MTN-026

A Randomized, Double Blind, Placebo-Controlled, Phase 1 Safety and Pharmacokinetic Study of Dapivirine Gel (0.05%) Administered Rectally to HIV-1 Seronegative Adults

Microbicide Trials Network

Funding Agencies:
Division of AIDS, 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

Grant Numbers:
UM1AI068633, UM1AI068615, UM1AI106707

DAIDS Protocol ID:
12021

IND Sponsor:
DAIDS

IND#: [XXXXX]

Protocol Chair:
Ross D. Cranston, MD, FRCP

Version 2.0

July 21, 2017

MTN-026

A Randomized, Double Blind, Placebo-Controlled, Phase 1 Safety and Pharmacokinetic Study of Dapivirine Gel (0.05%) Administered Rectally to HIV-1 Seronegative Adults

TABLE OF CONTENTS

TABLE OF FIGURES

TABLE OF TABLES

MTN-026

A Randomized, Double Blind, Placebo-Controlled, Phase 1 Safety and Pharmacokinetic Study of Dapivirine Gel (0.05%) 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
AST	aspartate aminotransferase
AUC	area under the curve
BAT	Dosing Before and After Sex </= Two doses in 24h
BRWG	Behavioral Research Working Group
BV	bacterial vaginosis
CASI	computer assisted self-interview
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence Interval
C_{max}	maximum concentration
CNS	central nervous system
CRF	case report form
CRS	Clinical Research Site
CT	*Chlamydia trachomatis,* Chlamydia
CTA	Clinical Trial Agreement
CVL	cervicovaginal lavage
CWG	Community Working Group
CYP3A	cytochrome P450, family 3, subfamily A genetic locus
DAERS	DAIDS Adverse Event Reporting System
DAIDS	Division of AIDS
DAPY	di-amino-pyrimidine
DLV	delavirdine
DNA	deoxyribonucleic acid
DOD	directly observed dosing
DPV	dapivirine
EAE	expedited adverse event
EC	ethics committees
EC_{50}	50% effective concentration
EFV	efavirenz
ENR	enrollment
FDA	(US) Food and Drug Administration
FHCRC	Fred Hutchinson Cancer Research Center
g	grams
GC	*Neisseria gonorrhoeae,* gonorrhea

GCP	Good Clinical Practices
GEE	generalized estimating equations
GMP	Good Manufacturing Practices
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
ICF	informed consent form
ICH	International Conference on Harmonisation
IDI	In-Depth Interview
IL	interleukin
IND	Investigational New Drug
INR	International normalized ratio
IoR	Investigator of Record
IPM	International Partnership for Microbicides
IRB	Institutional Review Board
IUD	intrauterine device
kg	kilogram
LC	Laboratory Center
LDMS	Laboratory Data Management System
LOC	Leadership and Operations Center
µg	microgram
MDP	Microbicides Development Programme
mg	milligram
mL	milliliter
mM	millimolar
MO	Medical Officer
mOsm	milliosmole
MPA	medroxyprogesterone acetate
MT-2	human melatonin receptor 2
MTN	Microbicide Trials Network
MTT	(3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a tetrazole)
n	number
N-9	nonoxynol-9
NAAT	nucleic acid amplification test

NF	National Formulary
ng	nanogram
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
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
PBL	peripheral blood lymphocytes
PBS	phosphate-buffered saline
PCR	polymerase chain reaction
PD	pharmacodynamics
PEP	post-exposure prophylaxis
pH	potential of hydrogen
PK	pharmacokinetics
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
PT	prothrombin time
PTID	participant identification
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 immunodeficient
SCR	screening
SDMC	Statistical Data Management Center
SHIV	simian human immunodeficiency virus
SMC	Study Monitoring Committee
SOP	standard operating procedure
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
TFV-DP	tenofovir-diphosphate
T_{max}	time at which C_{max} is observed
TPGS	tocopheryl polyethylene glycol succinate
UA	urinalysis
ULN	upper limit of normal
UPMC	University of Pittsburgh Medical Center
USA	United States of America
USP	United States Pharmacopoeia
UTI	urinary tract infection
WHO	World Health Organization
w/w	weight/weight
wt	wild type

MTN-026

A Randomized, Double Blind, Placebo-Controlled, Phase 1 Safety and Pharmacokinetic Study of Dapivirine Gel (0.05%) Administered Rectally to HIV-1 Seronegative Adults

PROTOCOL TEAM ROSTER

Protocol Chair

Ross D. Cranston, MD, FRCP
Protocol Chair
Fundació Lluita Contra la Sida
Hospital Universitari Germans Trias I Pujol
Caratera de Canyet
Badalona
Barcelona, Spain 08916
Phone: 34-934-657-897
Fax: 34-934-657-602
E mail: rdcranston@outlook.com

Site Investigators

Ken Ho, MD
Site Investigator
UPMC, Keystone Building, Suite 533
3520 Fifth Avenue
Pittsburgh, PA 15213 USA
Phone: 412-383-7178
Fax: 412-383-2900
Email: hok2@upmc.edu

Eileen F. Dunne, MD, MPH
Site Investigator
Thailand MOPH-U.S. CDC Collaboration
DDC 7 Building, 4th floor
Ministry of Public Health, Soi 4
Nonthaburi 11000 Thailand
Phone: 66 02-580-0669 ext 454
Fax: 66 02-580-0712
Email: dde9@cdc.gov

Craig Hoesley, MD
Site Investigator
University of Alabama at Birmingham
1530 3rd Avenue South, VH 201
Birmingham, AL 35294 USA
Phone: 205-934-3365
Fax: 205-975-3232
Email: choesley@uab.edu

US National Institutes of Health (NIH)

Roberta Black, PhD
Chief, Clinical Microbicide Research Branch
Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID),
National Institutes of Health (NIH) - U.S. Department of Health and Human Services (HHS)
5601 Fishers Lane, Room 8B62, MSC 9831
Rockville, MD 20852 USA
Phone: 301-496-8199
Email: rblack@niaid.nih.gov

Naana Cleland, MHCA
Health Specialist, Clinical Microbicide Research Branch (CMRB)
Prevention Sciences Program (PSP) DAIDS, NIAID
NIH- U.S. Department of Health and Human Services (HHS)
5601 Fishers Lane, Room 8B27, MSC 9831
Rockville, MD 20852 USA
Phone: 240-292-4779
Email: clelandn@niaid.nih.gov

Jeanna Piper, MD
DAIDS Senior Medical Officer
DAIDS/NIAID
5601 Fishers Lane, Room 8B68, MSC 9831
Rockville, MD 20852 USA
Phone: 240-292-4798
Email: piperj@niaid.nih.gov

Dianne M. Rausch, PhD
Director
DAIDS Research, NIMH
5601 Fishers Lane, Room 8D20, MSC 9831
Rockville, MD 20852 USA
Phone: 240-627-3874
Fax: 240-627-3467
Email: drausch@mail.nih.gov

Microbicide Trials Network (MTN) Leadership and Operations Center (LOC) - Pitt

Jose A. Bauermeister, MPH, PhD
BRWG Representative
University of Pennsylvania
418 Curie Blvd., Suite 402
Philadelphia, PA 19104
Phone: 215-898-9993
Email: bjose@upenn.edu

Katherine Bunge, MD
Protocol Safety Physician
Magee-Womens Hospital of UPMC
300 Halket Street
Pittsburgh, PA 15213 USA
Phone: 412-641-3464
Fax: 412-641-1133
Email: kbunge@mail.magee.edu

Sharon Hillier, PhD
MTN Principal Investigator
Microbicide Trials Network
204 Craft Avenue
Pittsburgh, PA 15213 USA
Phone: 412-641-8933
Fax: 412-641-6170
Email: shillier@mail.magee.edu

Cindy Jacobson, PharmD
Director of Pharmacy Affairs
Microbicide Trials Network
204 Craft Avenue
Pittsburgh, PA 15213 USA
Phone: 412-641-8913
Fax: 412-641-6170
Email: cjacobson@mail.magee.edu

Ian McGowan, MD, PhD, DPhil, FRCP
Director, Rectal Microbicide Program
Microbicide Trials Network
204 Craft Avenue
Pittsburgh, PA 15213 USA
Phone: 412-641-8999
Fax: 412-641-6170
Email: imcgowan@pitt.edu

Sharon A. Riddler, MD, MPH
Protocol Physician
UPMC, Keystone Building, Suite 510
3520 Fifth Avenue
Pittsburgh, PA 15213 USA
Phone: 412-383-1741 or 412-383-1675
Fax: 412-383-2900
Email: riddler@dom.pitt.edu

