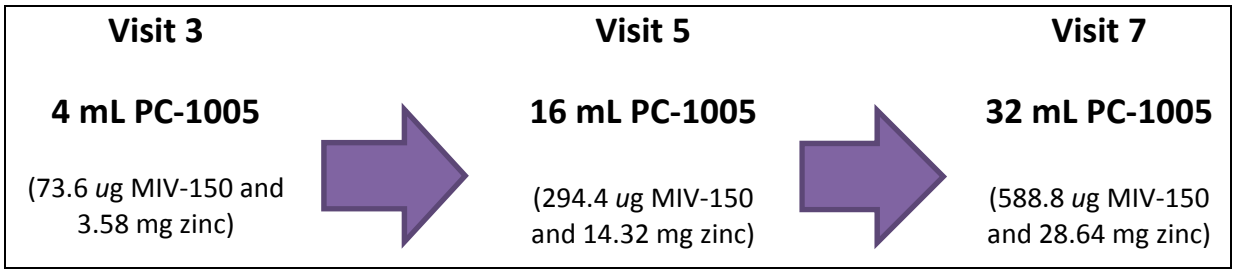
Should any participant report concurrent participation in contraindicated studies after enrolling in MTN-037, the IoR/designee will consult the PSRT regarding ongoing product use and other potential safety considerations associated with co-enrollment.

# 6 STUDY PRODUCT

## 6.1 Regimen

Approximately 12 participants will each receive three single escalating doses of rectally administered PC-1005; 4mL, 16 mL and 32 mL. After each dose is administered in the clinic, PK and PD sampling will be conducted. A safety evaluation will be performed approximately 24 hours after dosing. If there are no safety issues identified following a two to six week washout period, the next dose will be administered in the clinic per clinical management guidelines as outlined in Section 9 .

**Table 10: Study Product Regimen**




## 6.2 Administration

Participants will be instructed to present to the clinic for each of the 3 doses of rectal gel. Administration of the study gel will be performed by study staff.

## 6.3 Study Product Formulation

PC-1005 is a fixed dose combination of 73.6 µg MIV-150 and 3.58 mg Zn per 4 mL of gel. PC-1005 gel should be stored at 25°C (77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F).

## 6.4 Study Applicator

The site pharmacist will prepare the dose of PC-1005 gel for each administration. The gel will be dispensed in a BD™ Luer-Lok™ Tip syringe with a cap and a rectal administration tip. The clinic staff will need to replace the cap with the rectal tip prior to administration.

## 6.5 Study Product Supply and Accountability

### 6.5.1 Study Product Supply

The Population Council (New York, NY) will provide single dose amber vials containing 20 mL of PC-1005 gel. The vials are Fisher Scientific Fisherbrand™Type 1 Class A glass amber vials with a fitted cap.

The BD™ Luer-Lok™ syringes supplied by HealthCare Logistics (Circleville, OH) are sterile, latex-free disposable syringes. These syringes will be provided in 5 mL, 20 mL and 60 mL sizes to accomodate the 4 mL, 16 Ml and 32 mL doses, repectively. A red sterile Luer Lock tip cap will be placed on the tip of each syringe.

The syringe tip is a Luer Lock supplied by the Professional Compounding Centers of America (Houston, TX).

### 6.5.2 Study Product Accountability

The Clinical Research Site (CRS) Pharmacist of Record (PoR) is required to maintain complete records of the study product received and subsequently dispensed. All unused study products must be returned to the MTN LOC Pharmacist after the study is complete unless otherwise instructed by the MTN LOC Pharmacist.

## 6.6 Study Product Dispensing

Study products will be dispensed by the pharmacist to study staff upon receipt of a written prescription from an authorized prescriber. An authorized prescriber includes the IoR or a licensed clinician directly responsible to the IoR as noted on the United States (US) Food and Drug Administration (FDA) 1572 Form.

## 6.7 Ancillary Study Supplies

Clinic staff will utilize study-provided lubricant to facilitate the insertion of the study product via the rectal administration tip. Clinic staff will also offer condoms to all participants.

### 6.7.1 Retrieval of Unused Study Product

Clinic staff will be instructed to return any unused doses to the site pharmacy.

## 6.8 Concomitant Medications and Practices

Enrolled study participants may use concomitant medications during study participation with the exception of medications and products noted as prohibited. All concomitant medications reported throughout the course of the study will be recorded in the study database. Concomitant medications include all prescription medications, over-the-counter preparations, vitamins, nutritional supplements, and herbal preparations.

### Concomitant Medications

The use of PEP and PrEP are prohibited during study participation. Use of rectally-administered products, and any products containing N-9, is also prohibited. Participants are also prohibited from using CYP3A inhibitors and inducers. A listing of these specific prohibited agents are provided in the MTN-037 SSP Manual available at www.mtnstopshiv.org. It is important to note that single dose oral fluconazole for the

treatment of vaginal fungal infections is permitted.

Use of anticoagulants or blood-thinners (such as heparin, Lovenox®, warfarin, Plavix® [clopidogrel bisulfate]), is also prohibited during study participation. See Section 9.3 for additional information.

Participants will be counseled to abstain from using aspirin (greater than 81 mg) and other non-steroidal anti-inflammatory drugs (NSAIDS) within 72 hours prior to and following a PK sample collection visit. Should a participant report taking any of the medications noted above, which may increase risk of bleeding, or report the use of rectal products within 72 hours prior to biopsy collection, the visit should be rescheduled within the visit window, if possible. If it is determined that rescheduling the visit within the window is not possible, the visit may proceed at IoR discretion after proper participant counseling has occurred.

**Concomitant Practices**

All participants are to abstain from inserting any non-study products (including sex toys) into the rectum and receptive anal intercourse for 72 hours prior to and following clinic visits. Female participants should abstain from inserting anything into the vagina for 72 hours prior to each clinic visit, including spermicides, vaginal medications (including hormones), vaginal douches, lubricants and moisturizers, sex toys (vibrators, dildos, etc.) and vaginal intercourse.

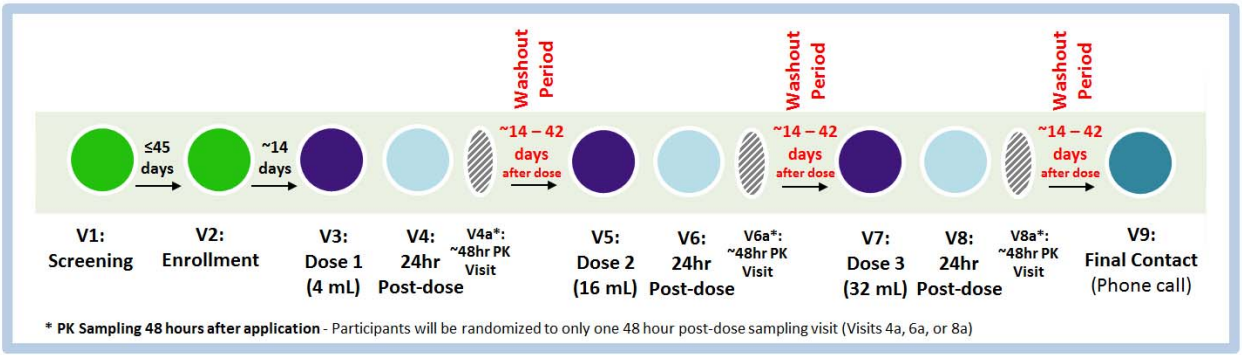
All participants are to abstain from the following sexual activities for 72 hours prior to and after biopsy collection: receptive anal intercourse (RAI), rectal stimulation via fingers, and rectal insertion of sex toys. All participants are to abstain from receptive oral anogenital stimulation for 72 hours after biopsy collection.

If desired, the IoR may request rapid PSRT consultation to assist in making the determination as to whether or not to proceed with the visit at that time or to reschedule as an interim visit. If the decision is made to reschedule as an interim visit, any missed procedures (including biopsy collection) should be performed during the interim visit.

# 7 STUDY PROCEDURES

An overview of the study visit and evaluations schedule is presented in Appendix I. Presented in this section is additional information on visit-specific study procedures. Detailed instructions to guide and standardize procedures as well as information regarding the study visit windows are provided in the MTN-037 SSP Manual available at http://www.mtnstopshiv.org/studies.

**Figure 2: MTN-037 Study Visit Schedule**




## 7.1 Pre-screening

As part of participant outreach and recruitment strategies, study staff can pre-screen potential study participants at either on-site or off-site locations. During these interactions, study staff may explain the study to potential participants and ascertain elements of presumptive eligibility (e.g., willingness to use the study product, willingness to adhere to the study rules, etc.), to be confirmed at an on-site screening visit. Process information (e.g., number of potential participants contacted, number presumptively eligible) may be recorded and stored at study sites in the absence of written informed consent from potential participants, provided the information is collected in such a manner that it cannot be linked to participant identifiers, unless a waiver is granted from the local IRB. Procedures and documentation will comply with local IRB requirements.

## 7.2 Screening

A Screening Visit will take place up to 45 days prior to the Enrollment Visit (Day 0). Multiple visits may be conducted to complete all required screening procedures, if necessary. Written informed consent for Screening/Enrollment will be obtained before any screening procedures are initiated. For participants who do not meet the eligibility criteria, Screening will be discontinued once ineligibility is determined.

**Table 11: Screening Visit**

| Visit 1-Screening Visit | | |
|---|---|---|
| **Component** | | **Procedures** |
| **Administrative and Regulatory** | | • Obtain written informed consent<br>• Assess consent form comprehension<br>• Assign a unique Participant Identification (PTID) number<br>• Assess eligibility<br>• Collect demographic information<br>• Collect locator information<br>• Provide reimbursement<br>• Schedule next visit/contact* |
| **Behavioral/Counseling** | | • HIV pre- and post-test counseling<br>• HIV/STI risk reduction counseling<br>• Protocol counseling |
| **Clinical** | | • Collect medical history<br>• Perform physical examination<br>• Perform male genital examination*<br>• Perform pelvic examination* ♀<br>• Perform rectal examination<br>• Collect concomitant medications<br>• Treat or prescribe treatment for RTI/UTI, or STIs*<br>• Disclose available test results |
| **Laboratory** | **Pharyngeal** | • NAAT for GC/CT |
| | **Urine** | • NAAT for GC/CT<br>• Urine dipstick/culture*<br>• Qualitative hCG ♀ |
| | **Blood** | • CBC with differential and platelets<br>• Chemistries (AST/ALT/Creatinine)<br>• Syphilis serology<br>• HIV-1/2 test<br>• Coagulation (PT/INR) |
| | **Pelvic** | • NAAT for GC/CT/TV♀ |
| | **Anorectal** | • NAAT for GC/CT<br>• HSV 1/2 detection* |
| **Study Product/Supplies** | | • Offer condoms |

* If indicated ♀Female participants

## 7.3 Enrollment (Day 0)

The Enrollment Visit can occur up to 45 days after the Screening Visit. All Enrollment procedures must occur on the same day.

**Table 12: Enrollment Visit**

| Enrollment Visit – Visit 2 | | |
|---|---|---|
| **Component** | | **Procedures** |
| **Administrative and Regulatory** | | • Review informed consent/ confirm participant's willingness to participate in study<br>• Assess and confirm eligibility<br>• Review/update locator information<br>• Provide reimbursement<br>• Schedule next visit/contact*<br>• Randomize to rectal tissue sampling schedule |
| **Behavioral/Counseling** | | • HIV pre- and post-test counseling<br>• HIV/STI risk reduction counseling<br>• Protocol counseling<br>• Behavioral assessment |
| **Clinical** | | • Review/update medical history<br>• Perform physical examination<br>• Perform male genital examination*<br>• Perform pelvic examination*♀<br>• Perform rectal examination<br>• Review/update concomitant medications<br>• Treat or prescribe treatment for RTI/UTI, or STIs*<br>• Disclose available test results |
| **Laboratory** | **Pharyngeal** | • NAAT for GC/CT* |
| | **Urine** | • NAAT for GC/CT*<br>• Urine dipstick/culture*<br>• Qualitative hCG ♀ |
| | **Blood** | • CBC with differential and platelets*<br>• Chemistries (AST/ALT/Creatinine)*<br>• Syphilis serology*<br>• HIV-1/2 test<br>• Plasma for archive |
| | **Pelvic** | • NAAT for GC/CT/TV*♀ |
| | **Anorectal** | • Anal swab for HPV<br>• Rectal fluid for PD and biomarker<br>• Rectal enema effluent for PD prior to biopsy collection<br>• Rectal tissue for PD, histology, and archive<br>• HSV 1/2 detection*<br>• NAAT for GC/CT* |
| **Study Product/Supplies** | | • Offer condoms |

* If indicated ♀Female participants

## 7.4 Follow-up Visits

### 7.4.1 Dosing – Visits 3, 5, and 7

The first dosing on Visit 3 should occur approximately 14 days after the Enrollment Visit.

After a two-to-six-week washout period (to accommodate scheduling around the menstrual cycles of female participants) following each dosing visit, participants will return to the clinic for assessment. If no adverse events (AEs) that preclude continuation to the next dose are identified (based on product hold criteria in Section 9 and discretion of the IoR/designee), participants will receive the next scheduled dose of the study gel. Please see the SSP Manual for additional information.

All participants will undergo PK and PD assessments within 24 hours after each gel administration. Participants will be randomized 1:1:1:1 to one of the following 4 time frames to provide samples of rectal tissue, rectal fluid, vaginal fluid (if applicable), and effluent from rectal lavage: 0.5-1 hour, 1.5-3 hours, 3.5-5 hours, and 24 hours following PC-1005 gel application. This time frame will remain consistent across gel volumes.. Procedures for the day of dosing are listed in

Table 13 below.

**Table 13: Dosing Procedures**

| Dosing Procedures – Visits 3 , 5, and 7 | | |
|---|---|---|
| **Component** | | **Procedures** |
| **Administrative and Regulatory** | | • Review/update locator information<br>• Provide reimbursement<br>• Schedule next visit/contact |
| **Behavioral/Counseling** | | • Protocol counseling<br>• Behavioral assessment |
| **Clinical** | | • Review/update medical history<br>• Perform targeted physical examination*<br>• Perform male genital examination*<br>• Perform pelvic examination*♀<br>• Perform rectal examination<br>• Review/update concomitant medications<br>• Treat or prescribe treatment for RTI/UTI, or STIs*<br>• Disclose available test results<br>• Record/update AEs |
| **Laboratory** | **Pharyngeal** | • NAAT for GC/CT* |
| | **Urine** | • NAAT for GC/CT*<br>• Urine dipstick/culture*<br>• Qualitative hCG ♀ |
| | **Blood** | • CBC with differential and platelets*<br>• Chemistries (Creatinine only)<br>• Syphilis serology*<br>• Blood for PK♦ |
| | **Pelvic** | • Vaginal fluid for PK⌂♀<br>• NAAT for GC/CT/TV*♀ |
| | **Anorectal** | • Rectal enema effluent for PD prior to biopsy collection⌂☼<br>• Rectal fluid for PK and PD⌂ ☼<br>• Rectal tissue for PK, PD, histology, and archive⌂☼<br>• HSV 1/2 detection*<br>• NAAT for GC/CT* |
| **Study Product/Supplies** | | • Administration of study product▲<br>• Offer condoms |

* If indicated. ♀Female participants.
☼ Please reference the MTN-037 SSP Manual for additional details (www.mtnstopshiv.org)
▲ Participants will receive a single dose of study product (4 mL, 16 mL, or 32 mL) depending on dosing visit.

⌂= Participants will be randomized 1:1:1:1 to provide samples of rectal tissue, rectal fluid, vaginal fluid (if applicable), and effluent from rectal lavage in one of the following time periods after dose administration across gel volumes: 0.5-1 hour; 1.5-3 hours; 3.5-5 hours, or 24 hours. (Those assigned to the 24 hour time point to provide samples will do so at the 24-hr Post-dose visit instead of the Dosing visit).
♦ Blood will be collected pre-dose administration and at 1 hour, 2 hours, 3 hours, 4, hours, 5-6 hours and 24 hours after dose administration
**NOTE:** Participants will be instructed to call in to the clinic to report any issues related to the collection of samples via the flexible sigmoidoscopy. See SSP Manual for additional details.

### 7.4.2 24-Hour Post-Dosing Visits

Safety laboratory tests and blood for PK will be collected from all participants at the 24 hour post-dosing visit. Additionally, participants randomized to sample collection at 24 hours will have PK and PD samples collected.

**Table 14: 24-Hour Post-Dosing Visits**

| 24-Hour Post-Dosing Visits - Visits 4, 6, and 8 | | |
|---|---|---|
| **Component** | | **Procedures** |
| **Administrative and Regulatory** | | • Review/update locator information<br>• Provide reimbursement<br>• Schedule next visit/contact ☦ |
| **Behavioral/Counseling** | | • HIV pre- and post-test counseling (Visit 8 only)<br>• HIV/STI risk reduction counseling (Visit 8 only)<br>• Protocol counseling<br>• IDI (Visit 8 only) |
| **Clinical** | | • Review/update medical history<br>• Perform targeted physical examination*<br>• Perform male genital examination*<br>• Perform pelvic examination*♀<br>• Perform rectal examination<br>• Review/update concomitant medications<br>• Treat or prescribe treatment for RTI/UTI, or STIs*<br>• Disclose available test results<br>• Record/update AEs |
| **Laboratory** | **Pharyngeal** | • NAAT for GC/CT* |
| | **Urine** | • NAAT for GC/CT*<br>• Urine dipstick/culture* |
| | **Blood** | • CBC with differential and platelets<br>• Chemistries (AST/ALT/Creatinine)<br>• Syphilis serology*<br>• HIV-1/2 test (Visit 8 only)<br>• Blood for PK♦☦ |
| | **Pelvic** | • Vaginal fluid for PK⌂♀<br>• NAAT for GC/CT/TV*♀ |

| 24-Hour Post-Dosing Visits - Visits 4, 6, and 8 | | |
|---|---|---|
| **Component** | | **Procedures** |
| | **Anorectal** | • Anal swab for HPV<br>• Rectal enema effluent for PD prior to biopsy collection⌂π<br>• Rectal fluid for PK and PD⌂π<br>• Rectal tissue for PK, PD, histology, and archive⌂π<br>• HSV 1/2 detection*<br>• NAAT for GC/CT* |

* If indicated. ♀Female participants.
π Please reference the MTN-037 SSP Manual for additional details (www.mtnstopshiv.org) regarding the appropriate procedures to complete for an Early Termination Visit.
⌂= Participants will be randomized 1:1:1:1 to provide samples of rectal tissue, rectal fluid, vaginal fluid (if applicable), and effluent from rectal lavagein one of the following time periods after dose administration across gel volumes: 0.5-1 hour; 1.5-3 hours; 3.5-5 hours, or 24 hours. (Those assigned to the 24 hour time point to provide samples will do so at the 24-hr Post-dose visit instead of the Dosing visit).
♦= Blood will be collected pre-dose administration and at 1 hour, 2 hours, 3 hours, 4, hours, 5-6 hours and 24 hours after dose administration
**NOTE:** Participants will be instructed to call in to the clinic to report any issues related to the collection of samples via the flexible sigmoidoscopy. See SSP Manual for additional details.

### 7.4.3 48-Hour Post-Dosing Visits

Participants will be randomly assigned 1:1:1 to provide samples of blood, rectal tissue, rectal fluid, vaginal fluid (if applicable), and effluent from rectal lavage samples 48 hours following PC-1005 administration for one of the 3 gel volume levels (4 mL, 16 mL, or 32 mL). Participants will only attend one 48-hour visit during the study.

**Table 15: 48-Hour Post-Dosing Visits**

| 48-Hour Post-Dosing Visits - Visits 4a, 6a, and 8a | | |
|---|---|---|
| **Component** | | **Procedures** |
| **Administrative and Regulatory** | | • Review/update locator information<br>• Provide reimbursement<br>• Schedule next visit/contact |
| **Behavioral/Counseling** | | • Protocol counseling |
| **Clinical** | | • Review/update medical history<br>• Perform targeted physical examination*<br>• Perform male genital examination*<br>• Perform pelvic examination*♀<br>• Perform rectal examination<br>• Review/update concomitant medications<br>• Treat or prescribe treatment for RTI/UTI, or STIs*<br>• Disclose available test results<br>• Record/update AEs |
| **Laboratory** | **Pharyngeal** | • NAAT for GC/CT* |
| | **Urine** | • Urine dipstick/culture*<br>• NAAT for GC/CT* |

| 48-Hour Post-Dosing Visits - Visits 4a, 6a, and 8a | | |
|---|---|---|
| **Component** | | **Procedures** |
| | **Blood** | • Blood for PK<br>• Chemistries (AST/ALT/Creatinine)*<br>• CBC with differential and platelets*<br>• Syphilis serology* |
| | **Pelvic** | • Vaginal fluid for PK♀<br>• NAAT for GC/CT/TV*♀ |
| | **Anorectal** | • Rectal enema effluent for PD prior to biopsy collection ☼<br>• Rectal fluid for PK and PD ☼<br>• Rectal tissue for PK, PD, histology, and archive ☼<br>• HSV 1/2 detection*<br>• NAAT for GC/CT* |

* If indicated. ♀Female participants.
☼ Please reference the MTN-037 SSP Manual for additional details (www.mtnstopshiv.org)
**NOTE**: Participants will be instructed to call in to the clinic to report any issues related to the collection of samples via the flexible sigmoidoscopy. See SSP Manual for additional details.

### 7.4.4 Final Contact

The *Final Contact* (Visit 9) will occur either in-person or by phone approximately two to six weeks after the third dosing visit (32 mL) of PC-1005 gel application. This contact will also serve as the participant's study termination.

**Table 16: Final Contact**

| Final Contact – Visit 9 | | |
|---|---|---|
| **Component** | | **Procedures** |
| **Administrative and Regulatory** | | • Review/update locator information<br>• Provide reimbursement ~<br>• Schedule next visit/contact* |
| **Behavioral/Counseling** | | • HIV pre- and post-test counseling*<br>• HIV/STI risk reduction counseling*<br>• Protocol counseling* |
| **Clinical** | | • Review/update medical history<br>• Perform targeted physical examination*<br>• Perform male genital examination*<br>• Perform pelvic examination*♀<br>• Perform rectal examination*<br>• Review/update concomitant medications<br>• Treat or prescribe treatment for RTI/UTI, or STIs*<br>• Disclose available test results<br>• Record/update AEs |
| ♂ | **Pharyngeal** | • NAAT for GC/CT* |

| Final Contact – Visit 9 | | |
|---|---|---|
| **Component** | | **Procedures** |
| | **Urine** | • NAAT for GC/CT*<br>• Urine dipstick/culture*<br>• Qualitative hCG* ♀ |
| | **Blood** | • CBC with differential and platelets*<br>• Chemistries (AST/ALT/Creatinine)*<br>• Syphilis serology*<br>• HIV-1/2 test* |
| **Study Product/Supplies** | | • Offer condoms* |

* If indicated. ♀Female participants. ~ Sites to reference SOPs regarding participant reimbursement.

## 7.5 Follow-up Procedures for Participants Who Permanently Discontinue Study Product

### 7.5.1 Participants Who Become Infected with HIV-1/2

If a participant tests positive for HIV-1/2 after the Enrollment Visit, he/she will be referred to local care and treatment services and may return to the research clinic for additional counseling and other support services, as needed. Continued study participation would be of no added benefit, thus follow-up visits will be discontinued and the participant will be considered terminated from the study. An Early Termination Visit (please refer to the MTN-037 SSP Manual for specific procedures) will be conducted, if the participant is willing. Participants who seroconvert after enrollment may be offered additional laboratory testing (such as HIV RNA and HIV drug resistance testing), as clinically indicated, per discussions between the site IoR and LC. Please reference the MTN-037 SSP Manual for additional details (www.mtnstopshiv.org).

### 7.5.2 Participants Who Become Pregnant

If a participant becomes pregnant, she will be referred to local health care services and may return to the research clinic for additional counseling, as needed. Continued study participation would be of no added benefit to the participant, thus follow-up visits will be discontinued and the participant will be considered terminated from the study. An Early Termination Visit will be conducted, if the participant is willing. A participant who is pregnant at study termination will continue to be followed until the pregnancy outcome is ascertained, see Section 9.6 for additional details.

Participants who become pregnant while on study product will be offered enrollment in MTN-016 (www.mtnstopshiv.org) which includes follow-up throughout the pregnancy and for the first year of the infant's life. Additionally, for participants who choose not to enroll in MTN-016, the study site will make every reasonable effort to contact participants and collect infant outcome at approximately one year after delivery for those pregnancies that result in live birth. For additional details regarding obtaining pregnancy and infant outcomes, please reference the MTN-037 SSP Manual (www.mtnstopshiv.org).

### 7.5.3 Participants Who Permanently Discontinue Study Product for Other Reasons

Participants who permanently discontinue study product use for any reason (clinician-initiated or self-initiated) will be considered terminated from the study and the PSRT should be notified. Continued study participation would be of no added benefit, thus follow-up visits will be discontinued and the participant will be considered terminated from the study. An Early Termination Visit will be conducted, if the participant is willing. Participants who permanently discontinue study product use due to an AE must continue to be followed off-study until resolution or stabilization of the AE is documented.

## 7.6 Interim Visits

Interim visits may be performed at any time during the study, for the following or other reasons:

- For administrative reasons, e.g., a participant may have questions for study staff, or may need to re-schedule a follow-up visit or to perform missed procedures.
- In response to AEs and/or SAEs. When interim contacts or visits are completed in response to participant reports of AEs and/or SAEs, study staff will assess the reported event clinically and provide or refer the participant to appropriate medical care (see also Section 9).
- For STI counseling and testing in response to STI symptoms.
- For HIV counseling and testing in response to participant report of symptoms consistent with acute infection or presumed exposure to HIV
- To provide participants with the results of confirmatory HIV test results, per the algorithm in Appendix II.
- For other reasons at participant request, e.g., social harm.

All interim contacts and visits will be documented in participants' study records.

## 7.7 Protocol Counseling: Adherence and Contraception Counseling

At the Dosing Visit, participants will receive study product counseling appropriate to the visit. Study staff will document administration of study product and that the counseling was provided. Protocol adherence counseling will be provided to study participants upon enrollment into the study. Contraception counseling will be provided to female study participants beginning at the Screening Visit. Counseling will be provided in accordance with standard study methods. Counseling also will include reminders regarding concomitant medication and behavioral restrictions prior to and following collection of biopsies.

## 7.8 Clinical Evaluations and Procedures

**Physical Examination**

The physical examination will include the following assessments:

- General appearance
- Weight*
- Vital signs
  - Temperature
  - Pulse
  - Blood pressure
  - Respirations
- Height*
- Abdomen*
- Head, Eye, Ear, Nose and Throat (HEENT) Examination*
- Oral mucosa*
- Lymph nodes*
- Neck*
- Heart*
- Lungs*
- Extremities*
- Skin*
- Neurological*
- Other components as indicated by participant symptoms

  * = May be omitted after Enrollment Visit

**Rectal Examination**

The rectal examination may include the following:

- Visual exam
- Digital exam
- Anoscopy
- Flexible sigmoidoscopy

**Male Genital Examination**

The male genital examination may include the following:

- General inspection via naked eye and hand-held magnifying glass of the following:
  - Entire penile surface
    - Glans
    - Urethral meatus
    - Internal and external foreskin (if present)
    - Shaft
  - Scrotum
  - Inguinal lymph nodes

**Pelvic Examination**

The pelvic examination may include the following:

- Visual exam
- Speculum exam
- Bimanual exam

*Note: Detailed information regarding the pelvic, rectal and male genital examination, as well as the associated procedures required for collecting specimens at each visit, can be found in the MTN-037 SSP Manual.*

Additional clinical assessments may be performed at the discretion of the examining clinician in response to symptoms or illnesses present at the time of the exam.

### 7.9 Behavioral Assessments

The behavioral measures of this protocol will focus mainly on the overall acceptability of the rectal gel, as well as comparative acceptability across the different volumes of gel used during the volume escalation trial. Microbicide acceptability in MTN-037 will be assessed considering the following factors:

- **Vehicle-associated:** Formulation, amount (tolerability), and perceived product texture, viscosity and scent
- **Use-associated:** Perceived post-application side-effects (e.g., odor, leakage, lubrication and/or drying effects), perceived satisfaction with product, and desirable/appealing elements of product
- **Related Co-variables:** History of anal product use, frequency of anal sex

Participants will respond to brief web-based self-interviews (WSI) at the Enrollment Visit (Visit 2) and at the three dosing visits: Visits 3, 5 and 7. The Visit 2 assessment will include, among other topics, questions on participants' prior experience and comfort using rectal products as well as douching or other rectal hygiene practices. The Visits for dosing (Visits 3, 5 and 7) will explore reactions to product, with an emphasis on identification of product attributes likely to challenge and/or facilitate future sustained use when applied rectally by participants (secondary objective: acceptability). Consistent with data harmonization efforts, major components of these WSI assessments have been validated in prior rectal microbicide trials (e.g., MTN-006, MTN-007, MTN-017) and will be used as part of MTN-037.