Devika Singh, MD, MPH
Protocol Safety Physician
Box 359927, Dept. of Global Health, ICRC
325 Ninth Ave.
Seattle WA 98104 USA
Phone: 206-744-8311
Fax: 206-520-3831
Email: dsingh@u.washington.edu

Jennifer Thomas, MSc
Protocol Development Manager
Microbicide Trials Network
204 Craft Avenue
Pittsburgh, PA 15213 USA
Phone: 412-641-5579
Fax: 412-641-6170
Email: thomasj15@mwri.magee.edu

MTN Laboratory Center (LC)

Charlene S. Dezzutti, PhD
LC Director/BSWG Representative
Microbicide Trials Network
204 Craft Avenue
Pittsburgh, PA 15213 USA
Phone: 412-641-3462
Fax: 412-641-6170
Email: dezzuttics@upmc.edu

Craig Hendrix, MD
Pharmacology LC Principal Investigator
Johns Hopkins University
600 North Wolfe Street, Harvey 502
Baltimore, MD 21287 USA
Phone: 410-955-9707
Fax: 410-955-9708
Email: cwhendrix@jhmi.edu

Ratiya Pamela Kunjara Na Ayudhya, BSMT, ASCP
Laboratory Manager
Microbicide Trials Network
204 Craft Avenue
Pittsburgh, PA 15213 USA
Phone: 412-641-6393
Fax: 412-641-6170
Email: pkunjara@mwri.magee.edu

Mark Marzinke, PhD, DABCC
Johns Hopkins University School of Medicine
1800 Orleans Street, Sheikh Zayed Tower,
Room B1-1020G
Baltimore, MD 21287
Office: 443-287-7516
CPAL Office: 410-550-9702
Fax: 410-955-0767
Email: mmarzin1@jhmi.edu

MTN LOC – FHI 360

Sherri Johnson, MPH
Sr. Clinical Research Manager
FHI 360
1825 Connecticut Avenue, NW
Washington, DC 20009 USA
Phone: 202-884-8000 Ext. 18677
Fax: 202-884-8844
Email: sjohnson@fhi360.org

Jonathan Lucas, MPH
Sr. Community Program Manager
FHI 360
359 Blackwell Street, Suite 200
Durham, NC 27703 USA
Phone: 919-544-7040, Ext. 11458
Fax: 919-544-0207
Email: jlucas@fhi360.org

MTN Statistical Data Management Center (SDMC)

Elizabeth Brown, ScD
SDMC Principal Investigator
Fred Hutchinson Cancer Research Center (FHCRC)- Statistical Center for HIV/AIDS Research & Prevention (SCHARP)
1100 Fairview Avenue North, M2-C200
PO Box 19024
Seattle, WA 98109-1024 USA
Phone: 206-667-1731
Fax: 206-667-4812
Email: erbrown@fhcrc.org

Holly Gundacker, MS
Statistical Research Associate
FHCRC-SCHARP
1100 Fairview Ave North, M2-C200
PO Box 19024
Seattle, WA 98109-1024 USA
Phone: 206-667-6480
Email: hgundack@scharp.org

Melissa A. Peda, MPA
SDMC Clinical Data Manager
1100 Fairview Avenue North, E3-129
PO Box 19024
Seattle, WA 98109-1024 USA
Phone: 206-667-7672
Work Mobile: 206-295-5843
Email: mapeda@scharp.org

MTN Community Working Group (CWG) Representative

Sherri Karas, MEd
CWG Representative
University of Pittsburgh
Presbyterian University Hospital
3520 Fifth Avenue
Pittsburgh, PA 15213 USA
Phone: 412-383-1313
Fax: 412-383-2900
Email: sjk91@pitt.edu

MTN-026

A Randomized, Double Blind, Placebo-Controlled, Phase 1 Safety and Pharmacokinetic Study of Dapivirine Gel (0.05%) Administered Rectally to HIV-1 Seronegative Adults

INVESTIGATOR SIGNATURE FORM

Version 2.0; July 21, 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

IND Sponsor:

DAIDS (DAIDS Protocol ID: 12021)

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

MTN-026

A Randomized, Double Blind, Placebo-Controlled Phase 1 Safety and Pharmacokinetic Study of Dapivirine Gel (0.05%) Administered Rectally to HIV-1 Seronegative Adults

PROTOCOL SUMMARY

Short Title: Dapivirine Gel Rectal Safety and PK Study

Clinical Phase: Phase 1

IND Sponsor: DAIDS

Protocol Chair: Ross D. Cranston, MD, FRCP

Sample Size: MTN-026 will enroll approximately 27 participants.

Study Population: HIV-uninfected men and women between the ages of 18 and 45 years (inclusive)

Study site(s): Sites selected by MTN leadership

Study Design: Phase 1, multi-site, randomized (2:1), double-blind, placebo-controlled trial

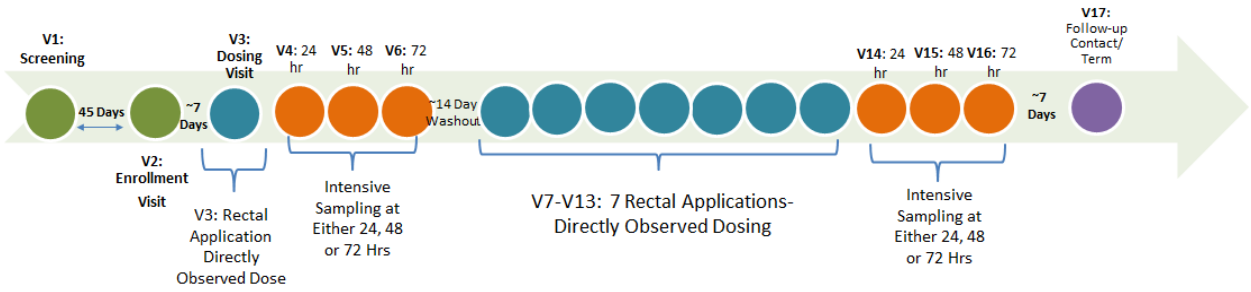
Study Duration: Approximately 40 days of follow-up per participant is planned with a projected accrual period of 6-8 months

Study Products: Dapivirine gel (0.05%)
Universal HEC placebo gel

Study Regimen: Participants will be randomized to receive a single dose of either dapivirine gel or universal HEC placebo gel rectally, followed by 7 daily doses of the same product to be administered under direct observation in the clinic.

Study specific visits and an overview of procedures are illustrated in Figure 1.

Figure 1: Study Visit Schedule



Primary Objectives:

Safety

- To evaluate the safety of dapivirine gel formulation when applied rectally.

Pharmacokinetics

- To characterize the systemic and compartmental pharmacokinetics of dapivirine gel following rectal 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

- Dapivirine concentrations
  - Blood
  - Rectal fluid
  - Rectal mucosal tissue homogenates

Secondary Objectives:

Acceptability

- To identify product attributes considered likely to challenge and facilitate future sustained use of rectally applied dapivirine gel.

Mucosal Safety

- To evaluate the mucosal safety of dapivirine gel when applied rectally.

Secondary Endpoints:

Acceptability

- Product attributes considered likely to challenge future sustained use.

Mucosal Safety

- Rectal proteomics
- Rectal transcriptome
- Rectal microflora
- Rectal histology
- Rectal tissue flow cytometry

Exploratory Objectives:

***Ex Vivo* Efficacy**

- To assess the preliminary (*ex vivo)* efficacy of dapivirine gel formulation after product is applied rectally.

Pharmacokinetics

- To characterize the vaginal pharmacokinetics of dapivirine gel following rectal application in women.

Exploratory Endpoints:

***Ex Vivo* Efficacy**

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

Pharmacokinetics

- Dapivirine concentrations
  - Cervicovaginal fluid♀
  - Cervical tissue♀

♀Female participants only

1 KEY ROLES

1.1 Protocol Identification

Protocol Title:	A Randomized, Double Blind, Placebo-Controlled, Phase 1 Safety and Pharmacokinetic Study of Dapivirine Gel (0.05%) Administered Rectally to HIV-1 Seronegative Adults
Protocol Number:	MTN-026
Short Title:	Dapivirine Gel Rectal Safety and PK Study
Date:	July 21, 2017

1.2 Funding Agencies, Sponsor and Monitor Identification

Funding Agencies:	US Division of AIDS (DAIDS)/National Institute of Allergy and Infectious Diseases (NIAID) National Institutes of Health (NIH) 5601 Fishers Lane Rockville, MD 20852 USA US National Institute of Mental Health (NIMH) 6001 Executive Boulevard Rockville, MD 20852 USA US *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal and Pediatric Infectious Diseases (MPID) Branch 6100 Executive Boulevard Bethesda, MD 20892 USA
IND Sponsor:	US Division of AIDS (DAIDS)/National Institute of Allergy and Infectious Diseases (NIAID) National Institutes of Health (NIH) 5601 Fishers Lane Rockville, MD 20852 USA
Monitor:	Pharmaceutical Product Development (PPD), Inc. 929 North Front St. Wilmington, NC 28401-3331 USA

1.3 Medical Officer

Medical Officer: Jeanna Piper, MD
DAIDS/NIAID
5601 Fishers Lane, Room 8B68, MSC 9831
Rockville, MD 20852 USA

1.4 Clinical Laboratories

Network: MTN Laboratory Center (LC)
204 Craft Ave.
Pittsburgh, PA 15213 USA

Pharmacology: MTN Pharmacology LC
600 N. Wolfe Street, Osler 527
Johns Hopkins University
Baltimore, MD 21287 USA

1.5 Data Center

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

1.6 Study Implementation

FHI 360
359 Blackwell Street, Suite 200
Durham, NC 27701 USA

2 INTRODUCTION

2.1 Dapivirine Gel

Dapivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), is a substituted di-amino-pyrimidine (DAPY) derivative with potent antiviral activity against HIV-1. Dapivirine was initially developed as an oral antiretroviral drug for treatment of HIV/AIDS, and many animal studies and several clinical trials were performed using the oral route of administration. Following the subsequent switch to the microbicide indication, additional preclinical animal studies and clinical trials were performed to evaluate vaginal administration of dapivirine gel and vaginal ring formulations.[1] More recently, a study in rabbits was conducted to evaluate the rectal administration of dapivirine gel.

The preclinical safety studies and clinical trials performed to date support the favorable safety profile and tolerability of microbicide dapivirine dosage forms. The highest daily dose of dapivirine delivered from a vaginal gel to date (approximately 1250 µg/day) is 280 times lower than the maximum tolerated single dose for oral dapivirine (350 mg) and 480 times lower than the maximum tolerated multiple dose for oral dapivirine (300 mg twice a day for 14 days). The same dose of dapivirine gel is proposed for rectal administration. MTN-026 is the first study to assess the safety of dapivirine gel applied rectally.

Multiple gel formulations of dapivirine have been developed for vaginal use. Dapivirine Gel 4759 (Gel 4759) is the gel formulation planned for this trial. The Gel 4759 is highly viscous and opaque. Dapivirine 0.05% gel has an osmolality of approximately 870 mOsm/kg, similar to the safe and acceptable reduced glycerin 1% tenofovir formulation that was used in MTN-007, which had an osmolality of approximately 850 mOsmol/kg[2] (see Section 2.4.2 for additional information regarding the MTN-007 study). Please refer to Section 2.4.1 for further evidence of safety and acceptability of dapivirine gel.

2.1.1 Description and Mechanism of Action

NNRTIs bind to the HIV reverse transcriptase (RT) enzyme preventing viral replication and consequently production of infectious virus. The primary ingredient of dapivirine gel is water, with hydroxyethylcellulose (HEC) and polycarbophil used as thickening agents. Other ingredients of the gel include methyl- and propylparaben, as preservatives, propylene glycol as solvent, and sodium hydroxide for pH adjustment. The excipients contained in the drug product formula are United States Pharmacopoeia (USP) grade components (e.g., propylene glycol) with a history of use in currently approved vaginal products.

Table 1: Dapivirine Gel 4759, 0.05%, 2.5 g Formulation

Name	Quality Standard	Function	% Composition/Dose (dose = 2.5 g gel [2.5 mL])
Dapivirine	Manufacturer's Certificate of Analysis	Active pharmaceutical ingredient (API)	0.05
Purified water	USP	Solvent	90.99
HEC	National Formulary (NF)	Thickening/binding agent	3.50
Polycarbophil	USP	Thickening agent	0.20
Propylene Glycol	NF	Solvent	5.00
Methylparaben	NF	Preservative	0.20
Propylparaben	NF	Preservative	0.05
Sodium Hydroxide	NF	pH adjustment	0.01

2.1.2 Strength of Study Product

The dapivirine gel strength proposed for use in MTN-026 is 0.05%.

2.2 Universal Placebo gel

2.2.1 Description

The "Universal Placebo" is a HEC-based gel that was developed for use in clinical evaluations of investigational microbicides. This formulation is sufficiently stable as a vaginal gel formulation, is safe and is sufficiently inactive for use in the clinical study of investigational microbicides. The gel is isotonic and clear in color.

Table 2: Universal HEC Placebo Gel Formulation

Ingredient	Quality Standard	Function	Amount (w/w)
Purified Water	USP	Solvent	96.3
HEC	NF	Tonicity agent	2.7
Sodium Chloride	USP	Preservative	0.85
Sorbic Acid	NF	Thickening/binding agent	0.1
Sodium Hydroxide	NF	pH adjustment	As needed for pH adjusted to 4.4 (+0.2)

2.2.2 Strength of Study Product

There is no active ingredient in the Universal Placebo gel.

2.3 Non-Clinical Studies

2.3.1 Virology and Pharmacology

Dapivirine

Anti-HIV-1 Activity

The activity of dapivirine against wild-type (wt) HIV-1, African isolates of HIV-1 (including subtype C virus), and a panel of NNRTI-resistant viruses has been established using *in vitro* models, with 50% effective concentration (EC_{50}) values ranging from 0.3 ng/mL (0.9 nM) against laboratory isolates to <33 ng/mL (<100 nM) for HIV-1 isolates encoding one or more known NNRTI resistance mutations. The anti-HIV activity was also confirmed in an *ex vivo* model of human cervical explant cultures and a humanized severe combined immunodeficient (hu-SCID) mouse model.[3,4]

Resistance

A panel of recombinant viruses was constructed from clinical isolates derived from different geographical origins, representing strains from HIV-1 group M subtypes A, B, C, D, F and H as well as circulating recombinant forms: CRF01_AE, CRF02_AG, CRF05_DF and HIV-1 group O. All group M viruses tested were sensitive to dapivirine with EC_{50} values below 1.0 ng/mL and fold change in EC_{50} values below 4. Eight of the group M viruses carried mutations in the RT coding region at positions associated with NNRTI resistance (positions 98, 101, 106, and 179). The group O virus tested (V029524) naturally harbored amino acids at positions 98 (G), 179 (E) and 181 (C), which are associated with NNRTI resistance in HIV-1 strains from group M. This virus displayed significantly reduced sensitivity to nevirapine (NVP) (89-fold change), delavirdine (140-fold change), efavirenz (EFV) (42-fold change), and dapivirine (150-fold change, which is typical of Type O strains treated with NNRTI).[1]

Cross-resistance

In comparison with NVP, delavirdine (DLV), emivirine, and EFV, dapivirine showed significantly better *in vitro* activity against laboratory and recombinant HIV strains resistant to one or more drugs of the same class. The EC_{50} was below 32.9 ng/mL (100 nM) for 80% of the strains, compared with only 56% of the strains for efavirenz.

When tested against 433 clinical isolates with phenotypic resistance to at least one of the NNRTIs NVP, delavirdine, EFV or dapivirine, dapivirine was able to inhibit 46% (202/433) of the samples including 41% (142/350) of the strains resistant to EFV. In contrast, only 10% (24/231) of the dapivirine-resistant strains were inhibited by EFV.[1]

Spermatozoa Motility

Assays using human semen samples from normal, healthy, male donors showed that dapivirine did not affect the motility of spermatozoa at a concentration of up to 2 mM (659 µg/mL), which exceeded the limit of solubility.

Safety Pharmacology

In a series of preclinical safety pharmacology studies, dapivirine was generally devoid of adverse effects on overt behavior, reflexes and other body functions. Although these studies revealed no cardiovascular effects, there was evidence of an increase in QT interval during the 1- and 6-month oral toxicity studies in dogs. However, this was only seen at 30 mg/kg/day at which C_{max} and area under the curve (AUC) values were more than 1600 and 850 times greater, respectively, than the values achieved in women following daily use of dapivirine gels 4750 and 4789.