An in-depth interview is planned 24 hours following the third and final dose of study product (Visit 8). The in-depth interviews will include, among other topics, questions on user acceptability of the product, user-centered suggestions for product design and delivery, and experiences during the volume escalation trial, including reactions to the BD™ Luer-Lok™ Tip syringe with cap and rectal administration tip, and administration method.

### 7.10 Pharmacokinetics, Pharmacodynamics and Biomarkers of Mucosal Safety

Each participant will have a total of 5 flexible sigmoidoscopies:

- at baseline;
- within 24 hours of each of the three gel applications (to be determined at random to be one of the following times after gel administration: 0.5-1 hr, 1.5-3 hours, 3.5-5 hours, or 24 hours after gel administration), and

- 48 hours after one of the three gel applications (to be determined at random).

During the flexible sigmoidoscopy procedure, approximately 9 tissue samples will be taken at 10-15 cm, except at baseline where only 6 samples will be taken.

**Table 17: Specimens to be Collected to Assess PK, Ex Vivo Antiviral Activity, Histology**

| Visit | Specimens Collected for PK | Specimens Collected for PD | Specimens Collected to Assess Biomarkers of Mucosal Safety |
|---|---|---|---|
| Enrollment (Visit 2) (Baseline Samples) | | • Rectal sponge<br>• Rectal enema effluent prior to biopsy collection<br>• Rectal tissue (~3 biopsies) | • Rectal sponge<br>• Rectal tissue for histology (1 biopsy)<br>• Rectal tissue for archive (2 biopsies) |
| Dosing Visits (Visits 3, 5, and 7) | • Blood ♦<br>• Rectal fluid ⌂<br>• Rectal tissue (~3 biopsies) ⌂<br>• Vaginal fluid⌂♀ | • Rectal fluid ⌂<br>• Rectal enema effluent ⌂<br>• Rectal tissue (~3 biopsies) ⌂ | • Rectal tissue for histology (1 biopsy) ⌂<br>• Rectal tissue for archive (2 biopsies) ⌂ |
| 24h Post-Dosing Visits (Visits 4, 6, and 8) | • Blood ♦<br>• Rectal fluid ⌂<br>• Rectal tissue (~3 biopsies) ⌂<br>• Vaginal fluid⌂ ♀ | • Rectal fluid ⌂<br>• Rectal enema effluent ⌂<br>• Rectal tissue (~3 biopsies) ⌂ | • Rectal tissue for histology (1 biopsy) ⌂<br>• Rectal tissue for archive (2 biopsies) ⌂ |
| 48h Post-Dosing Visits■ (Visits 4a, 6a, and 8a) | • Blood<br>• Rectal fluid<br>• Rectal tissue (~3 biopsies)<br>• Vaginal fluid♀ | • Rectal fluid<br>• Rectal enema effluent<br>• Rectal tissue (~3 biopsies) | • Rectal tissue for histology (1 biopsy)<br>• Rectal tissue for archive (2 biopsies) |

♦= Blood will be collected pre-dose administration and at 1 hour, 2 hours, 3 hours, 4, hours, 5-6 hours and 24 hours after dose administration
♀=Female participants
⌂= Participants will be randomized 1:1:1:1 to provide samples of rectal tissue, rectal fluid, vaginal fluid (if applicable), and effluent from rectal lavage in one of the following time periods after dose administration across gel volumes: 0.5-1 hr, 1.5-3 hours, 3.5-5 hours, or 24 hours
■=Participants will be randomly assigned 1:1:1 to provide samples of blood, rectal tissue, rectal fluid, vaginal fluid (if applicable), and effluent from rectal lavage samples 48 hours following PC-1005 gel application for one of the 3 gel volume levels (4 mL, 16 mL, or 32 mL).

## 7.11 Laboratory Evaluations

**Local Laboratory**

The local laboratory will run the following, as indicated:

- Pharyngeal specimens
  - NAAT for GC/CT
- Vaginal specimens
  - GC/CT/TV
- Urine specimens
  - Urine hCG
  - Urine GC/CT by NAAT

    - Dipstick/culture
- Anorectal specimens
    - Rectal fluids for:
        - Rectal GC/CT by NAAT
        - HSV 1/2 viral detection
    - Rectal tissue for:
        - PD
- Blood specimens
    - HIV-1/2 testing, with confirmatory testing as needed
    - CBC with differential and platelets
    - Syphilis serology
    - Creatinine, AST, ALT
    - Coagulation (PT/INR)

**Network Laboratory Center (LC)**

- Vaginal specimens
    - Fluid for PK (Pharmacology Core)
- Blood specimens
    - PK (Pharmacology Core)
    - Plasma archive
- Anorectal specimens
    - Anal swab for HPV
    - Rectal fluids and/or lavage for:
        - PK (Pharmacology Core)
        - PD (Protocol Support Core)
    - Rectal tissue for:
        - PK (Pharmacology Core)
        - Mucosal safety (archive)
        - Histology

Once all required study analyses of collected specimens are complete, any remaining sample may be shipped to the MTN LC for use in study-related quality assurance and quality control testing. If study samples will be used for assay validation or proficiency testing that is not study related, all participant identifiers (PTID) will be removed from the samples prior to use. Specimens obtained from participants who do not consent to long term storage will not be used for assay validation or proficiency testing purposes.

### 7.12 Specimen Management

Study sites will adhere to the standards of good clinical laboratory practice (https://www.niaid.nih.gov/sites/default/files/gclp.pdf), in accordance with current US Division of AIDS (DAIDS) Laboratory Requirements, MTN-037 Study Specific Procedures Manual (http://www.mtnstopshiv.org/studies) and site standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens to standardize procedures. Specimen collection, testing, and storage at the site laboratories will be documented when applicable using the Laboratory Data Management System

(LDMS). In cases where laboratory results are not available due to administrative or laboratory error, the site is permitted to re-draw specimens. Further, as part of quality control, researchers may need to look at short pieces of non-coding repetitive DNA sequence (3-7 base pairs) from blood in the event of sample mix-up. This test will only let researchers know the number of times this short segment is repeated and not specific genes or specific sequences of base pairs. This sequence element does not contain any information about genes, therefore researchers will not be able to identify if participants are predisposed to specific diseases or any other genetic information based on this information. This test will be an important tool for distinguishing whether two samples collected at the same or different time points are likely from the same person. The test will only be used as part of a sample investigation with the knowledge of the site in situations where a known or suspected sample mix-up has occurred. No genetic testing (limited or genome-wide) is planned on leftover samples that are stored for the purposes of future research.

### 7.13 DAIDS Laboratory Oversight

All laboratories participating in DAIDS Sponsored and/or Funded Laboratories in Clinical Trials will adhere to the DAIDS Laboratory Policy (https://www.niaid.nih.gov/research/daids-clinical-research-policies-us-labs)

### 7.14 Biohazard Containment

As the acquisition 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 recommended by the CDC and National Institutes of Health (NIH). All biological specimens will be transported using packaging mandated by Code of Federal Regulations (CFR) 42 Part 72. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations. Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

# 8 ASSESSMENT OF SAFETY

### 8.1 Safety Monitoring

Site IoRs are responsible for continuous close safety monitoring of all study participants and for alerting the Protocol Team if unexpected concerns arise. A sub-group of the Protocol Team, including the Protocol Chair, DAIDS Medical Officer, a Population Council representative, and MTN Protocol Safety Physicians will serve as the PSRT. The MTN Statistical Data and Management Center (SDMC) prepares routine AE and clinical data reports for review by the PSRT, which meets via conference call to review safety data, discuss product use management, and address any potential safety concerns.

## 8.2 Clinical Data and Safety Review

A multi-tiered safety review process will be followed for the duration of this study. The study site investigators are responsible for the initial evaluation and reporting of safety information at the participant level and for alerting the PSRT if unexpected concerns arise. Participant safety is also monitored at the Network level through a series of routine reviews conducted by the SDMC, the PSRT and study sponsors. Additional reviews may be conducted at each of these levels as dictated by the occurrence of certain events.

MTN SDMC staff will review incoming safety data on an ongoing basis. Events identified as questionable, inconsistent, or unexplained will be queried for verification. AE reports submitted in an expedited manner to the DAIDS Safety Office will be forwarded to the DAIDS Medical Officer and SDMC Clinical Safety & Coding Group staff for review.

The PSRT will meet approximately every month via conference call to review clinical data reports generated by the MTN SDMC. The content, format and frequency of the clinical data reports will be agreed upon by the PSRT and the SDMC in advance of study implementation. In addition to the routine safety data reviews, the PSRT will convene on an ad hoc basis to make decisions regarding the handling of any significant safety concerns. If necessary, experts external to the MTN representing expertise in the fields of microbicides, biostatistics, HIV acquisition and medical ethics may be invited to join the PSRT safety review. A recommendation to pause or stop the trial may be made by the PSRT at this time or at any such time that the team agrees that an unacceptable type and/or frequency of AEs has been observed.

The Study Monitoring Committee (SMC) will review participant safety data as part of their regular reviews (see Section 10.7), since no Data and Safety Monitoring Board oversight is planned for MTN-037. The SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. Members of the SMC will be independent investigators with no interest (financial or otherwise) in the outcomes of this study. If at any time a decision is made to discontinue enrollment and/or study product use in all participants, DAIDS will notify the FDA and Site IoRs will notify the responsible IRB expeditiously.

In addition to the safety monitoring, the MTN SMC will conduct interim reviews of study progress, including rates of participant accrual, retention, completion of primary and main secondary endpoint assessments, and study or lab issues. These reviews will take place approximately every 4-6 months, or as needed. At the time of these reviews, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued.

## 8.3 Adverse Events Definitions and Reporting Requirements

### 8.3.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product. This definition is applied to all study groups, and is applied to all groups beginning at the time of enrollment through the termination visit. The term "investigational product" for this study refers to PC-1005 (0.002% MIV-150/0.3% Zinc acetate [ZA] in 3.0% Carrageenan [CG] gel).

Study participants will be provided instructions for contacting the study site to report any untoward medical occurrences they may experience. In cases of potentially life-threatening events, participants will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation where a study clinician is based, and to request that the clinician be contacted upon their arrival. With appropriate permission of the participant, whenever possible, records from all non-study medical providers related to untoward medical occurrences will be obtained and required data elements will be captured in the study database. All participants reporting an untoward medical occurrence will be followed clinically until the occurrence resolves (returns to baseline) or stabilizes.

Study site staff will document in source documents and in the study database all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, and/or Addenda 1, 2 and 3 (Female Genital [Dated November 2007], Male Genital [Dated November 2007] and Rectal [Clarification Dated May 2012] Grading Tables for Use in Microbicide Studies).

Please note:

- Asymptomatic BV and asymptomatic candidiasis will not be reportable AEs;
- Fetal losses (e.g., spontaneous abortions, spontaneous fetal deaths, stillbirths) will not be reported as AEs (however, fetal loss data will be collected);
- Untoward maternal conditions that either result in or result from fetal losses are reported as reproductive system AEs.

Bleeding at the time of BD™ Luer-Lok™ Tip syringe with cap and rectal administration tip use, anoscope, flexible sigmoidoscope insertion/removal, and/or biopsy collection that is judged by the clinician to be within the range of what is normally anticipated will not be reportable as an AE. Bleeding of greater quantity or longer duration than what is typical, per clinician assessment, will be reportable as an AE. Fecal urgency, bloating and

flatulence associated with rectal procedures deemed to be within the range of what is normally expected will not be reportable as AEs.

### 8.3.2 Serious Adverse Events

An SAE will be defined by the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, January 2010), as an AE that:

- Results in death
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization
  *Note:* Per ICH SAE definition, hospitalization itself is not an AE, but is an outcome of the event. Thus, hospitalization in the absence of an AE is not regarded as an AE, and is not subject to expedited reporting. The following are examples of hospitalization that are not considered to be AEs:
    - Protocol-specified admission (e.g., for procedure required by study protocol)
    - Admission for treatment of target disease of the study, or for pre-existing condition (unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator)
    - Diagnostic admission (e.g., for a work-up of an existing condition such as persistent pretreatment lab abnormality)
    - Administrative admission (e.g., for annual physical)
    - Social admission (e.g., placement for lack of place to sleep)
    - Elective admission (e.g., for elective surgery)

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

### 8.3.3 Adverse Event Relationship to Study Product

Relatedness is an assessment made by a study clinician of whether or not the event is related to the study agent. Degrees of relatedness will be categorized according to current DAIDS-approved guidelines. Per the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, January 2010), the relationship categories that will be used for this study are:

- *Related:* There is a reasonable possibility that the AE may be related to the study agent(s)
- *Not Related:* There is not a reasonable possibility that the AE is related to the study agent(s)

## 8.4 Adverse Event Reporting Requirements

### 8.4.1 Expedited Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the DAIDS RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited adverse event (EAE) reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS EAE Form. This form is available on the DAIDS RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting.

For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Please note that site queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS RSC Safety Office at (DAIDSRSCSafetyOffice@tech-res.com).

### 8.4.2 Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study. The study agent for which expedited reporting is required is: PC-1005 (0.002% MIV-150/0.3% zinc acetate [ZA] in 3.0% carrageenan [CG] gel).

### 8.4.3 Grading Severity of Events

The grading of severity of events and the reporting period will be the same as for all AEs, as described in Section 8.3.1. The most current Division of AIDS Table for Grading Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, and Addenda 1, 2 and 3 (Female Genital [Dated November 2007], Male Genital [Dated November 2007] and Rectal [Clarification Dated May 2012] Grading Tables for Use in Microbicide Studies) will be used and are available on the RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables.

### 8.4.4 Expedited AE Reporting Period

The EAE reporting period for this study begins at enrollment and continues through the participant's termination from the study.

After the protocol-defined AE reporting period, unless otherwise noted, only Suspected, Unexpected Serious Adverse Reactions (SUSARs) as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

### 8.5 Pregnancy and Infant Outcomes

Pregnant women are excluded from this study.

A participant who becomes pregnant after enrollment will continue to be followed until the pregnancy and, if applicable, infant outcome is ascertained, see Section 9.6 for additional details. Pregnancy outcomes will not be expeditiously reported to the Population Council or the DAIDS Medical Officer (MO) unless there is an associated AE in the pregnant participant that meets expedited reporting criteria or the pregnancy results in a congenital anomaly meeting the Manual for Expedited Reporting of EAEs to DAIDS (Version 2.0, January 2010) guidelines for expedited reporting.

A participant who becomes pregnant during the course of study participation will be offered participation in MTN-016, HIV Prevention Agent Pregnancy Exposure Registry: EMBRACE Study. This registry study captures pregnancy outcomes as well as infant health information, (including growth) for the first year of life, to evaluate the safety and teratogenic risks of microbicide and oral PrEP exposure in pregnancy. Additionally, for participants not enrolled in MTN-016, the study site will make every reasonable effort to contact participants and collect infant outcome at approximately one year after delivery for those pregnancies that result in live birth.