Universal Placebo Gel

Anti-HIV-1 Activity

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

Cytotoxicity

Dilutions of the Universal Placebo gel in culture medium exhibited negligible toxicity to human vaginal epithelial cells (standard [1-(4,5-dimethylthiazol-2-yl)-3,5 diphenylformazan (MTT)] assay), even at the lowest dilution tested (1:2).[5] Exposure of human vaginal epithelial cells to the Universal Placebo gel resulted in minimal IL-1α induction, even at the lowest dilutions tested (1:2).[6]

Transmission of SHIV

The effect of the Universal Placebo gel on vaginal transmission of simian human immunodeficiency virus $(SHIV)_{162p3}$ ($10^3 TCID_{50}$) to rhesus monkeys (n=5, n=3, respectively) was determined in two separate studies.[3] Macaques pretreated with MPA were vaginally administered 1 mL of the Universal Placebo gel formulation 15 minutes prior to challenge with 0.5 mL $SHIV_{162p3}$. Investigators monitored total ribonucleic acid (RNA) load in the animal plasma for a total of 8 weeks by means of a standard quantitative reverse transcriptase polymerase chain reaction (RT-PCR). The first study utilized the Universal Placebo gel formulation at pH 6.5; the second study utilized a formulation of pH 4.4. In both studies, all monkeys were infected, as determined by the presence of viral RNA in circulation blood, regardless of the pH of the formulation.[6]

Anti-Herpes Simplex Virus (HSV) Activity

CF-1 mice (n=10 per group) pretreated with medroxyprogesterone acetate (MPA) were administered 0.02 mL of Universal Placebo gel or phosphate-buffered saline (PBS) vaginally, followed by a 0.01 mL of HSV-2 viral inoculum of 10 ID_{50} 0.3 minutes later.[7] On Day 3, vaginal lavage was cultured on human foreskin fibroblasts, and mice were

considered infected if a cytopathic effect was observed after 3 days of incubation. Infection rate following pretreatment with Universal Placebo gel (90%) was not significantly different from pretreatment with PBS (80%) or from mice given no treatment (80%). Universal Placebo gel did not enhance susceptibility of mice to HSV-2 when administered 12 hours before vaginal challenge.[7]

Spermatozoa Motility

Analyses of pH (Universal Placebo gel mixed with human seminal plasma, pH 8.03± 0.26) found the HEC formulation did not show significant buffering capacity and could not acidify the alkaline pH of seminal plasma, a favorable result in a placebo formulation.[6] *In vitro* assessments of spermicidal activity utilizing human semen from healthy donors showed the Universal Placebo gel had no significant deleterious effects on sperm motility, even after 60-minute incubation.

2.3.2 Pharmacokinetics

Dapivirine

Systemic exposure to dapivirine was low following vaginal administration of dapivirine gels to rabbits.[1] Much higher systemic exposures were obtained in single-dose oral and subcutaneous toxicity studies in mice and rats, and in repeat dose oral toxicity studies in rats, dogs and monkeys. The free fraction of dapivirine in plasma was 0.19-0.34% in the male rat, 0.18-0.39% in the female rat, 0.21-0.22% in the dog and 0.15% in humans. In rats, tissue to plasma AUC_{0-24} ratios following a single oral dose were 11 in liver, 7-8 in lung, kidney and adrenals, about 4 in spleen and lymph nodes, and 2-3 in brain, heart and muscle. Plasma/tissue equilibrium was rapid, and there was no undue retention of dapivirine in tissues. Following a single oral or vaginal dose of ^{14}C-dapivirine, absorption and distribution of drug-related material to the tissues was moderate in non-pregnant and slow in pregnant female rats. Vaginal dosing did not result in greater distribution to the reproductive tissues (except the vaginal wall) than oral dosing. For virtually all tissues, maximal concentrations after vaginal dosing were <1% of those after oral dosing. Drug-related material was shown to freely cross the placenta to the fetus. In dogs, dapivirine concentrations following oral administration for 14 days were about 9 times higher in liver and muscle, and about 5 times higher in lymph nodes and brain than in plasma. Preliminary metabolism studies demonstrated the presence of free and conjugated metabolites in rats, dogs, monkeys and humans, but the molecular structures have not been elucidated. There was evidence of extensive cytochrome P450 (particularly CYP3A4) mediated metabolism.[1]

2.3.3 Toxicology

Dapivirine

General toxicity

The gel formulation to be used in this trial was evaluated in a study in rabbits in which dapivirine concentrations of 0.05%, 0.2%, and 0.5% (w/w) were administered rectally

once daily for 14 days using a dose volume of 1 mL. Three animals died or were killed prematurely during the study but none of the deaths were attributed to treatment. The no observable effect level (NOEL) was considered to be 0.5% (w/w). In addition, this formulation was evaluated in two intravaginal studies in female rats. In a 13-week study in which gels containing 0.2% and 0.5% (w/w) dapivirine were administered intravaginally using a daily dose volume of 0.2 mL, no evidence of local or systemic toxicity was observed. The carcinogenic potential of dapivirine was also evaluated when administered intravaginally at concentrations of 0.05, 0.2 and 0.5% (w/w) using a dose volume of 0.2 mL for 104 weeks. There were no neoplastic or non-neoplastic findings that were attributable to treatment with dapivirine. It was concluded that the NOEL was 0.5%. Furthermore, in other intravaginal studies in rabbits using various formulations of dapivirine gel, there were no significant local or systemic findings following repeat administration at up to 20 mg/mL for 14 days, up to 5 mg/mL for 13 weeks or up to 2 mg/mL for 39 weeks. In studies conducted via the oral route of administration, a no observed adverse effect level (NOAEL) was not established in the rat. However, the main findings (effects on liver, thyroid, and pituitary) were considered adaptive rather than adverse responses, and therefore the NOAEL was considered to be 20 mg/kg/day. This dosage was also the NOAEL in the dog. At higher dose levels, hepatotoxicity was observed in dogs and slight hematological and clinical chemistry changes were observed in rats. In the guinea pig, dapivirine (2 mg/mL) did not demonstrate any potential to cause contact sensitization when evaluated using a maximization test.[1]

Mutagenicity

Dapivirine was considered to be non-genotoxic based on the results from a range of *in vitro* and *in vivo* mutagenicity assays, including the Ames Test, L5178Y Mouse Lymphoma Test, Human Peripheral Lymphocyte Test, Mouse Micronucleus Test, and Unscheduled DNA Synthesis Test.

Reproductive Toxicity

In rats, some effects on the developing fetus were observed following oral administration at maternally toxic doses (80 and 320 mg/kg) of dapivirine. However, there were no effects in rats at the maternally non-toxic dose of 20 mg/kg/day, or in rabbits at up to 90 mg/kg. No toxicity to maternal animals or the developing embryo/fetus was seen in embryo-fetal development studies performed via the vaginal route in rats (up to 3.3 mg/mL using a dose volume of 0.2 mL/kg) and rabbits (up to 2 mg/mL using a dose volume of 1.0 mL).

2.3.4 Animal Studies of Universal Placebo Gel

Intravenous Administration

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

Local Tolerance

A 10-day rabbit vaginal irritation study (10 per arm, 2 arms, placebo gel vs. 0.9% saline control) found the HEC-based placebo gel was not irritating to the vaginal mucosa of rabbits when dosed daily for 10 days.[5, 7] One animal in the HEC-based placebo gel group had an instance of vaginal redness (compared to four animals in the saline group), which did not persist and was not evident at the end of the study. Diarrhea, few feces, and soiling of the anogenital area were noted in that animal. Body weight changes were noted to be normal. In 9 of 10 animals, necropsy results were normal. Histopathologic changes observed were similar to those seen in the control group and likely attributable to those that occur because of the repeated insertion of a catheter, rather than due to any effect of the test samples.

Universal Placebo gel was also used as the placebo comparator in a rectal safety study of a combination microbicide in a macaque model.[8] A third study arm received no product and served as a negative control. Rectal safety of the active product and Universal Placebo gel was evaluated following four daily applications of study products. Rectal flora, pH, and rectal lavage samples were assessed pre- and post-dosing and showed no evidence of toxicity in the macaques that received Universal Placebo gel. The infrequent evidence of epithelial sloughing and rare incidence of associated blood cells in rectal lavage samples was similar in the Universal Placebo and negative control arm of this study.

Reproductive Toxicity

Intraperitoneal administration of unformulated HEC to pregnant mice in a 1% and 4% concentration caused an increase in resorption, but no detectable increase in birth defects.[9] While no epidemiological studies of congenital anomalies in infants born to women exposed to HEC during pregnancy have been reported, the Teratogen Information System considers the magnitude of teratogenic risk to a child born after exposure during gestation to be none.