### 8.6 Regulatory Requirements

Information on all reported AEs will be included in reports to the FDA and other applicable government and regulatory authorities. Site IoRs/designees will submit AE and any relevant safety information in accordance with local regulatory requirements.

### 8.7 Social Harms Reporting

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others and that social harms may result. Social harms that are judged by the IoR/designee to be serious or unexpected will be reported to the PSRT and responsible site IRBs according to their individual requirements.

# 9 CLINICAL MANAGEMENT

Guidelines for clinical management and permanent discontinuation of study product are outlined in this section. In general, the IoR/designee has the discretion to permanently discontinue study product use at any time if he/she feels that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary. IoRs/designees will document all permanent discontinuations on applicable CRFs.

## 9.1 Grading System

AE severity grading is described in Section 8.4.3.

## 9.2 Dose Modification Instructions

No dose modifications will be undertaken in this study. However, participants will not proceed to the next sequential dose if they meet any of the criteria for product hold or discontinuation as found in Section 9.3 and Section 9.4.

## 9.3 General Criteria for Permanent Discontinuation of Study Product

Permanent Discontinuation
A participant will be permanently discontinued from product use by the IoR/designee for any of the following reasons:

- Acquisition of HIV infection; for those who acquire HIV, study product should be held beginning immediately upon recognition of the first positive/reactive HIV test
- Pregnancy or breastfeeding
- Anogenital STIs
- Participant is unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being by continuing product use, according to the judgment of the IoR/designee.
- Reported use of PEP or PrEP
- Anticoagulant use (e.g., heparin, Lovenox, warfarin and Plavix)
- Use of CYP3A inhibitors and inducers (as specified in MTN-037 SSP Manual)

At the discretion of the IoR/designee, a participant may be permanently discontinued for reported use of the following medications

- Aspirin (greater than 81 mg/day), other non-steroidal anti-inflammatory drugs (NSAIDS)
- Rectally administered products

## 9.4 Follow-up in Response to Observed Adverse Events

**Grade 1 and Grade 2 Unrelated**
In general, a participant who develops a Grade 1 AE as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, and/or Addenda 1, 2 and 3 (Female Genital [Dated November 2007], Male Genital [Dated November 2007] and Rectal [Clarification Dated May 2012] Grading Tables for Use in Microbicide Studies), regardless of relationship to study product, may continue product use. Participants who develop a Grade 2 AE that is judged by the IoR/designee to be unrelated to study product may also continue product use. If the IoR/designee opts to temporarily hold study product, the PSRT must be notified.

**Grade 2 Related**

For participants who develop a Grade 2 AE that is judged by the IoR/designee to be related to product, study product must be held and the IoR must consult with PSRT regarding continued study product use.

If a recurrence of the same Grade 2 AE judged to be related to study product recurs at any time during the study, study product must be temporarily held until the PSRT can be consulted regarding permanent discontinuation or other further management.

**Grade 3 or Grade 4**

For participants who develop a Grade 3 or 4 AE study product must be permanently discontinued and the PSRT notified.

### 9.5 HIV-1 Infection

Participants who test positive for HIV-1 must have study product permanently discontinued by the IoR/designee. A participant who is confirmed to be HIV-1 positive during the course of the study will have study product discontinued, all follow-up visits will be discontinued and the participant will be considered terminated from the study, as per Section 7.5.1. Guidance regarding management and referral for participants confirmed to be HIV-positive is located in Section 13.10.

### 9.6 Pregnancy

Female participants will be encouraged to report all signs or symptoms of pregnancy to study staff. The IoR/designee will counsel any participant who becomes pregnant regarding possible risks to the fetus according to site SOPs. The IoR/designee also will refer the participant to all applicable services; however, sites will not be responsible for paying for pregnancy-related care.

A participant who becomes pregnant during the course of the study will have study product discontinued and will be terminated from the study, as per Section 7.5.2. A participant who is pregnant at study termination will continue to be followed until the pregnancy outcome is ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained). Pregnancy and infant outcomes will be reported on relevant CRFs; outcomes meeting criteria for EAE reporting also will be reported on EAE forms.

A participant who becomes pregnant during the course of study participation will be offered participation in MTN-016, HIV Prevention Agent Pregnancy Exposure Registry: EMBRACE Study. This registry study captures pregnancy outcomes as well as infant health information, (including growth) for the first year of life, to evaluate the safety and teratogenic risks of microbicide and oral PrEP exposure in pregnancy. Additionally, for participants not enrolled in MTN-016, the study site will make every reasonable effort to contact participants and collect infant outcome at approximately one year after delivery for those pregnancies that result in live birth.

### 9.7 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. IoRs/designees also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures, after consultation with the PSRT. Participants also may be withdrawn if NIAID, MTN, government or regulatory authorities, including the FDA and Office for Human Research Protections (OHRP), or site IRBs terminate the study prior to its planned end date. Every reasonable effort is made to complete a final evaluation of participants who withdraw or are withdrawn from the study prior to completing follow-up (see details regarding the Early Termination Visit in Section 7.5). Study staff members will record the reason(s) for all withdrawals in participants' study records.

# 10 STATISTICAL CONSIDERATIONS

### 10.1 Overview and General Design

MTN-037 is a phase 1, open label, sequential dose/volume escalation trial designed to characterize the PK and safety profiles of a single dose of PC-1005 (0.002% MIV-150/0.3% zinc acetate [ZA] in 3.0% carrageenan [CG] gel) administered rectally via applicator in the clinic. Twelve HIV-uninfected men and women, 18 years or older will receive a single dose of each dose/volume (4 mL, 16 mL, and 32 mL) in sequential order allowing time for adequate washout before application of the subsequent dose.

### 10.2 Study Endpoints

**Primary Endpoints**

Consistent with the primary study objectives to (1) evaluate the safety of PC-1005 gel formulation (0.002%MIV-150/0.3% zinc acetate [ZA] in 3.0% carrageenan [CG] gel) when applied rectally and (2) characterize the systemic and compartmental pharmacokinetics of PC-1005 gel following rectal application, the following endpoints will be assessed:

- **Safety**
  Grade 2 or higher AEs as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, and/or Addenda 1, 2 and 3 (Female Genital [Dated November 2007], Male Genital [Dated November 2007] and Rectal [Clarification Dated May 2012] Grading Tables for Use in Microbicide Studies)
- **Pharmacokinetics**
  MIV-150 concentrations
  - Plasma
  - Rectal fluid
  - Rectal mucosal tissue homogenates

## 10.3 Primary Study Hypotheses

MTN-037 hypothesizes that PC-1005 gel (0.002% MIV-150/0.3% ZA in 3.0% CG gel) will be safe when applied to the rectum and well-tolerated among healthy men and women who have a history of receptive anal intercourse (RAI).

## 10.4 Sample Size and Power Calculations

### Safety Endpoints

The proposed total sample size for assessing safety is approximately N=12 participants. This sample size is based upon the size of similar Phase 1 studies of microbicides for HIV prevention.

As a means to characterize the statistical properties of this study, Table 18 below presents the probability of observing zero, at least one, and two or more safety endpoints among the 12 participants for various "true" event rates:

**Table 18: Analysis of Safety Event Frequency**

| Event Rate | P (0 events \| n=12) | P (≥1 event \| n=12) | P (≥2 events \| n=12) |
|---|---|---|---|
| 1% | 88.6 | 11.4 | 0.6 |
| 5% | 54.0 | 46.0 | 11.8 |
| 10% | 28.2 | 71.8 | 34.1 |
| 15% | 14.2 | 85.8 | 55.7 |
| 25% | 3.2 | 96.8 | 84.2 |
| 35% | 0.6 | 99.4 | 95.8 |

An alternative way of describing the statistical properties of the study design is in terms of the 95% confidence interval for the true rate based on the observed data. Table 19 below shows the exact 2-sided 95% confidence intervals for the probability of an event based on a particular observed rate. If none of the 12 participants receiving a particular dose/volume of gel experience a safety event, the 95% exact 2-sided upper confidence bound for the true rate of such events for that dose/volume is 26.4%.

**Table 19: Exact 2-sided 95% Confidence Intervals Based on Observing a Particular Rate of Safety Endpoints for Arms of Size 12**

| Observed event rate | Confidence interval (%) |
|---|---|
| 0/12 | 0.0, 26.4 |
| 1/12 | 0.2, 38.4 |
| 2/12 | 2.1, 48.4 |

Additional participants may enroll in the study, at the discretion of the protocol team, to replace currently enrolled participants lost to follow-up or to permanent product discontinuation. Thus, in the event that additional participants are recruited for this purpose, the total sample size at the end of the study may slightly exceed 12 participants who received any dose/volume of PC-1005.

## 10.5 Randomization Procedures

There will be no randomization to dose/volume of PC-1005 in this open-label, sequential dose/volume escalation trial. However, upon enrollment a participant will be assigned to a randomly selected sequence of pharmacokinetic sampling times for administration of flexible sigmoidoscopy biopsy procedures.
Each participant will have a total of 5 flexible sigmoidoscopies:

- at baseline (1 set of biopsies);
- within 24 hours of each of the three dose/volume gel applications (one of the following randomly selected times: 0.5-1 hour, 1.5-3 hours, 3.5-5 hours, or 24 hours after gel administration for each dose/volume of gel) (total of 3 sets of biopsies), and
- 48 hours after one of the three dose/volume gel applications (to be determined at random) (1 set of biopsies).

The sampling schedule for a participant will be preassigned at the enrollment visit.

The determination of the sample schedule will achieve the following characteristics:

- All 12 participants will have flexible sigmoidoscopy at enrollment.
- For the 4 mL, 16 mL, and 32 mL dose/volumes, participants will be randomly assigned 1:1:1:1 to one of the following 4 time frames to provide samples of rectal tissue, rectal fluid, vaginal fluid (if applicable), and effluent from rectal lavage: 0.5-1 hour, 1.5-3 hours, 3.5-5 hours, and 24 hours following PC-1005 gel application.
- There will be 3 sets of biopsies available at each time frame (0.5-1 hour, 1.5-3 hours, 3.5-5 hours, and 24 hours following PC-1005 gel application) for each dose/volume (4 mL, 16 mL, and 32 mL).
- Across the three dose/volumes (4 mL, 16 mL, and 32 mL), participants will be randomly assigned 1:1:1 to provide samples of blood, rectal tissue, rectal fluid, vaginal fluid (if applicable), and effluent from rectal lavage48 hours following PC-1005 gel application for one of the three dose/volumes.
- There will be 4 sets of biopsies available at 48 hours following PC-1005 gel application for each dose/volume (4 mL, 16 mL, and 32 mL).
- Randomizations will be stratified by gender so as to incorporate 1-2 participants of each gender at each of four time frames between 0.5 and 24 hours, and to incorporate 2 participants of each gender at 48 hours for each dose/volume.

The randomization scheme will be generated and maintained by the MTN SDMC.

## 10.6 Participant Accrual, Follow-up and Retention

Based on previous studies of rectal products with similar eligibility requirements, the accrual of approximately 12 eligible participants will take approximately 6-8 months. Individuals lost to follow-up or to permanent product discontinuation may be replaced after statistical and team input have been received. However, every effort will be made to

complete the regularly scheduled safety evaluations and retain all enrolled participants in follow-up to minimize possible bias associated with loss-to-follow-up.

## 10.7 Data and Safety Monitoring and Analysis

### 10.7.1 Study Monitoring Committee

No Data and Safety Monitoring Board oversight is planned for this study. The MTN SMC will conduct interim reviews of participant safety data and study progress, including rates of participant accrual, retention, completion of primary and main secondary endpoint assessments, and study or lab issues. These reviews will take place approximately every 4-6 months, or as needed. At the time of this review, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued.

### 10.7.2 Primary Analysis

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

#### Safety Endpoints

All visits in which a participant has been exposed to the study product will be included in the primary analyses of safety. Secondary intent to treat analyses may also be performed. The number and the percentages of participants experiencing each safety endpoint (see Section 10.2) will be tabulated by dose/volume of gel. Each participant will contribute once in each category (i.e., only for highest severity AE for each participant) for the calculation of event rates for each dose/volume of gel.

To assess the overall tolerability of the 3 dose/volumes of gel, participants in each dose/volume may be compared for characteristics including safety events and laboratory measurements using descriptive statistics. Due to the small sample size, formal comparisons will not be done.

#### Pharmacokinetic/Pharmacodynamic Analysis

We will use descriptive statistics such as the mean and median and corresponding 95% confidence intervals to describe the MIV-150 concentrations in all biological matrices assessed at all scheduled time points. For each dose/volume of gel, the 0.5 to 48 hour time points will be used to describe the concentrations beginning soon after a gel dose through time to peak concentrations through initial elimination among different matrices.

Concentrations will be compared among and between volume arms using paired analyses.

Ex vivo HIV explant data will use cumulative p24 to compare baseline with study product. Concentration-response relationships will also be explored using appropriate linear and non-linear models. Rectal lavage fluid will be assessed for anti-HIV activity and the percent inhibition will be correlated to MIV-150 concentrations.

### 10.7.3 Missing Data

Every effort will be made to complete the regularly scheduled safety and PK evaluations and retain all enrolled participants in follow-up over the three dose/volume evaluations lasting 14 to 42 days each, including washout. Based on previous MTN trials, we expect to have minimal missing data. If participants are lost to follow-up or to permanent product discontinuation, they may be replaced, as mentioned above. If missing data rates are higher than anticipated (over 15%) for a particular dose/volume safety evaluation or for individual pharmacokinetic measure time points, then additional participants may enroll in the study, at the discretion of the protocol team, to replace currently enrolled participants.

# 11 DATA HANDLING AND RECORDKEEPING

## 11.1 Data Management Responsibilities

Data collection tools will be developed by the MTN SDMC in conjunction with the protocol team. Quality control and data integrity are managed manually and systematically with reports and queries routinely generated and provided by the SDMC to the study sites for verification and resolution. As part of the study activation process, each study site will identify all CRFs to be used as source documents. Study CRF data will be entered and cleaned using the Medidata Rave EDC tool, a data management system compliant with the International Council on Harmonization (ICH) Good Clinical Practices (GCP) and US CFR guidelines for electronic data capture.

## 11.2 Source Documents and Access to Source Data/Documents

All study sites will maintain source data/documents in accordance with current DAIDS policies. (https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf)
Each IoR/designee will maintain, and store securely, complete, accurate and current study records throughout the study. In accordance with U.S. regulations, for the investigational products tested, IoRs/designees will maintain all study documentation for at least two years following the date of marketing approval for the indication in which they were studied. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the investigation is discontinued and the US FDA is notified.

Study records must be maintained on site for the entire period of study implementation. Thereafter, instructions for record storage will be provided by DAIDS. No study records may be moved to an off-site location or destroyed prior to receiving approval from DAIDS.

### 11.3 Quality Control and Quality Assurance

Study sites will conduct quality control and quality assurance procedures in accordance with current DAIDS policies (https://www.niaid.nih.gov/sites/default/files/qmppolicy.pdf).

# 12 CLINICAL SITE MONITORING

Study monitoring will be carried out by Pharmaceutical Product Development, Inc. (PPD) (Wilmington, NC) in accordance with current DAIDS policies. Study monitors will visit study sites to do the following:

- Review informed consent forms, procedures, and documentation
- Assess compliance with the study protocol, Good Clinical Practices (GCP) guidelines, and applicable regulatory requirements (US and non-US), including CFR Title 45 Part 46 and Title 21 Parts 50, 56, and 312
- Perform source document verification to ensure the accuracy and completeness of study data
- Verify proper collection and storage of biological specimens
- Verify proper storage, dispensing, and accountability of investigational study products
- Assess implementation and documentation of internal site quality management procedures

IoRs/designees will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, CRFs), as well as observe the performance of study procedures. IoRs/designees also will allow inspection of all study-related documentation by authorized representatives of the MTN LOC, SDMC, LC, the Population Council, NIAID, FDA, OHRP, IRBs and other local, US, or international regulatory authorities. A site visit log will be maintained at study sites to document all visits.

# 13 HUMAN SUBJECTS PROTECTIONS

Site investigators will make efforts to minimize risks to participants. Participants and study staff members will take part in a thorough informed consent process. Before beginning the study, IoRs/designees will have obtained IRB approval and the protocol will have been submitted to the FDA. IoRs/designees will permit audits by the NIH, the FDA, OHRP, MTN LOC, IRBs, SDMC, and other local, US, or international regulatory authorities or any of their appointed agents.

## 13.1 Institutional Review Boards/Ethics Committees

The participating institution is responsible for assuring that this protocol, the associated site-specific informed consent forms (ICFs), and study-related documents (such as participant education and recruitment materials) are reviewed by an IRB responsible for oversight of research conducted at each study site. Any amendments to the protocol must be approved by the responsible IRBs prior to implementation.

Subsequent to the initial review and approval, the responsible IRBs must review the study at least annually. Each IoR/designee will make safety and progress reports to the IRBs at least annually and within three months after 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. In addition, the results of all SMC reviews of the study will be provided to the IRBs. Study sites will submit documentation of continuing review to the DAIDS Protocol Registration Office (PRO) in accordance with the DAIDS Protocol Registration Policy and Procedures Manual.

## 13.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, sites must have the protocol and the protocol consent forms approved, as appropriate, by its local IRB and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) *will* be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) *will not* be

reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in site regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

## 13.3 Study Coordination

DAIDS holds the Investigational New Drug (IND) application for this study. Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement (CTA) executed by NIAID and the Population Council.

Study implementation will be directed by this protocol, which may not be amended without prior written approval from the Protocol Chair and DAIDS Medical Officer. Study implementation will also be guided by a common Study-Specific Procedures (SSP) Manual that provides further instructions and operational guidance on conducting study visits; data and forms processing; specimen collection, processing, and shipping; AE assessment, management and reporting; dispensing study products and documenting product accountability; and other study operations. Standardized study-specific training will be provided to sites by the MTN LOC, SDMC, LC and other designated members of the Protocol Team.

Close coordination between protocol team members is necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. The PSRT will address issues related to study eligibility and AE management and reporting as needed to assure consistent case management and documentation. Rates of accrual, adherence, follow-up, and AE incidence will be monitored closely by the team as well as the SMC.

## 13.4 Risk Benefit Statement

### 13.4.1 Risks

It is not expected that this trial will expose human subjects to unreasonable risk.

<u>Vaginal Fluid Collection</u>
Collection of vaginal fluid may cause discomfort or pressure in the vagina or genital area.

<u>Phlebotomy and IV Cannula Placement</u>
Phlebotomy may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling, having a blood clot, excessive bleeding, and/or infection.

<u>Pharyngeal Swab</u>
Pharyngeal (throat) swab collection often causes a momentary gagging reflex.

Rectal Enema
An enema is a standard procedure that may be used prior to insertion of a flexible sigmoidoscope since fecal matter can obscure the test. The main risk from having an enema is temporary discomfort. A hollow tube about the thickness of a pencil will be used to put approximately 120 mL of normal saline 0.9% into the rectum and flush it out again (a larger volume may be required if the initial volume does not produce results), along with any stool that is there. Some air may be pumped into the rectum as well, causing flatulence. There is a risk of a bloated/cramping feeling. The tube is small, but it might cause some anal or rectal discomfort if the subject has any hemorrhoids or other painful conditions.

Anoscopy
Insertion of a lubricated anoscope will likely cause some discomfort.

Flexible Sigmoidoscopy and Rectal Biopsy Collection
Flexible sigmoidoscopy is a commonly practiced endoscopic medical procedure and will not involve any increased risk over usual sigmoidoscopy performed for clinical indications. There is a low risk of infection, mild rectal irritation, low blood pressure, and feeling a sudden urge to defecate during or after the flexible sigmoidoscopy procedure. There is a very low risk of an intestinal tear during the flexible sigmoidoscopy procedure.

There is a risk of limited rectal bleeding 1-2 days after flexible sigmoidoscopy, associated with collection of biopsy samples. The rate of perforation of a hollow viscus following endoscopic biopsy occurs less than 88 out of every 100,000 times.[49] A recent retrospective analysis of approximately 1,000 research flexible sigmoidoscopies (including collection of rectal biopsies) conducted at the University of Pittsburgh demonstrated an overall adverse event rate of 1.6%. The majority of AEs were gastrointestinal in nature and of mild/moderate severity.[50]

Participants will be instructed to refrain from sexual intercourse and counseled not to use NSAIDs, aspirin (over 81 mg per day) and/or other drugs that are associated with the increased likelihood of bleeding for 72 hours before and after PK sample collection visits. If participants engage in sexual intercourse before the biopsy has healed they may experience some temporary discomfort. If participants are sexually active they may also be at increased risk for STIs and HIV acquisition, if exposed. There is a small risk of infection and heavier bleeding. Participants will be instructed to contact the clinic if symptoms are bothersome, if heavy bleeding is noted or if the participant develops any abnormal odor or discharge from the rectum.

Rectal Fluid Collection
There is the risk of mild discomfort in addition to a slight risk of bleeding with the insertion of rectal swabs and sponges for collection of rectal fluid.

Rectal Applicator (for Administration of Study Product)
Use of an applicator to deliver a microbicide into the rectal compartment may be associated with minor anorectal trauma including lacerations and bruising in the anorectal area. Side effects observed with rectal application of microbicides in previous research

studies include: mild rectal fullness; incontinence or diarrhea; flatulence; mild abdominal pain; and proctalgia.

Other Risks

Disclosure of HIV and STI status may cause worry, sadness or depression. Disclosure of HIV-positive status has been associated with depression, suicidal ideation, and denial as well as social isolation. Trained counselors will be available to help participants deal with these feelings.

Participation in clinical research includes the risks of loss of confidentiality and discomfort with the personal nature of questions when discussing sexual behaviors.

Sexual partner notification in response to diagnosed STI or HIV infection could cause problems in participants' relationships. Participants also could have problems in their partner relationships associated with study-required abstinence.

Site staff will make every effort to protect participant privacy while in the study. Although study sites will make every effort to protect participant privacy and confidentiality, 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-positive 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.

Risks Associated With PC-1005 Gel

AEs among a small number of female participants who dosed vaginally with PC-1005 gel included:

- Metrorrhagia
- Vaginal discharge
- Vulvovaginal pruritus
- Abdominal discomfort
- Constipation
- Urinary tract infection
- Uterine spasm (cramps)

These side effects may or may not be associated with rectal use of PC-1005 gel.

In previously completed studies involving rectally-applied products, the following gastrointestinal AEs were common and/or occurred at a Grade 3 or higher:

- Abdominal distension
- Abdominal bloating
- Abdominal pain/cramps
- Defecation urgency
- Diarrhea
- Flatulence
- Tenesmus

Previously tested rectal gels (not the gel being used in this study) have also been associated with anal discharge. These side effects may or may not be associated with the use of PC-1005 gel.

### 13.4.2 Benefits

Participants in this study may experience no direct benefit. 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 safe and effective interventions to prevent HIV, HSV-2, and HPV acquisition and transmission. Participants also may appreciate the opportunity to contribute to the field of HIV prevention research.

Participants will receive HIV/STI risk reduction counseling, HIV and STI testing, physical examination, and routine laboratory testing related to blood, liver, and kidney function. Participants may be provided or referred for STI treatment free of charge, and STI testing and treatment may be offered and/or referrals may be provided (for their partners). For other medical conditions identified as part of the study screening and/or follow-up procedures, participants will be referred to other sources of care available in their community. Some volunteers may have the opportunity to access expedient treatment and decreased morbidity due to early diagnosis and treatment of abnormalities identified during tests, examinations and referrals.

## 13.5 Informed Consent Process

Written informed consent will be obtained from each study participant prior to screening. Written informed consent also will be obtained for long-term specimen storage and possible future testing, although consent for long-term specimen storage is not required for study participation. In obtaining and documenting informed consent, IoRs and their designees will comply with applicable local and US regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf). Participants will be provided with copies of the ICF if they are willing to receive them.

In addition to the ICF, the Protocol Team will work with study staff and community representatives to develop appropriate materials about the study and a standardized approach to the informed consent process to be implemented at study sites, which will be detailed in the SSP Manual.

The informed consent process will cover all elements of informed consent required by research regulations. In addition, the process specifically will address the following topics of importance to this study:

- The unknown safety and unproven efficacy of the study product
- The need to abstain from sexual intercourse for protocol defined periods

- The importance of participants to the success of the study
- The importance of adherence to the study visit and procedures schedule
- The potential medical risks of study participation (and what to do if such risks are experienced)
- The potential social harms associated with study participation (and what to do if such harms are experienced)
- The real yet limited benefits of study participation
- The distinction between research and clinical care
- The right to withdraw from the study at any time

### 13.6 Participant Confidentiality

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality to the extent possible. Study sites will implement confidentiality protections that reflect the local study implementation plan and the input of study staff and community representatives to identify potential confidentiality issues and strategies to address them.

All study-related information will be stored securely. All participant information will be stored in locked areas with access limited to study staff. All laboratory specimens, study data, and administrative forms will be identified by coded number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored securely. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participants' identification numbers to identifying information will be stored in a locked file in an area with limited access. Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing by the following:

- Representatives of the US Federal Government, including the US FDA, the US OHRP, NIH, and/or contractors of the NIH, and other local, US, or international regulatory authorities
- PPD
- Representatives of the Population Council, including study monitors
- Representatives of the MTN LOC, SDMC, and/or LC Study staff
- Site IRBs

The MTN has a Certificate of Confidentiality from the US Department of Health and Human Services that is applicable to this study. This Certificate protects study staff from being compelled to disclose study-related information by any US Federal, State or local civil, criminal, administrative, legislative or other proceedings. It thus serves to protect the identity and privacy of study participants.

## 13.7 Special Populations

### 13.7.1 Children

The NIH has mandated that children be included in research trials when appropriate. This study meets “Justifications for Exclusion” criteria for younger children as set forth by the NIH. Specifically, “insufficient data are available in adults to judge potential risk in children” and “children should not be the initial group to be involved in research studies.” This study does not plan to enroll children under 18 years old.

## 13.8 Compensation

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

## 13.9 Communicable Disease Reporting

Study staff will comply with local requirements to report communicable diseases, including HIV-1 identified among study participants to health authorities. Participants will be made aware of reporting requirements during the informed consent process.

## 13.10 Access to HIV-related Care

### 13.10.1 HIV Counseling and Testing

HIV test-related counseling will be provided to all potential study participants who consent to undergo HIV-1 screening to determine their eligibility for this study, and to all enrolled participants at each follow-up HIV-1/2 testing time point. Testing will be performed in accordance with the algorithm in Appendix II. Counseling will be provided in accordance with standard HIV counseling policies and methods at sites and additionally will emphasize the unknown efficacy of the study products in preventing HIV-1 and HIV-2 infection. In accordance with the policies of the NIH, participants must receive their HIV-1/2 test results to take part in this study.

### 13.10.2 Care for Participants Identified as HIV-Positive

An individual who has been identified as infected with HIV-1 will be managed or referred for management according to the local standard of care. Should a participant test positive for HIV after the Enrollment Visit, follow-up procedures will be performed as per Section 7.5.1.

## 13.11 Study Discontinuation

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

# 14 PUBLICATION POLICY

DAIDS/NIAID and MTN policies and a CTA between NIAID and the Population Council will govern publication of the results of this study. Any presentation, abstract, or manuscript will be submitted by the investigator to the MTN Manuscript Review Committee, DAIDS, NIAID, NIMH, and the Population Council for review prior to submission.