2.4 Clinical Studies

2.4.1 Clinical Studies of Dapivirine Gel

To date, 28 Phase 1 and Phase 1/2 clinical trials of dapivirine have been conducted: nine trials in which 501 participants used dapivirine gel, eight trials in which 298 participants used dapivirine rings, and 11 trials in which 211 participants used oral dapivirine.[1] In addition, one Phase 1 clinical trial has been conducted in 48 male participants to evaluate the safety and tolerability of dapivirine vaginal gel (Gel 4759) following multiple topical penile exposures.[10, 11] Three Phase 1 clinical trials that evaluated the vaginal film formulation of dapivirine in 81 women have been conducted.[12-14]

Importantly, recent results from two Phase 3 trials demonstrate the safety and efficacy of dapivirine delivered through vaginal rings (VRs). In the Phase 3 trial, MTN-020

(ASPIRE), there was no significant difference detected between the dapivirine and placebo treatment groups in frequency of the primary safety endpoint [15], defined as the incidence of any SAE, any Grade 3 or 4 AE, and any Grade 2 AE that was assessed by the investigator as being related to the investigational product. The primary safety endpoint was observed in 180/1313 (14%) of the dapivirine VR arm compared to 186/1316 (14%) in the placebo arm (P=0.80 for the overall comparison by chi-square test)[15]. The DPV VR resulted in a 27% (95% CI: 1-46%, p=0.05) relative reduction in HIV-1 incidence overall, a 37% (95% CI: 12-56%, p=0.007) reduction in an analysis defined early in the study, excluding data from two study sites with lower retention and adherence, and a 56% (95% CI: 31-71%, p<0.001) reduction in a post-hoc analysis among women older than 21 years of age[15]. In the Phase 3 trial, IPM 027 (The Ring Study), no clinically significant differences in the frequency of treatment emergent adverse events between the DPV and placebo groups were detected[16]. In The Ring Study, dapivirine VR use reduced the risk of HIV-1 infection by 30.7% relative to placebo, and a 37.5% reduction in HIV-1 infection was observed in a subgroup analysis of women older than 21 years of age[17].

Pharmacokinetics

Dapivirine Gels 4759 and 4789

The particular formulation of dapivirine gel planned for this trial was tested in IPM 020[18], IPM 014A[19], MTN-012/IPM 010[1, 20], and FAME-02B[21]. IPM 020 was a double-blind, randomized, placebo-controlled Phase 1/2 expanded safety study conducted in the USA. The trial enrolled 128 healthy, sexually active, HIV-negative women to assess the safety of Dapivirine Gel 4759, 0.05% 2.5g and Dapivirine Gel 4789, 0.05% 2.5g as compared to the HEC-based Universal Placebo gel. Three SAEs were reported during the trial, one by a participant in the Dapivirine Gel 4759 group and two by participants in the Universal placebo gel group. In the Gel 4759 group, one woman was reported with Grade 3 (severe) breast cellulitis. In the Universal placebo gel arm, one woman was reported with Grade 3 abdominal pain of unclear origin and one woman with Grade 3 asthma. None of these events were assessed by the Investigator as related to product use. Two TEAEs resulted in early trial discontinuation of two participants, both from the Dapivirine Gel 4759 group: worsening of a cervicovaginal human papillomavirus (HPV) infection that was reported by the Investigator as Grade 1 (mild), and Grade 1 (mild) hypersensitivity (reported as an allergic response; symptoms reported included vaginal burning, itching and erythema); both events were regarded by the Investigator as probably related to IP. Three TEAEs led to the permanent discontinuation of gel use in two participants assigned to the Gel 4789 and one participant in the placebo gel group, who in return withdrew their consent due to these TEAEs. In the Gel 4789 group, one participant was reported with vulvovaginal pruritus (Grade 2) which was assessed by the Investigator as probably not related to IP. Another participant, also in the Gel 4789 group, was reported with vulvovaginal discomfort (Grade 2) and vulvovaginal pruritus (Grade 2) which were both assessed by the Investigator as probably related to IP. In the placebo gel group, one woman experienced a mild (Grade 1) ulcer on the clitoral hood and discontinued gel use permanently; however, she completed all trial visits. The event was regarded by the Investigator as possibly related to the placebo gel.

In addition to IPM 020, the safety of Gel 4759 was also tested in IPM 014A, conducted in 280 healthy, sexually active, HIV-negative women in South Africa, Rwanda, Malawi and Kenya.[19] IPM 014A was a double-blind, randomized, placebo-controlled Phase 1/2 study to evaluate the safety and acceptability of Dapivirine Gel 4759, 0.05%, 2.5g, administered daily over a 6-week period. The trial was conducted using daily monitored adherence. No SAEs were reported and no participants were discontinued from the trial. Additionally, there were no permanent discontinuations from dapivirine or placebo gel use due to TEAEs during the trial.

MTN-012/IPM 010 was a penile tolerance study conducted in Pittsburgh, PA USA with twenty-four circumcised and 24 uncircumcised (N=48) healthy HIV-negative male participants aged 18 years or older.[20] The males were randomized 2:1:1 to apply dapivirine 0.05% gel (Gel 4759), matched placebo gel, or Universal Placebo gel, respectively, to their penis once daily for 7 sequential days. The safety, acceptability, and pharmacokinetic (PK) profile of DPV 0.05% gel were assessed by the presence of Grade 2 or higher genitourinary adverse events (AEs) and systemic AEs, a behavioral questionnaire, and PK plasma blood draw, respectively, at the final clinic visit. Topical seven-day penile application of dapivirine 0.05% gel was locally and systemically safe, was acceptable to male participants, and resulted in systemic exposure to the drug. There were no Grade 2 genitourinary AEs in 47 participants completing the final clinic visit. There were 13 AEs reported; all were Grade 1 except one Grade 2 corneal laceration unrelated to study product. Dapivirine was detectable in plasma in all 23 dapivirine arm study participants at the final clinic visit, as one participant failed to present to the clinic for the final study visit. On average, the circumcised participants' dapivirine concentrations were 54% of those in uncircumcised participants ($p = 0.07$).

FAME-02B was a Phase 1, two-arm, randomized crossover study conducted in Baltimore, MD that compared the multi-compartment PK and *ex vivo* PD characteristics between the Gel 4579 and vaginal film formulations of dapivirine.[21] Ten healthy, HIV-uninfected women ages 18-45 years old were randomized (1:1) to receive either a single dose of dapivirine Gel 4579 followed by a single dose of dapivirine vaginal film one week later, or to receive a single dose of vaginal film followed by a single dose of Gel 4579 a week later. PK was assessed in blood, cervical tissue and CVF, while PD was assessed via HIV tissue explant challenge. No SAEs were recorded, and 75% (18 of 24) of AEs were Grade 1. No AEs were determined to be related to study product, and the AEs that occurred during the dosing intervals were evenly distributed between the two study products (10 with film and 11 with gel). There were no statistically significant PK or PD differences between the film and gel study products for plasma, CVF or tissue, except for a greater dapivirine concentration in mid-vaginal CVF for film as compared to gel. CVF DPV concentrations 5 hr after dosing were greater than tissue concentrations, and both were greater than plasma concentrations. Plasma half-life was significantly greater than estimated maximum half-life for both CVF and cervical tissue, which were similar to each other.

<u>Dapivirine Gel 4750</u>

A similar formulation (Gel 4750) was studied in IPM 012. Gel 4750 contained dapivirine drug substance, purified water, HEC, Vitamin E TPGS, polycarbophil, propylene glycol,

methyl paraben, and sodium hydroxide. Gel 4750 and the gel being tested in this study, Gel 4759 are essentially the same except 4750 included the Vitamin E TPGS (dispersing agent, 0.50).[1] In IPM 012, the safety and pharmacokinetics of two formulations of dapivirine vaginal gel were compared with the HEC-based Universal Placebo gel in 36 healthy, HIV-negative, sexually abstinent women 18 to 40 years of age. This Phase 1, randomized, double-blind, placebo-controlled trial was conducted at one research center in Belgium. Women were randomized in a 1:1:1 ratio to once daily applications of Gel 4750 (0.05%, 2.5 g), Gel 4789 (0.05%, 2.5 g), or placebo gel for 11 days (Day 1 followed by a 3-day washout period and then for 10 consecutive days, Days 5-14). Dapivirine concentrations were measured in cervicovaginal fluids and plasma on Days 1, 2, 5, 9, 11, 14-17, 19, 21, and 24.