# 15 APPENDICES

## APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

Please note: Procedures consistently listed as "If indicated" at study visits will not be listed in Appendix I.

| | **Screening** Visit 1 | **Enrollment** Visit 2 | **Dosing Visits** Visit 3, 5, 7 | **24 Hr Post-Dosing Visits** Visits 4, 6, 8 | **48 Hr Post-Dosing Visits** ■ Visits 4a, 6a, 8a | **Final Contact** Visit 9 |
|---|---|---|---|---|---|---|
| **ADMINISTRATIVE AND REGULATORY** | | | | | | |
| Informed consent (SCR/ENR) | X | | | | | |
| Assess consent form comprehension | X | | | | | |
| Assign PTID | X | | | | | |
| Assess and/or confirm participant eligibility | X | X | | | | |
| Demographic information | X | | | | | |
| Locator information | X | X | X | X | X | X |
| Provide reimbursement | X | X | X | X | X | X ~ |
| Schedule next study visit/contact | * | * | X | X π | X | * |
| Review informed consent/ confirm participant willingness to participate in study | | X | | | | |
| Assign to rectal tissue sampling schedule | | X | | | | |
| **BEHAVIORAL/COUNSELING** | | | | | | |
| HIV pre-/post-test counseling | X | X | | X (Visit 8 only) | | * |
| HIV/STI risk reduction counseling | X | X | | X (Visit 8 only) | | * |
| Protocol counseling | X | X | X | X | X | * |
| Behavioral assessment | | X | X | | | |
| Behavioral assessment (IDI) | | | | X (Visit 8 only) | | |
| **CLINICAL** | | | | | | |
| Medical history | X | X | X | X | X | X |
| General/Targeted physical exam | X | X | * | * | * | * |
| Perform rectal examination | X | X | X | X | X | * |
| Concomitant medications | X | X | X | X | X | X |
| Provide available test results | X | X | X | X | X | X |
| Record/update AEs | | | X | X | X | X |
| **LABORATORY** | | | | | | |
| **PHARYNGEAL** | | | | | | |
| NAAT for GC/CT | X | * | * | * | * | * |
| **URINE** | | | | | | |
| NAAT for GC/CT | X | * | * | * | * | * |
| Qualitative hCG ♀ | X | X | X | | | * |
| **BLOOD** | | | | | | |
| CBC with differential and platelets | X | * | * | X | * | * |
| Chemistries (AST/ALT/Creatinine) | X | * | X (creatinine only) | X | * | * |
| Syphilis serology | X | * | * | * | * | * |
| HIV-1/2 test | X | X | | X (Visit 8 only) | | * |
| Coagulation (PT/INR) | X | | | | | |
| Plasma for archive | | X | | | | |
| Blood for PK | | | ♦ | ♦ | X | |

| | Screening Visit 1 | Enrollment Visit 2 | Dosing Visits Visit 3, 5, 7 | 24 Hr Post-Dosing Visits Visits 4, 6, 8 | 48 Hr Post-Dosing Visits ■ Visits 4a, 6a, 8a | Final Contact Visit 9 |
|---|---|---|---|---|---|---|
| **PELVIC SAMPLES ♀** | | | | | | |
| Vaginal fluid for PK | | | ⌂ | ⌂ | X | |
| NAAT for GC/CT/TV | X | * | * | * | * | |
| **ANORECTAL SAMPLES** | | | | | | |
| Anal swab for HPV | | X | | X | | |
| Rectal enema effluent for PD prior to biopsy collection | | X | X⌂☼ | ⌂π | X☼ | |
| Rectal fluid for PK and PD | | X (PD only) | X⌂☼ | ⌂π | X☼ | |
| Rectal tissue for PD, histology, and archive | | X | X⌂☼ | ⌂ π | X☼ | |
| Rectal tissue for PK | | | X⌂☼ | ⌂π | X☼ | |
| NAAT for GC/CT | X | * | * | * | * | |
| **STUDY PRODUCT/SUPPLIES** | | | | | | |
| Administration of study product | | | ▲ | | | |
| Offer condoms | X | X | X | | | * |

X = Required. * = As indicated. ♀ = For female participants.

♦ = Blood will be collected pre-dose administration and at 1 hour, 2 hours, 3 hours, 4, hours, 5-6 hours, and 24 hours after dose administration.

⌂ = Participants will be randomized (1:1:1:1) to provide samples of rectal tissue, rectal fluid, vaginal fluid (if applicable), and effluent from rectal lavage in one of the following time periods after dose administration across gel volumes: 0.5-1 hour; 1.5-3 hours; 3.5-5 hours, or 24 hours. Those assigned to the 24 hour time point to provide samples will do so at the 24-hr Post-dose visit instead of the Dosing visit.

☼ Please reference the MTN-037 SSP Manual for additional details (www.mtnstopshiv.org)

▲= Participants will receive a single dose of study product (4 mL, 16 mL, or 32 mL) depending on dosing visit.

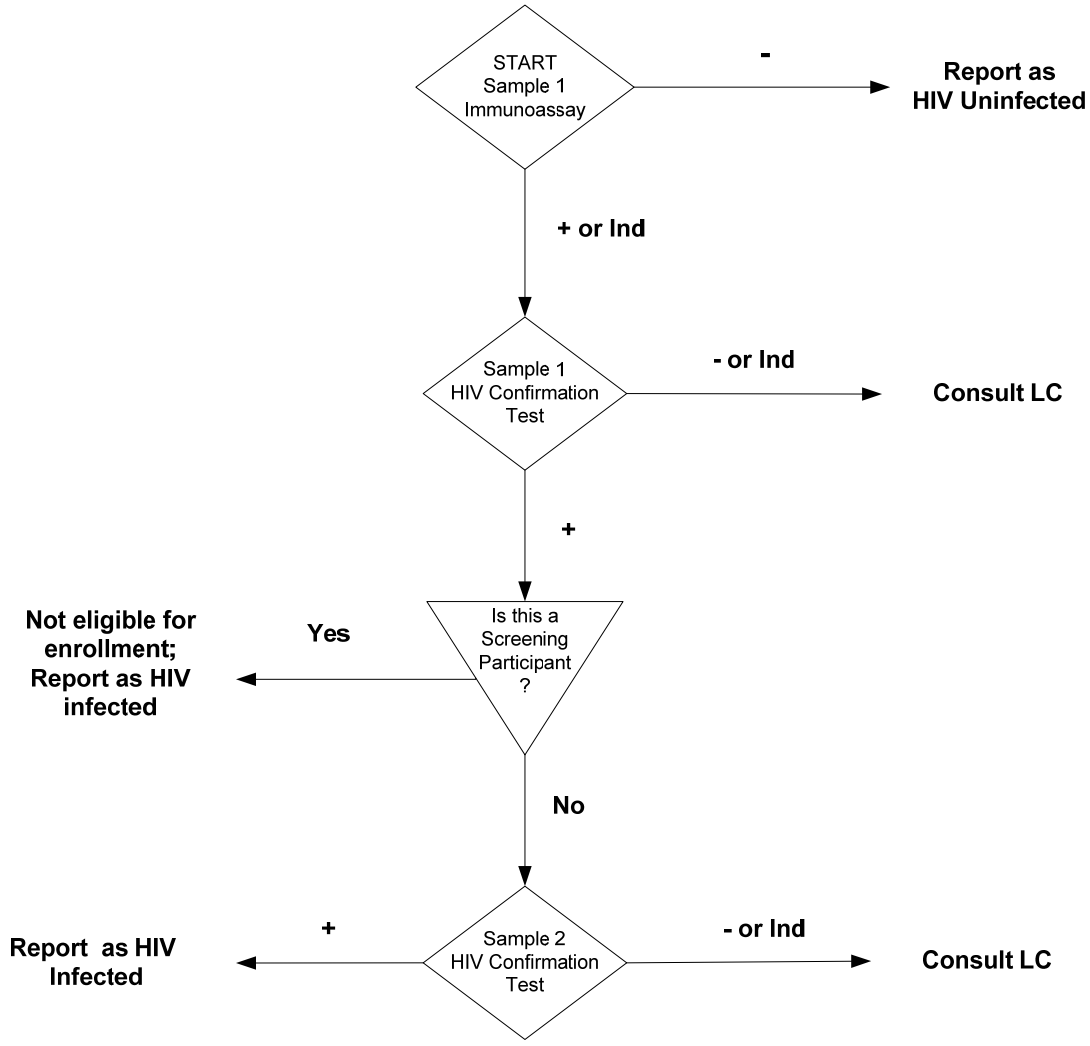
■ = Participants will be randomly assigned 1:1:1 to provide samples of blood, rectal tissue, rectal fluid, vaginal fluid (if applicable), and effluent from rectal lavage samples 48 hours after one of the three dose administrations.

~ = Sites to reference SOPs regarding participant reimbursement.

π = Please reference the MTN-037 SSP Manual for information regarding Early Termination visit (www.mtnstopshiv.org)

**NOTE**: Participants will be instructed to call in to the clinic to report any issues related to the collection of samples via the flexible sigmoidoscopy.

## APPENDIX II: ALGORITHM FOR HIV TESTING FOR SCREENING AND FOLLOW-UP




Ind: Indeterminate test results
LC: Laboratory Center

## APPENDIX III: SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, LONG-TERM STORAGE AND FUTURE TESTING)

**DIVISION OF AIDS, NIAID, NIH**

**MTN-037**

**A Phase 1 Safety and Pharmacokinetic Study of PC-1005 (MIV-150/Zinc Acetate/Carrageenan Gel) Administered Rectally to HIV-1 Seronegative Adults**

**Version 1.0**

**November 9, 2017**

**PRINCIPAL INVESTIGATOR:** ***[Sites to insert]***
**PHONE:** ***[Sites to insert]***
**Short Title for the Study:** Safety and PK Study of PC-1005 Applied Rectally

**INFORMED CONSENT**

You are being asked to take part in this research study because you are a healthy, HIV-uninfected man or woman (cis or transgender) aged 18 or older and reported at least one experience of consensual receptive anal sex in your lifetime. Approximately 12 people will participate in this study at two sites in the United States. The US National Institutes of Health (NIH) sponsors this Microbicide Trials Network (MTN) study. The Population Council supplies product for this study. At this site, the person in charge of this study is ***[INSERT NAME OF PRINCIPAL INVESTIGATOR]***.

Before you decide if you want to join this study, we want you to learn more about it. This consent form gives you information about the study. Study staff will talk with you and answer any questions you may have. Once you read and understand the study and its requirements, you can decide if you want to join. If you do decide to take part in the trial, you will sign your name on this form. A copy of this document will be offered to you. Signing this consent form does not mean you will be able to join the study. You must first complete the screening tests and exams to see if you are eligible. You may decide to stop being in the study at any time.

***What happens if you do not want to take part?***
*Before you learn more about the study it is important that you understand:*

- You do not have to be in this study if you do not want to.
- You can stop taking part at any time. This will not affect the service you get at this clinic.
- If you decide to stop taking part, you may join another study, if we have one and you qualify.

***Why is this research being done?***
There are two main purposes of this study. The first is to test if PC-1005 gel is safe when inserted into the rectum (the last 6 to 8 inches of the large intestine); the second is to better understand how PC-1005 is absorbed by and eliminated from the body when inserted into the rectum via applicator.

Additionally, researchers would like to understand whether you find it acceptable to use the gel when inserted into the rectum via a lubricated applicator.

PC-1005 is a potential multipurpose prevention technology (MPT) microbicide in early development that has been shown to be active against human immunodeficiency (HIV), human papillomavirus (HPV), and herpes simplex virus type- 2 (HSV-2).

PC-1005 is considered to be investigational. This means it has not been approved by the US Food and Drug Administration (FDA) for preventing HIV and other sexually transmitted infections (STIs). PC-1005 is a carrageenan-based gel containing MIV-150 and zinc acetate.

- MIV-150 is an anti-retroviral (ARV) drug that has been tested as a treatment for HIV (the virus that causes AIDS) in 63 men who took it orally in the form of a tablet in four different studies.
- Zinc acetate is a substance used in a number of cosmetic products and over-the-counter products, such as calamine lotion and cold medicines.
- Carrageenans come from seaweed and are used in many foods and cosmetics, including toothpaste and baby formula. Carrageenan is a Generally Recognized As Safe (GRAS) food substance.

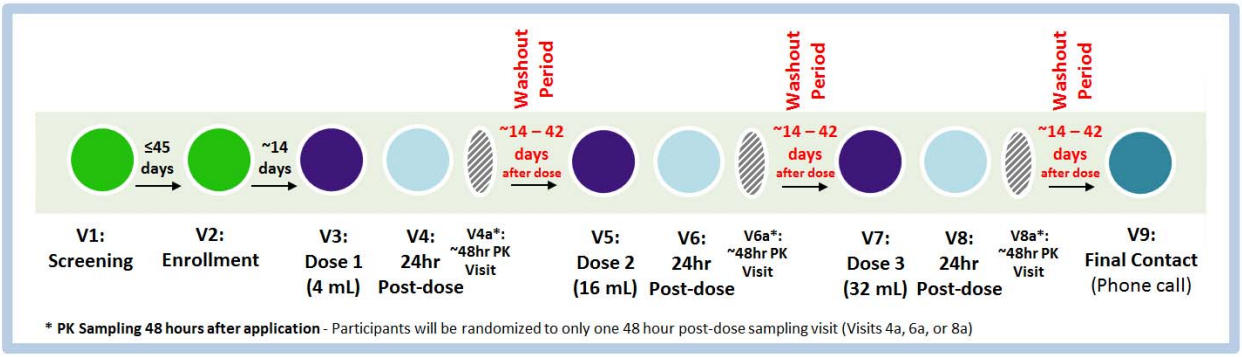
PC-1005 has been found to be safe in laboratory testing and has been tested in animal studies. It has been tested in and was well-tolerated and found acceptable by 25 women who applied the gel vaginally once a day for up to 14 days under close observation. Now researchers would like to know more about how PC-1005 is processed within the body when PC-1005 gel is applied rectally. In this study, PC-1005 is being tested for the first time in humans as a rectally-applied gel.

***Who will be in this research study and what will I be asked to do if I join?***

There will be approximately 6 participants enrolled at each site. Approximately 12 participants will be enrolled in the MTN-037 study at 2 sites. Each participant will receive three doses of PC-1005, the study rectal gel. The dose of gel administered will increase over the course of the study (4mL, 16mL and 32mL). Participation in this study will last approximately 3-5 months. The study includes a total of 9 clinic visits and one contact (via phone or in person), including the Screening Visit which is taking place today. Visits will take place here, at this study clinic. Multiple visits may be conducted to complete all required screening procedures. The study includes a Screening and an Enrollment Visit, three Dosing visits (at which the study gel is administered), three 24-Hour Post-Dosing Visits and one 48-Hour Post-Dosing Visit (at which rectal and other samples are collected), and the Final Contact, which may occur in person or by phone.

After each dose of PC-1005 is administered, you will have more laboratory tests to make sure you do not have any side effects. If there are no safety concerns, you will have the next higher dose approximately 2-6 weeks after the previous dose. During this time, you will not use any product; this is called a washout period.

**Study Visit Schedule**




***What will happen during study visits?***

**Screening Visit**

The procedures done today will take about ***[SITES TO INSERT TIME]***.

You will:

- Answer questions to confirm you are able and willing to join the study
- Answer questions about where you live, your medical health (including what medications you are taking), and your sexual practices
- Provide study staff your contact information (i.e. about how we can contact you)
- Be asked to abstain from some medications during your participation in the study:
  - Anticoagulant medications (blood thinners)
  - Rectally-administered medications
  - PrEP (oral Truvada® or other PrEP)
  - PEP (post-exposure prophylaxis)
- Have a physical exam
- Talk with study staff about sexually transmitted infections (STIs), HIV, HIV/STI testing, and ways to avoid HIV and other infections passed through sex, including use of oral Truvada® for PrEP
- Talk with study staff about the requirements of the study including, but not limited to, restrictions on sexual practices:

You will be asked to abstain from the following activities at these timepoints during the study:

For males and females:

| *Activity:* | *Abstain For How Long?* |
|---|---|
| • Receptive anal intercourse<br>• Inserting any non-study products or objects into your rectum, including:<br>  o Fingers<br>  o Rectal medications<br>  o Enemas<br>  o Lubricants<br>  o Sex toys (dildos, anal plugs, etc.)<br>• Using aspirin (greater than 81 mg) and other non-steroidal anti-inflammatory drugs (NSAIDS) | • 72 hours (3 days) prior to each study visit at which rectal fluid/tissue is scheduled to be collected<br>• 72 hours (3 days) following rectal fluid/tissue collection |
| • Receptive oral anogenital stimulation (e.g., partner placing their mouth on your anogenital area) | • 72 hours (3 days) following rectal fluid/tissue collection |

Females will be asked to abstain from the following additional activities:

| *Activity:* | *Abstain For How Long?* |
|---|---|
| • Receptive penile-vaginal intercourse<br>• Inserting any non-study products or objects into your vagina, including:<br>  o Spermicides<br>  o Vaginal medications (including hormones)<br>  o Vaginal douches<br>  o Lubricants or moisturizers<br>  o Sex toys (vibrators, dildos, etc.)<br>  o Fingers | • 72 hours (3 days) prior to each study visit at which rectal fluid/tissue and/or vaginal fluid is scheduled to be collected |

At your Screening Visit, you will also:

- Have your urine tested for sexually-transmitted diseases and other infections
- Provide a blood sample ***[SITES TO INSERT AMOUNT]***:
  - To test the health of your blood, liver and kidneys.
  - To test for infections that typically are passed through sex, including HIV and syphilis.
    - You will be told your test results as soon as they are available. You will talk with the study staff about the meaning of your results, how you feel about them, and learn about ways to prevent HIV and other sexually transmitted infections. Sometimes HIV tests are not clearly positive, but also not clearly negative. In that case, we will do more tests until we are sure of your status. To participate in the study you must receive the results of your HIV test. If the test shows you have HIV, you cannot join the study. We will refer you to available sources of medical care and other services you may need. The study staff will tell you about other studies you may be eligible for, if any.

- Have a pharyngeal (throat) swab (like a Q-tip) collected, to test for infections passed through sex.
- Have a rectal examination. Rectal fluid will be collected with a swab; these will be used to test for sexually transmitted infections (STIs).
- For females:
    - Your urine will be tested for pregnancy
        - If you are pregnant you cannot join this study.
        - Staff will discuss with you ways to avoid getting pregnant.
    - You will have some fluids collected from your cervix using a swab to test for STIs and other problems if they feel it necessary.
- Be given treatment or a referral for treatment of sexually transmitted infections, if needed.
- Be informed about other services, if needed.
- Be given the results of your tests, when available. It is expected that all of your results will be available by ***[SITES TO SPECIFY TIMEFRAME]***.
- Be given male condoms, if you need them
- Be reimbursed for your visit
- Schedule your next visit to enroll in the study, if you are willing and eligible.

If you decide not to join MTN-037, blood and other samples collected at this visit will not be kept or used for any tests other than those listed above.

**Enrollment Visit:**

Your Enrollment Visit (the visit where you enter the study) will take about ***[SITES TO INSERT TIME.]***

The following procedures are specific to the Enrollment Visit, which will take place up to 45 days after your Screening Visit.

You will:

- Answer questions to confirm you are able and willing to join the study
- Update study staff with your contact information (about where you live and how we can contact you)
- Be assigned to a study sample collection sequence.
    - During this visit, you will be assigned to specific timepoints to collect rectal fluid and tissue (and vaginal fluid if you are female). This may affect how long some of your study visits will last. At some of your study visits after the Enrollment Visit, these samples may be collected one time at: 30-60 minutes after receiving the study gel, between 90 minutes to 3 hours later, between 3 ½ to 5 hours later, or 24 hours later, depending on the timing of sample collection you have been assigned to. You will also be asked to attend one 48-Hour Post-Dosing Visit. You will be able to find out today at which visit(s) you will be asked to stay longer and for how long you will have to stay at the clinic to complete these procedures.
    - These samples will help researchers learn how PC-1005 is absorbed by and eliminated from the body.

- Talk with study staff about the following:
    - The instructions and procedures of the study and how to follow the study guidelines, including the sexual abstinence requirement and use of non-study products/objects. **If you do not think you can be sexually abstinent for the required length of time before and after study visits then you should not join this study.**
    - Sexually transmitted infections (STIs), HIV, HIV/STI testing, and ways to avoid HIV and other infections passed through sex.
- Discuss any health or medical problems you may have had in the past or since your last visit (including what medications you are taking)
- Be asked some questions about your experience and comfort using rectal products, as well as douching or other rectal hygiene practices, among other things. These questions will be asked via computer.
- Provide a blood sample ***[SITES TO INSERT AMOUNT]***:
    - In case there's a question about your test results at a later time.
    - To test your blood for HIV, the virus that causes AIDS
- Have a physical exam
- Have a rectal exam where rectal fluid and tissue samples will be collected. The samples collected at your Enrollment Visit (before you receive any doses of study gel) and at other visits will help researchers better understand how the study drug enters and exits the body, what effect the drug has, and test for infections passed through sex. When these samples are collected at future visits, similar tests will be done.
    - To collect rectal fluid samples: Study staff will insert a short hollow tube called an anoscope inside your rectum. The clinician will insert swabs and/or sponges through the hollow tube to collect the sample.
    - To collect rectal tissue samples: A flexible sigmoidoscopy will be performed.
        - A flexible sigmoidoscope is a flexible, hollow tube that is placed inside your rectum so that the study clinician can take samples of tissue.
    - In preparation for the sample collection you will have an enema.
        - During an enema, a hollow tube about the thickness of a pencil will be used to put some saline solution (salt water) through your anus and squeeze it into your rectum to flush it out and cleanse the bowel of fecal matter (stool). An enema may be standard procedure prior to insertion of an anoscope or flexible sigmoidoscope, since fecal matter can obscure the test. This may need to be repeated so that any stool that is there is removed.
    - The fluid (effluent) left over from the enema will be collected, and then the study clinician will collect approximately 6 tissue samples, each about the size of a grain of rice.
- (For females):
    - Have a urine test for pregnancy and discuss with study staff ways to avoid getting pregnant
- Be given test results, if available
- Be given male condoms, if you need them
- Be reimbursed for your visit
- Schedule your next visit, if applicable.

**Dosing Visits (Visits 3, 5, and 7)**

Your first Dosing Visit is the visit at which you will receive your first dose of the study gel. This visit will take between ***[SITES TO SPECIFY TIMEFRAME]*** to complete. You will have two additional Dosing Visits after the first visit.

All participants will have the same gel dosing visit schedule. All participants will receive PC-1005 gel; study staff will apply the study gel in your rectum using an applicator (a syringe [not intended for injection] with a cap and a rectal administration tip). The dose/volume of gel to be administered will increase from visit to visit.

- At Visit 3, 4 mL of PC-1005 gel will be administered.
- At Visit 5, 16 mL of PC-1005 gel will be administered.
- At Visit 7, 32 mL of PC-1005 gel will be administered.

Neither you nor the study staff can choose or change the order in which you will receive the study gel doses/volumes.

You will:

- Update study staff with your contact information
- Review the instructions and procedures of the study and how to follow the guidelines, including about sexual abstinence and insertion of non-study products or objects
- Discuss any health or medical problems you may have had since your last visit (including what medications you are taking)
- Be asked some questions about your experience receiving the study product. These questions will be asked via computer.
- Have one dose of study gel inserted by study staff using a lubricated applicator,
- Have a rectal examination and have rectal fluid and tissue collected using the anoscope and flexible sigmoidoscope. These samples will be collected after each dose of study gel is inserted at one of the following time points: 30-60 minutes after inserting the study gel, between 90 minutes to 3 hours later, between 3 ½ to 5 hours later, or 24 hours later (at your 24-Hour Post-Dosing Visit). You will be randomly assigned to one of these four time points at the beginning of the study and will provide samples at the same time point after each of the three dose administrations.
    - In preparation for the tissue collection you will have an enema (rectal lavage). The fluid (effluent) left over from the enema will be collected.
    - The study clinician will then collect approximately 9 tissue samples, each about the size of a grain of rice
- (For females):
    - Your urine will be tested for pregnancy
    - You will provide a small amount of vaginal fluid via swab for research purposes. This sample will be collected at the same timepoints as the rectal fluid and tissue samples are collected.
- Have blood samples collected ***[SITES TO INSERT AMOUNT]***
    - To test your blood for creatinine, a test which shows how well your kidneys are functioning
    - At several timepoints including prior to gel administration and at 1 hour, 2 hours, 3 hours, 4 hours, and 5-6 hours after dose administration. An intravenous cannula (IV tube) may be placed for up to 6 hours after administration of the gel for the

blood draws. These samples will be collected to help researchers better understand how the study drug enters and exits the body.

- Discuss with study staff about any problems that you may be experiencing as a result of administration of the study gel or applicator or as a result of procedures performed during your visit
- Be provided with any available test results and with treatment or a referral for treatment if your test results indicate that you require it.
- Be given male condoms, if you need them
- Be reimbursed for your visit
- Schedule your next visit or contact.

**24-Hour Post-Dosing Visits (Visits 4, 6, and 8)**

Your 24-Hour Post-Dosing Visits will take place approximately 24 hours (1 day) after you receive each dose of the study gel. Each of these visits will take between ***[SITES TO SPECIFY TIMEFRAME]*** to complete.

At these visits, you will:

- Update study staff with your contact information
- Talk with study staff about the following:
    - The instructions and procedures of the study and how to follow the guidelines, including about sexual abstinence and insertion of non-study products or objects
    - Sexually transmitted infections (STIs), HIV, HIV/STI testing, and ways to avoid HIV and other infections passed through sex. (Visit 8)
- Discuss any health or medical problems you may have had since your last visit (including what medications you are taking)
- Have a computer-administered interview. This interview may take approximately 30-45 minutes and will occur over video chat, e.g., Google Hangout, Skype, FaceTime, etc. This conversation will be recorded, but your responses will be kept private and confidential, and the audio-recording will be destroyed after it has been transcribed and checked. You will be asked questions about your thoughts on the study product, what might make the product more appealing to use and your experience with having the gel administered in the clinic. (Visit 8)
- Have a rectal examination
- Provide a rectal fluid sample to test for infections passed through sex. A swab will be used to collect the sample.
- Provide additional rectal samples (fluid and tissue), if they were not collected at your Dosing Visit the day prior. For instance, if you are assigned to give samples at the 24 hours after dose administration time point.
- (For females)
    - Provide a small amount of vaginal fluid via swab for research purposes, if it was not collected at your Dosing Visit the day prior.
- Provide a blood sample ***[SITES TO INSERT AMOUNT]***:
    - To test the health of your blood, liver and kidneys.
    - To test your blood for HIV, the virus that causes AIDS: (Visit 8)
        - You will be told your test results as soon as they are available.
    - To help researchers to better understand how the study drug enters and exits the body.

- Speak with study staff about any problems that you may be experiencing as a result of administration of the study gel or applicator or as a result of procedures performed during your visit
- Be given any available test results
- Be reimbursed for your visit
- Schedule your next visit or contact.

**48-Hour Post-Dosing Visits (Visits 4a, 6a, and 8a)**

You will be asked to attend one 48-Hour Post-Dosing Visit (Visit 4a, 6a, or 8a). You will be randomly assigned at the beginning of the study to which Post-Dose Visit you are to attend. This visit will take place approximately 48 hours (2 days) after one of your study gel dosing visits. The timing of this visit depends on to which 48-hour post-dosing visit you were assigned. This visit will take between ***[SITES TO SPECIFY TIMEFRAME]*** to complete.

At these visits, you will:

- Update study staff with your contact information
- Talk with study staff about the instructions and procedures of the study and how to follow the guidelines, including about sexual abstinence and insertion of non-study products or objects
- Discuss any health or medical problems you may have had since your last visit (including what medications you are taking)
- Have a rectal examination
- Provide rectal samples (fluid and tissue). These samples will help researchers to better understand how the study drug enters and exits the body and what effect the drug has.
- (For females)
    - Provide a small amount of vaginal fluid via swab for research purposes
- Provide a blood sample ***[SITES TO INSERT AMOUNT]***:
    - To help researchers to better understand how the study drug enters and exits the body
- Discuss with study staff about any problems that you may be experiencing as a result of administration of the study gel or applicator or as a result of procedures performed during your visit
- Be given any available test results
- Be reimbursed for your visit
- Schedule your next visit or contact.

**Final Contact (Visit 9)**

Your Final Contact will take place approximately two to six weeks after your final dosing visit. An in-clinic visit will take place, if needed; if not, your last study contact may take place by phone. This visit/contact will take approximately ***[SITES TO SPECIFY TIMEFRAME]*** to complete.

At this visit, you will:

- Update study staff with your contact information
- Discuss any health or medical problems you may have had since your last visit (including what medications you are taking)

- Discuss any problems that you may be experiencing as a result of using the study gel or applicator, or as a result of procedures performed during the study
- Talk with study staff about instructions and procedures of the study and how to follow the guidelines
- Be reimbursed for your visit, if required
- Schedule your next visit or contact (if necessary)
- Be given any available test results
- Be given male condoms, if you need them

It is important that you remember that at any time during the study, study staff can answer any questions you may have about the procedures mentioned above or any other aspect of this study.

***Other Procedures:***
In addition to the procedures listed above, it is possible that study clinicians may need to perform additional tests, if necessary (e.g., if you report having symptoms of a urinary, genital, or other infection and/or other issues). These tests might include the following:

- Physical exam
- Pelvic exam
- Genital exam
- Rectal exam
- Test rectal or throat samples for STIs
- Test cervix/vaginal samples for STIs
- Test your urine for STIs or other infections
- Test your blood for STIs
- Test your blood to check the health of your blood, liver and kidneys
- Give you treatment or refer you for treatment of STIs or other issues, if needed.

Further you may need to provide additional samples if any of the above procedures need to be repeated due to issues with sample processing, and/or testing or shipping. Additional testing may be performed as part of quality control.

## *What are the possible risks, side effects, and discomforts of this research study?*

**Risks from use of rectal gel**
The use of any rectal gel can cause some side effects. We do not yet know all the side effects of this gel. Previously tested rectal gels (not the gel being used in this study) have been associated with:

- Abdominal bloating, feeling full, or a sense of abdominal pressure and/or pain
- A sudden, almost uncontrollable, need to relieve the bowels
- Diarrhea (loose, frequent stools)
- Passing gas from the intestinal tract
- Feeling a constant need to pass stools, despite an empty bowel
- Anal discharge

These side effects may or may not be associated with rectal use of PC-1005 gel.