Systemic absorption of dapivirine was low.[22] C_{max} and $AUC_{0\text{-}24h}$ values for dapivirine in plasma were slightly higher for Gel 4750 than Gel 4789 on Days 1 and 14; however, the differences did not achieve statistical significance. For both gels, Day 14 values were 2- to 4-fold higher than values on Day 1. T_{max} was variable; on Day 1 the mean was 23.5 hours for both gels, whereas by Day 14 means were 10-12 hours. Terminal half-life was much longer in plasma (73-90 hours) than in cervicovaginal fluids (15-17 hours). [23]

Table 3: Treatment-Emergent AEs from Gel 4750 Use

	Dapivirine Gel
MedDRA SOC/Preferred Term	**Gel 4750 (N=12)**
	(%)
Participants with at least one TEAE	83.3
Gastrointestinal Disorders	**41.7**
Nausea	8.3
Vomiting	8.3
Abdominal pain	16.7
Diarrhea	16.7
General Disorders and Administration Site Conditions	**16.7**
Catheter site pain	8.3
Pyrexia	8.3
Malaise	8.3
Injury, Poisoning and Procedural Complications	**8.3**
Procedural pain	8.3
Musculoskeletal and Connective Tissue Disorders	**16.7**
Neck pain	8.3
Back pain	8.3
Nervous System Disorders	**41.7**
Headache	41.7
Reproductive Disorders and Breast Disorders	**25.0**
Breast discomfort	8.3
Vaginal hemorrhage	8.3
Cervix erythema	8.3
Respiratory, Thoracic and Mediastinal Disorders	**16.7**
Nasal congestion	8.3
Phayrngolaryngeal pain	8.3
Nasophayngitis	8.3
Skin and Subcutaneous Tissue Disorders	**8.3**
Dermatitis contact	8.3

Safety

Dapivirine Vaginal Gels

Gel 001 and 002

Vaginal application of Gel 001 and 002 were found to be well-tolerated by healthy participants. Details regarding treatment-emergent AEs with incidence ≥5% are summarized along with other safety data in Table 4. Additional information can be found in the Investigator's Brochure.

Dapivirine Gels 4750 and 4789

The pharmacokinetics of candidates Gel 4750 (the gel formulation most similar to the gel planned for this trial) and Gel 4789 (both 0.05%, 2.5 g) were tested in IPM 012, which was conducted in Belgium in 36 women who applied the vaginal gel once daily for 11 days.[1, 22] There were no SAEs or discontinuations due to treatment-emergent adverse events (TEAEs) in the trial. Most subjects (83-100%) in each group had at least one TEAE during the trial. Headache was the event that occurred most often; 42-67% of subjects in the dapivirine gel groups and 42% of subjects in the placebo gel group reported at least one headache. For most subjects with headaches (13/18; 72%), the event was assessed as possibly related to the investigational product.

All but two TEAEs were assessed as Grade 1 (mild). One subject in the Gel 4789 group had a Grade 2 (moderate) headache assessed as possibly related to the investigational product, and a different subject in the same group had Grade 2 pyrexia assessed as not related to the investigational product. Thirty-four percent (36/105) of TEAEs were assessed as possibly related to the investigational product, and one subject in the Gel 4789 group had two episodes of vulvovaginal pruritus that were assessed as probably related. Among participants using Gel 4750 (the gel formulation most similar to the one planned for this trial), the other TEAEs deemed related to the gel included malaise (1/12) and cervix erythema (1/12).

Of the treatment-emergent adverse events with incidence >5% in the Gel-001, Gel-002, Gel 4750, and Gel 4789 dapivirine trials involving HIV-negative participants the following were reported:

Table 4: Treatment-Emergent AEs from Dapivirine Gels across Vaginal Gel Trials* (Regardless of Causality)

MedDRA SOC/Preferred Term	Gel-001**, Gel-002, Gel 4750, Gel 4789 N=295	Gel 4759 N=184
	N (%)	N(%)
Metrorrhagia	28 (9.5)	41 (22.3)
Headache	45 (15.3)	13 (7.1)
Vaginitis Bacterial	38 (12.9)	13 (7.1)
Vaginal Candidiasis	18 (6.1)	10 (5.4)
Abdominal Pain Lower	17 (5.8)	5 (2.7)
Vulvovaginal Pruritus	7 (2.4)	14 (7.6)
Upper Respiratory Tract Infection	2 (0.7)	13 (7.1)
Blood Urine Present	14 (4.7)	0 (0.0)
Gynaecological Chlamydia Infection	6 (2.0)	7 (3.8)
Nasopharyngitis	10 (3.4)	3 (1.6)
Neutropenia	12 (4.1)	1 (0.5)
Oligomenorrhoea	8 (2.7)	5 (2.7)
Influenza	11 (3.7)	1 (0.5)
Urinary Tract Infection	6 (2.0)	6 (3.3)
Vaginal Discharge	9 (3.1)	3 (1.6)

* For comparisons across gel trials it should, however, be noted that these trials were conducted in different trial populations in Africa, Europe and the USA, and with different gel formulations.
** To compare results with those obtained for trials using Gel 002, Gel 4750, Gel 4789, and Gel 4759, only data for HIV-1 negative participants (Part A and Part B Group 1) are included here.

Oral Dapivirine

There have been 11 oral administration trials in which a total of 211 participants have been dosed with dapivirine. The maximum tolerated dose established was 350 mg for a single dose, and for multiple doses, 300 mg twice a day for 14 days. There were no deaths during clinical trials of oral dapivirine, and no trials were stopped for safety reasons. A total of 10 participants stopped dapivirine treatment prior to trial completion for safety reasons, six of whom stopped due to a clear dose dependent increase in central nervous system (CNS) and gastrointestinal TEAEs, thereby establishing the maximum tolerated dose at 300 mg twice a day. These TEAEs resolved within 1-2 days after discontinuation of use of oral dapivirine. One of the discontinuations was classified as an SAE, with hospitalization due to elevated liver function tests. This participant was also infected with hepatitis C virus. The only other SAE noted in these trials was a hospitalization due to a bicycle accident.

2.4.2 Clinical Studies of Universal Placebo Gel

Unformulated HEC is known to be a non-irritating substance in humans (skin sensitization is unusual), with doses less than 2 g/kg by ingestion not expected to be toxic.[24] No inhalation studies have been conducted, but exposure of humans to the dust in manufacturing operations over many years has not led to any known adverse effects.

Safety – Vaginal Administration

The HEC placebo formulation was developed and adopted for use in the HPTN 035 microbicide study, the Phase II/IIb Safety and Effectiveness Study of the Vaginal Microbicides Buffer Gel and 0.5% PRO2000/5 Gel (P) for the Prevention of HIV Infection in Women.

A randomized, closed label, Phase I study of daily vaginal Universal HEC Placebo Gel exposure was conducted in 2003.[25] In this trial, 30 women were randomized to twice-daily vaginal applications of 3.5 mL of the Universal HEC Placebo Gel or polystyrene sulfonate (PSS) vehicle. The primary objective of this study was to assess and compare the effects of the test articles on symptoms and signs of irritation of the external genitalia, cervix, and vagina as seen on naked eye exam after 7 and 14 days of use including disruption of the epithelium and blood vessels as seen on colposcopy after 14 days of use. Secondary objectives included: an assessment and comparison of differences in vaginal health by evaluating the results of wet mounts, pH, and Gram-stained vaginal smears (Nugent score and neutrophil counts) after 7 and 14 days of use and vaginal cultures after 14 days of use; and an assessment of acceptability of the study products after 14 days of use among participants.

Results of this trial indicated that both gels appear safe for vaginal use twice a day for 14 days in sexually abstinent women. Two out of 14 women (14.3%) randomized to the HEC group reported at least one symptom of mild severity of genital irritation, which included genital burning, soreness and pelvic pain. Three out of 14 women in the HEC group (21.4%) had colposcopic findings that included erythema, petechiae and peeling.[25] No deep genital disruption was observed in either product group. Minimal changes in wet mounts, pH, Nugent scores, neutrophils, and vaginal flora were observed in both product groups.