**Risks from study drug**
The gel can cause side effects. We do not yet know the side effects of PC-1005 gel on the rectum. The following side effects have been associated with the use of PC-1005 in female participants in other studies in which the gel was administered vaginally. These side effects may or may not be associated with the use of PC-1005 when the drug is placed into a rectal gel:

- Abdominal discomfort
- Constipation
- Urinary tract infection
- Abnormal bleeding from the uterus (metrorrhagia)
- Vaginal discharge
- Itching of the vagina (vulvovaginal pruritus)
- Cramps (uterine spasm)

It is also possible that you may have an allergic reaction to the study product. Signs of allergic reaction may include: rash, dizziness, itching, muscle aches, nausea, fainting, facial flushing, chest tightness, cough, hives, fever, and shortness of breath.

**Risks from phlebotomy and IV cannula placement (blood tests)**

- You may feel discomfort
- You may feel dizzy or faint
- You may have a bruise, swelling, small clot, or infection where the needle goes in your arm
- You may have excessive bleeding

**Risks of throat swab**

- A pharyngeal (throat) swab often causes a momentary gagging reflex.

**Risks of rectal enemas**

- The main risk from having an enema is temporary discomfort. A hollow plastic tube about the thickness of a pencil will be used to administer about 120-125 mL of enema fluid into the rectum.
- You may experience some mild discomfort and a bloated or “crampy” feeling.
- If you have any hemorrhoids or other painful conditions, you might feel anal or rectal discomfort.
- Some air may be pumped into the rectum as well, causing flatulence.

**Risks of finger and anoscope rectal exams**

- During rectal exams and collection of rectal fluid and tissue samples, insertion of a lubricated anoscope will likely cause mild discomfort.

**Risks of rectal swab/sponge insertion**

- Insertion of rectal swabs and sponges may cause mild discomfort, in addition to a slight risk of bleeding.

**Risks of flexible sigmoidoscopy**

- A flexible sigmoidoscopy is a commonly practiced medical procedure where a flexible tube with a small camera attached is used to look inside the rectum and lower colon. The procedures done in this study will not involve any increased risk over usual flexible

sigmoidoscopy performed for clinical indications (for routine medical diagnosis or treatment).
- The risks associated with these procedures include mild discomfort, a sudden urge to relieve the bowels, the feeling of having a "bloated stomach", low blood pressure, light bleeding following a bowel movement, abnormal odor or discharge from the rectum, as well as flatulence (gas passed through the anus/rectum) following the procedure.

**Risks of endoscopic biopsy**
- Endoscopic biopsies (biopsies done using a slender, lighted optical tube) to collect rectal tissue samples are painless and heal quickly within 3 days.
- On extremely rare occasions, the endoscopic procedure or biopsies may lead to pain, infection (sepsis), bleeding or perforation (small hole or tear) of the gastrointestinal tract. Perforation occurs less than once out of every 1,000 procedures (88/100,000 procedures). If this extremely rare complication occurs, antibiotics and surgery to repair the tear may be necessary.
- If you engage in sexual intercourse before the biopsy has healed, there exists the risk of temporary discomfort, and increased risk of STIs and HIV acquisition.

**Risks from the applicator**
- Use of an applicator to deliver the study gel into the rectum may be associated with minor trauma in and around the rectum and anus, including lacerations (minor cuts) and bruising.

**(For females) Risks of vaginal swab**
- During vaginal fluid collection, you may feel discomfort or pressure in your vagina or genital area.

**Other Possible Risks:**
- You may become embarrassed and/or worried when discussing your sexual practices, ways to protect against HIV and other infections passed through sex, and your test results.
- You may feel anxious while waiting for your test results, and after receiving them. Trained study counselors will help you deal with any feelings or questions you have.
- Finding out your HIV status could cause depression and/or suicidal thoughts. Finding out your HIV status could also cause problems between you and your partner(s). If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them.
- It is possible that you and/or your partner(s) may experience problems in your relationship(s) associated with maintenance of the study-required abstinence.
- It is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community.
- The interviews that take place at some of your clinic visits will be computer-administered and questions of a personal nature may be asked. Responding to these questions may make you uncomfortable. You may choose not to answer any question that makes you uncomfortable.

We will make every effort to protect your privacy and confidentiality during the study visits. Your visits will take place in private. Any names that might be mentioned during the interview will NOT be retained. Instead a generic description will be used in the records (i.e., if you refer to a friend's name, "FRIEND1" will be noted).

***What are possible benefits from taking part in this study?***

- There are no direct benefits for taking part in this study, but you or others may have future benefit from information learned in this study. You may also learn more about HIV and other diseases and ways to protect yourself from infection.
- It is important that you know that you will not be paid any additional money (beyond the reimbursement described below for study participation) if the study product being studied is eventually licensed for use.
- You will have physical and rectal exams. You will also have tests to check the overall health of your liver, kidneys, and blood cells. If these tests show that you might have any health problems, you will be told about medical care and other services available to you. This will be available to you even if you do not enroll in this study. This study cannot provide you with general medical care, but study staff will refer you to other available sources of care.
- You will get counseling and testing for HIV and STIs. If you have infections passed through sex, other than HIV infection, you will be offered medicine to treat them or provided information for where you may receive treatment, and study staff will discuss options available for counseling and treatment of your partner. This treatment or referral for treatment is available to you even if you do not enroll in this study.
- If you become infected with HIV, you will need to receive care from your own health care provider or we will provide you with a referral. This study does not provide medication for treatment of HIV/AIDS.
- You will receive free male condoms, if you need them.

***Will this study drug prevent HIV infection?***

We do not know if the drug contained within the gel works to protect men and women from getting HIV. This study is <u>not</u> testing to see if PC-1005 prevents HIV infection. Researchers are continuing to study PC-1005 to learn more about how it works in humans to protect against HIV infection. There are only two known effective ways to reduce your risk of contracting HIV: the use of condoms and/or the use of oral pre-exposure prophylaxis (PrEP) medication, Truvada®. PrEP is an HIV prevention method in which people who do not have HIV take an oral tablet to reduce their risk of becoming infected. Study staff can provide you with additional information about PrEP if you are interested in learning more. If you are interested in these alternative options you may also want to discuss them with your doctor. If you are currently taking PrEP or plan to take PrEP in the near future, you will not be eligible for this study.

**What if there is new information learned during this study?**

We will tell you about new information from this or other studies that may affect your willingness to stay in this study. You will also be told when study results may be available, and how to learn about them.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

***Is it possible that I may be taken out of the study without my consent?***

A study clinician may need to remove you from the study early without your permission if:

- The study is cancelled by the US FDA, US NIH, the Population Council (the nonprofit organization that supplies the rectal gel), the US Office for Human Research Protections (OHRP), MTN, the local government or regulatory agency, or the Institutional Review

Board (IRB). An IRB is a committee that watches over the safety and rights of research participants.

- The Study Monitoring Committee (SMC) recommends that the study be stopped early (A SMC reviews the progress of the study and the kinds of effects that people report while they are participating in the study)
- You are found to be infected with HIV (see “If You Become Infected With HIV“ section below) or an anogenital STI
- (Females) You become pregnant or are breastfeeding (see “If You Become Pregnant“ section below)
- You report the use of the following prohibited medications:
- PEP or PrEP
- Anticoagulants (e.g., heparin, Lovenox, warfarin and Plavix)
- CYP3A inhibitors or inducers (e.g., grapefruit, Prozac, Zoloft, Prednisone, Prilosec)
- A study clinician decides that using the study would be harmful to you, for example you have a bad reaction to the study gel
- Other reasons that may prevent you from completing the study successfully, such as you are not able to reliably keep appointments

**If You Become Infected With HIV**

Your participation in this study will not cause HIV infection. However, there is always a chance that through sexual activity or other activities you may become infected with HIV. In the unlikely event that you become infected with HIV, study staff will give you counseling and refer you to available medical care and other services you may need. The study does not pay for this care. Tests will be performed to see if you have HIV drug resistance. This will allow your doctor to know what HIV drugs would be best for the treatment of your type of HIV. If the HIV test shows that you have been infected with HIV, you will stop using the study gel. You may be referred to other research studies. Continued study participation would be of no added benefit to you, so your participation in the study will be discontinued.

**(For Females) If You Become Pregnant**

The study gel is not a birth control method. You must agree to use an effective method of birth control such as birth control pills or another hormonal-based method (except for vaginal rings), or an intrauterine device (IUD), unless you or your partner have been sterilized (i.e., no longer able to become pregnant), and/or you only have sex that cannot lead to pregnancy (no penile-vaginal intercourse).

We do not know what effect PC-1005 has on pregnancy, including the effect of PC-1005 on the fetuses of women who use the rectal gel when pregnant, or the babies of women who use the gel when breastfeeding. Because of this, pregnant women and women who are breastfeeding may not join this study. Women who join this study will have pregnancy tests while in the study.

If you become pregnant during the study, study staff will refer you to available medical care and other services you or your baby may need. The study does not pay for this care. You will stop using the gel and you will exit the study. We will contact you to find out about your pregnancy and the outcome of your pregnancy. The outcome of your pregnancy is important to study staff; therefore your pregnancy will be followed until the results of your pregnancy are known. If you become pregnant and you deliver a baby from that pregnancy, we will contact you approximately one year after your delivery to collect

information about the health of your baby. We will also contact you about a study that collects information about pregnancy and babies up to one year old.

In the event that you are removed from or choose to leave this study, you will be asked to complete some of the procedures described for the 24-Hour Post-Dosing Visit, if you are willing to do so.

The study clinician will ask you to stop using the study rectal gel but continue to come in for follow-up visits and procedures if you have a bad reaction to the study gel.

***Will there be any payments if I take part in this research study?***
**[SITES TO INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT:]** You will receive [***SITES TO INSERT AMOUNT*** **$xx**] for your time, effort, and travel to and from the clinic at each scheduled visit. You may receive [***SITES TO INSERT AMOUNT*** **$xx**] for any visits which occur in between your normally scheduled visits.

***What are the costs?***
***[SITES TO COMPLETE ACCORDING TO SITE CAPACITY]*** There is no cost to you for study related visits, physical/rectal examinations, laboratory tests or other procedures. Treatments available to you from the study site for infections passed through sex will be given to you free of charge or you will be referred for available treatment for the duration of the study.

***Are there any other studies if you cannot join this one?***
There may be other studies going on at this study clinic or in the community for which you may be eligible. If you wish, we will tell you about other studies that we know about. There may also be other places where you can go for HIV counseling and testing. We will tell you about those places if you wish. If you choose not to take part in this study, it will have no effect on the regular medical care that is available to you at this clinic or elsewhere.

***Who will know about my participation in this research study?***
Any information about you obtained from this research will be kept as private as possible. All records related to your involvement in this research study will be kept in a [***SITES TO INSERT***]. Your identity on these records will be indicated by a number rather than by your name, and the information linking these numbers with your name will be kept separate from the research records.

Efforts will be made to keep your information confidential. However, it is not possible to guarantee confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally. The study staff may use your personal information to verify that you are not in any other research studies. This includes studies conducted by other researchers that study staff know about.

Your records may be reviewed by:

- Study staff
- Site Institutional Review Boards
- PPD (a contract research organization that monitors clinical trials for safety and data quality)
- Representatives of the Population Council, the nonprofit organization that supplies the rectal gel
- Representatives of the US Federal Government, including the US Food and Drug Administration (FDA), US Office for Human Research Protections (OHRP), NIH, and/or contractors of NIH
- Other local, US, or international regulatory authorities

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

***[Sites to include/amend the following:]***
The researchers will do everything they can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have obtained a Certificate of Confidentiality from the US Federal Government. This Certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you give for study purposes. However, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. This Certificate does not prevent you from releasing information about yourself and your participation in the study.

***What if I am injured as a result of participating in this study?***
***[SITES TO SPECIFY INSTITUTIONAL POLICY:]*** It is unlikely that you will be injured as a result of study participation. If you are injured, the ***[institution]*** will give you immediate necessary treatment for your injuries. You ***[will/will not]*** have to pay for this treatment. You will be told where you can receive additional treatment for your injuries. The U.S. National Institutes of Health (NIH) does not have a mechanism to pay money or give other forms of compensation for research related injuries. You do not give up any legal rights by signing this consent form.

***May I withdraw my consent for participation in this research study?***
***[SITE TO SPECIFY INSTITUTIONAL POLICY:]*** Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. If you choose not to participate or to leave the study, you will not lose the benefit of services to which you would otherwise be entitled at this clinic, nor will the confidentiality of the care provided for you here be affected. You should feel free coming back to this facility even if you decide not to participate in this study. If you want the results of the study after the study is over, let the study staff members know.

***What do I do if I have questions?***
If you ever have any questions about the study, or if you have a research-related injury, you should contact ***[insert name of the investigator or other study staff]*** at ***[insert telephone number and/or physical address]***.

If you have questions about your rights as a research participant, you should contact **[insert name or title of person on the IRB or other organization appropriate for the site]** at **[insert physical address and telephone number]**.

**CONSENT FOR LONG-TERM STORAGE AND FUTURE TESTING OF SPECIMENS**

There might be a small amount of blood, rectal tissue, rectal fluid, or vaginal fluid left over after we have done all of the study-related testing. We would like to ask your permission to store these leftover samples and related health information for use in future studies, such as future research to fight HIV and other related diseases. This health information may include personal facts about you such as your race, ethnicity, sex, medical conditions and your age range.

If you agree, your samples and related health data will be stored safely and securely at facilities that are designed so that only approved researchers will have access to the samples. Some employees of the facilities will need to have access to your samples to store them and keep track of where they are, but these people will not have information that directly identifies you.

The type of testing planned for your leftover specimens is not yet known. However, samples may be used by the MTN Laboratory Center to complete additional quality assurance testing, ensuring that the tests work correctly and supply accurate data. No genetic testing on either a limited set or the full set of genes is planned for leftover samples that are stored for the purposes of future research. It is important that you know that any future testing or studies planned for these specimens must be approved by an Institutional Review Board before they can be done.

**You can still enroll in this study if you decide not to have leftover samples stored for future studies. If you do not want the leftover samples stored, we will destroy them. You can withdraw your consent for the storage and future testing of specimens at any time by providing your request in writing to the person in charge of this study. However, researchers will not be able to destroy samples or information from research that is already underway.**

| | |
|---|---|
| _____ Initials and Date | I DO agree to allow my biological specimens and health data to be stored and used in future research studies. |
| _____ Initials and Date | I DO NOT agree to allow my biological specimens and health data to be stored and used in future research studies. |

**SIGNATURES- VOLUNTARY CONSENT**

***[INSERT SIGNATURE BLOCKS AS REQUIRED BY THE LOCAL IRB/EC]:*** If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to the study, please sign your name or make your mark below.

| _____ | _____ | _____ |
|---|---|---|
| Participant Name (print) | Participant Signature/Mark | Date |
| _____ | _____ | _____ |
| Study Staff Conducting Consent Discussion (print) | Study Staff Signature | Date |
| _____ | _____ | _____ |
| Witness Name (print) | Witness Signature | Date |

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