Safety – Rectal Administration

In several rectal microbicide trials, the Universal HEC Placebo Gel has served as the placebo arm. RMP-01 using topical UC781 enrolled 36 subjects with 12 randomized to the HEC placebo arm. Following single topical rectal HEC exposure, four Grade 2 AEs were reported in 1 individual, shown to be in the placebo group. As this individual had no complaints during the subsequent 7-day exposure, the symptoms of fever, cramps, flatulence, and diarrhea were likely not related to the HEC gel. There were no other Grade 2 or Grade 3 AEs associated with HEC gel.[26]

In the second rectal microbicide Phase 1 safety trial, RMP-02/MTN-006, 18 subjects were studied with 6 randomized to the HEC placebo arm in the topical-exposed portion of the trial. With regards to gastrointestinal-related AEs following single-dose topical HEC exposure, no Grade 2 or Grade 3 AEs were reported. Following 7-day exposure, one Grade 2 event was reported in one subject receiving HEC gel (abdominal pain); three events were reported in 2 subjects in the tenofovir-treated group. None of the five gastrointestinal Grade 3 AEs reported in 2 subjects (all during 7-day exposure) were

related to HEC placebo; all were in the tenofovir-product group. No SAEs were reported.[27]

MTN-007 was a Phase 1, randomized, double-blinded, placebo-controlled safety and acceptability study of reduced glycerin tenofovir 1% gel when applied rectally.[28] Secondary objectives of MTN-007 were to evaluate the safety of HEC placebo gel when applied rectally. Participants were randomized to receive a single dose of reduced glycerin tenofovir 1% gel, 2% N-9 gel, placebo gel, or no treatment. A total of 65 participants were enrolled and randomized in the study; 16 participants were randomized to HEC. A single dose of the study gel was self-administered under observation. Within approximately 30 minutes, lavage, stool, and rectal biopsy specimens were collected. After a one-week recovery period, participants returned to the clinic for assessment. If no significant adverse events were reported, participants began to self-administer once-daily doses of the study gel for 7 days on an outpatient basis. Participants returned to the clinic for evaluation and specimen collection after completion of 7 days of daily dosing. HEC was found to be safe and well tolerated. There were no significant differences in the proportion of participants with $\geq$ Grade 2 or higher adverse events across the arms of the study: 3/16 (19%) in the TFV arm, 7/17 (41%) in the N-9 arm, 5/16 (31%) in the HEC arm, and 6/16 (38%) in the No Rx arm; when compared to the No Rx arm, one sided Fisher exact test yielded p-value 0.94 for the TFV arm, 0.56 for the N-9 arm, and 0.77 for the HEC arm. Likelihood of future product use (acceptability) was high for the HEC gel (93.3%).

2.5 Other Clinical Studies of Dapivirine

Several other studies of the safety and/or effectiveness of dapivirine for HIV prevention have been completed, are ongoing or are in development. These studies are included in the table below.

Table 5: Clinical Studies of Dapivirine

Trial Number	Description	Country	Gel-4759 (2.5 g)	Gel-4789 (2.5 g)	Gel-4759 & Gel-4789 (2.5 g)	Ring-001 reservoir (200 mg)	Ring-002 reservoir (25 mg)	Ring-003 matrix* (25mg)	Ring-004 matrix** (25mg)	Ring-004 matrix*** (25mg)	Ring-102 matrix** (200mg DPV/ 320 mg LNG)	Ring-104 matrix** (200 mg)	Placebo Ring or Gel
IPM 001	Safety and PK in women; 7 days	Belgium	--	--	--	12	--	--	--	--	--	--	12 (crossover)
IPM 008	Safety and PK in women; 7 days	Belgium	--	--	--	--	10	--	--	--	--	--	3
IPM 013	Safety and PK in women; 56/57 days	Belgium	--	--	--	--	--	--	36	--	--	--	12
IPM 014A	Safety and acceptability in women; 42 days	Kenya, Rwanda, South Africa, Malawi	141	--	141	--	--	--	--	--	--	--	139
IPM 014B[19]	Safety and acceptability in women; 42 days	South Africa	--	50	50	--	--	--	--	--	--	--	50
IPM 015	Safety and PK in women; 84 days	Multiple Countries in Sub-Saharan Africa	--	--	--	--	--	--	140	--	--	--	140
IPM 018	Safety and PK in women; 28 days	Belgium	--	--	--	--	8	8	--	--	--	--	8
IPM 020	Safety; 84 days	United States	43	43	86	--	--	--	--	--	--	--	42
IPM 024	Safety and PK in women; 28 days	Belgium	--	--	--	--	--	--	8	--	--	--	8
IPM 027	Safety and efficacy; 2 years	South Africa, Uganda	--	--	--	--	--	--	1307	--	--	--	652
IPM 028	Safety and PK in women, Drug-drug interaction; 112 days	Belgium	--	--	--	--	--	--	36	--	--	--	--
IPM 034	Safety and PK in women; 7 to 84 days	Belgium	--	--	--	--	--	--	40	--	--	--	--
MTN-012/IPM 010	Male tolerance; 7 days	United States	24	--	24	--	--	--	--	--	--	--	--
MTN-013/IPM 026[29]	Safety and PK in women; 52 days	United States	--	--	--	--	--	--	--	12	--	--	12
MTN-020	Safety and efficacy in women; median 1.6 years	Malawi, South Africa, Uganda, Zimbabwe	--	--	--	--	--	--	1313	--	--	--	1316
MTN-023/IPM 030	Safety in adolescent females; 24 weeks	United States	--	--	--	--	--	--	73	--	--	--	23

Trial Number	Description	Country	Gel-4759 (2.5 g)	Gel-4789 (2.5 g)	Gel-4759 & Gel-4789 (2.5 g)	Ring-001 reservoir (200 mg)	Ring-002 reservoir (25 mg)	Ring-003 matrix* (25mg)	Ring-004 matrix** (25mg)	Ring-004 matrix*** (25mg)	Ring-102 matrix** (200mg DPV/ 320 mg LNG)	Ring-104 matrix** (200 mg)	Placebo Ring or Gel
MTN-024/IPM 031	Safety in postmenopausal women; 12 weeks	United States	--	--	--	--	--	--	72	--	--	--	24
MTN-025	Safety and adherence in women; 1 year	Malawi, South Africa, Uganda, Zimbabwe	--	--	--	--	--	--	(Former MTN-020 participants)	--	--	--	--
MTN-029/IPM 039	PK in lactating women; 14 days	United States	--	--	--	--	--	--	16	--	--	--	--
MTN-030/IPM 041 (Enrollment not started)	Safety and PK in women; 14 days	United States	--	--	--	--	--	--	--	--	12	12	--
MTN-033 (Enrollment not started)	PK in males; two doses over 30 days	United States	16	--	--	--	--	--	--	--	--	--	--
MTN-034/IPM 045 (Enrollment not started)	Safety and adherence in adolescent & young adult females; 24-48 weeks	Kenya, South Africa, Zimbabwe	--	--	--	--	--	--	300	--	--	--	--
TOTAL participants			**224**	**93**	**301**	**12**	**18**	**8**	**3333**	**12**	**12**	**12**	**2441**

*Tin-catalyzed matrix ring
**Platinum-catalyzed matrix ring
***Platinum-catalyzed matrix ring Ring-004, but did not contain the silicone oil MED360 - only silicone elastomer and the API(s).

2.6 Study Hypotheses and Rationale for Study Design

2.6.1 Study Primary Hypotheses

It is hypothesized that dapivirine gel (0.05%) will be safe when applied to the rectum and well-tolerated among healthy men and women who have a history of receptive anal intercourse.

2.6.2 Rationale for Study Design

Rectal microbicides are needed for individuals at risk of acquiring HIV infection through unprotected receptive anal intercourse (RAI). It will be important to expand the rectal microbicide pipeline with the addition of products from different classes such as dapivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI).

Rationale for the Dosing and PK Sampling Schedule

MTN-026 is the first study to assess the safety of dapivirine gel applied rectally. A single dose exposure for each participant will allow for the identification of any safety concerns following single dose gel application. An additional benefit of this design is that it will collect valuable PK and pharmacodynamic (PD) data from men and women who have been exposed to a single dose of dapivirine gel rectally (which may be representative of episodic or coital dosing) as well as to 7 daily rectal doses (daily dosing). While the ideal dosing regimen for dapivirine gel applied rectally is not yet known (coital-dosing vs. daily dosing), this design will provide critical PK and PD data, while controlling for inter-personal variability.

Regarding the washout period, based on several prior dapivirine studies, the plasma half-life is ~72 hours and the vaginal tissue half-life is ~15 hours. In several prior studies, tissue dapivirine concentrations fall between 2 and 4 $\log_{10}$ over a 2 week period, often to undetectable levels. During the MTN-026 2-week washout, plasma concentrations will fall to less than 5% of peak concentrations and contribute negligibly to the concentrations in plasma during the repeated daily rectal dosing phase. After the week of repeated daily rectal dosing, concentrations due to the single dose phase will drop another 95% to undetectable levels, and visit 13 sampling will be influenced only by the multiple dose period.

3 OBJECTIVES

3.1 Primary Objectives

Safety

- To evaluate the safety of dapivirine gel formulation when applied rectally.

Pharmacokinetics

- To characterize the systemic and compartmental pharmacokinetics of dapivirine gel following rectal application.

3.2 Secondary Objectives

Acceptability

- To identify product attributes considered likely to challenge and facilitate future sustained use of rectally applied dapivirine gel.

Mucosal Safety

- To evaluate the mucosal safety of dapivirine gel when applied rectally.

3.3 Exploratory Objectives

***Ex Vivo* Efficacy**

- To assess the preliminary (*ex vivo)* efficacy of dapivirine gel formulation after product is applied rectally.

Pharmacokinetics

- To characterize the vaginal pharmacokinetics of dapivirine gel following rectal application in women.

4 STUDY DESIGN

4.1 Identification of Study Design

MTN-026 is a Phase 1, multi-site, randomized (2:1), double-blind, placebo-controlled trial.

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

- Dapivirine concentrations
  - Blood
  - Rectal fluid
  - Rectal mucosal tissue homogenates

Secondary Endpoints:

Acceptability

- Product attributes considered likely to challenge future sustained use.

Mucosal Safety

- Rectal proteomics
- Rectal transcriptome
- Rectal microflora
- Rectal histology
- Rectal tissue flow cytometry

Exploratory Endpoints:

***Ex Vivo* Efficacy**

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

Pharmacokinetics

- Dapivirine concentrations
  - Cervicovaginal fluid♀
  - Cervical tissue♀

♀Female participants only

4.3 Description of Study Population

The study population will consist of HIV-uninfected men and women who are between the ages of 18 and 45 years (inclusive) at Screening and meet the criteria outlined in Sections 5.2 and 5.3. Only sites with the capacity to enroll female participants will do so.

4.4 Time to Complete Accrual

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

4.5 Study Groups

MTN-026 will enroll up to 27 participants. Randomized (2:1) to dose rectally with either dapivirine gel (0.05%) or placebo gel.

4.6 Expected Duration of Participation

Each participant will be on study for approximately 40 days. The total duration of the study will be approximately 9-12 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 Sections 5.2 and 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 across sites, including outpatient clinics, universities and community-based locations. Recruitment materials will be approved by site Institutional Review Boards/Ethics Committees (IRBs/ECs) prior to use.

5.1.2 Retention

Once a participant is enrolled and randomized in MTN-026, the study site will make every effort to retain the participant in follow-up to minimize possible bias associated with loss-to-follow-up. A retention rate of 95% will be targeted at each site. Each study site 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. Age of 18 – 45 years (inclusive) 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. Per participant report, a history of consensual RAI at least once in the past calendar year
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 be sexually abstinent for 72 hours prior to each study visit, during the study product use periods and for 72 hours after biopsy collection

   Note: See Criteria 12 and 13 for additional restrictions for female participants

10. Willing to abstain from inserting any non-study products into the rectum for 72 hours prior to each study visit and during the study product use periods

    Note: See Criteria 12 and 13 for additional restrictions for female participants

Females must also meet the following additional inclusion criteria to be eligible for study inclusion:

11. Women over the age of 21 (inclusive) must have documentation of a satisfactory Pap within the past 3 years prior to Enrollment consistent with Grade 0 according to the Female Genital Grading Table for Use in Microbicide Studies Addendum 1 (dated November 2007) to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, or satisfactory evaluation with no treatment required of Grade 1 or higher Pap result

12. Willing to be sexually abstinent for 72 hours prior to each study visit and during the study product use periods and for 7 days after biopsy collection

13. Willing to abstain from inserting any non-study products into the vagina for 72 hours prior to each study visit, during the study product use periods and for 7 days after biopsy collection

14. Willing to use an effective method of contraception for at least 30 days (inclusive) prior to Enrollment and intending to continue use of an effective method for the duration of study participation; effective methods include: hormonal methods (except contraceptive ring), intrauterine device (IUD), sterilization (of participant and/or partner, as defined in site SOPs), or sexually abstinent for 90 days prior to Screening

5.3 Exclusion Criteria

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

1. At Screening:
   i. Hemoglobin Grade 1 or higher*
   ii. Platelet count Grade 1 or higher*
   iii. White blood count Grade 2 or higher*
   iv. Serum creatinine >1.3× the site laboratory upper limit of normal (ULN)
   v. International normalized ratio (INR) >1.5× the site laboratory ULN
   vi. Aspartate aminotransferase (AST) or alanine transaminase (ALT) Grade 1 or higher*
   vii. Positive for hepatitis C antibody
   viii. Positive for hepatitis B surface antigen
   ix. 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 (other than HIV, HBV or HCV) 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. Anticipated use of and/or unwillingness to abstain from the following medications during study participation:
    i. Heparin, including Lovenox®
    ii. Warfarin
    iii. Plavix® (clopidogrel bisulfate)
    iv. Aspirin (greater than 81 mg)
    v. Non-steroidal anti-inflammatory drugs (NSAIDS)
    vi. Any other drugs that are associated with increased likelihood of bleeding
    vii. CYP3A inducer(s) and/or inhibitor(s) as specified in the MTN-026 Study-Specific Procedures (SSP) Manual
    viii. Hormone-replacement therapy in tablet, injectable or gel form

3. Known adverse reaction to any of the components of the study products

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

5. Use of pre-exposure prophylaxis (PrEP) for HIV prevention within the 6 months prior to Enrollment, and/or anticipated use during trial participation

6. Use of systemic immunomodulatory medications within the 6 months prior to Enrollment, and/or anticipated use during trial participation

7. RAI without a condom and/or penile-vaginal intercourse with a partner who is known to be HIV-positive in the past 6 months

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

9. Participation in research studies involving drugs, medical devices, genital or rectal products, or vaccines within 45 days of the Enrollment Visit

10. At Screening, participant report of treatment for an anogenital STI within the past 3 months

11. At Screening, participant-reported symptoms and/or clinical or laboratory diagnosis of active anorectal or reproductive tract infection requiring treatment

per current World Health Organization (WHO) guidelines (http://www.who.int/hiv/pub/sti/pub6/en/) or symptomatic urinary tract infection (UTI). Infections requiring treatment include symptomatic Neisseria gonorrhea (GC), Chlamydia trachomatis (CT) infection, syphilis, active herpes simplex virus (HSV) lesions, anogenital sores or ulcers, or symptomatic genital warts, cervicitis, chancroid, pelvic inflammatory disease (PID), bacterial vaginosis (BV), symptomatic vaginal candidiasis, other vaginitis, trichomoniasis.

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

12. At Enrollment, active anorectal or reproductive tract infection requiring treatment per current WHO guidelines (http://www.who.int/hiv/pub/sti/pub6/en/) or symptomatic urinary tract infection (UTI). Infections requiring treatment include symptomatic GC, CT, syphilis, active HSV lesions, anogenital sores or ulcers, symptomatic genital warts, bacterial vaginosis, symptomatic vaginal candidiasis, other vaginitis, trichomoniasis, chancroid, cervicitis and PID.

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

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.

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

14. Pregnant or breastfeeding at either Screening or Enrollment or intends to become pregnant or start 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.

15. Last pregnancy outcome 90 days or less prior to Screening

16. Has had a hysterectomy

17. At Enrollment, has a clinically apparent Grade 1 or higher pelvic exam finding (observed by study clinician or designee) per the Female Genital Grading Table for Use in Microbicide Studies [Addendum 1, Dated November 2007]

    Note: Cervical friability bleeding associated with speculum insertion and/or specimen collection judged to be within the range of normal according to the clinical judgment of the IoR/designee is considered expected non-menstrual bleeding and is not exclusionary.

5.4 Co-enrollment Guidelines

As indicated in Sections 5.2 and 5.3, participants must not take part in other research studies involving drugs, medical devices, genital or rectal products, or vaccines after the Screening Visit and while taking part in MTN-026, 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-026 PSRT
- Participants who become infected with HIV may take part in observational and/or interventional studies for HIV-positive persons
- Participants who become pregnant may take part in observational studies, including pregnancy registries

Should any participant report concurrent participation in contraindicated studies after enrolling in MTN-026, 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

Twenty-seven participants will be randomized (2:1) to receive rectally administered dapivirine gel (0.05%) or placebo gel. Participants will receive a single dose of the gel administered by the study staff. Following a minimum two week washout period participants or study staff will administer daily rectal doses of study gel for 7 consecutive days under direct observation in the clinic.

Table 6: Study Product Regimen

Study	Study Products	Number of Participants	Frequency and Route
MTN-026	0.05% Dapivirine Gel Universal Placebo Gel	27	Single dose followed by washout period and then 7 consecutive doses rectally administered

6.2 Administration

Study staff will administer the single dose of study gel in the clinic to randomized participants. Study staff will observe each administration of the 7 daily doses of study gel. Participants will be instructed to present to the clinic daily for the 7-day period for directly observed dosing (DOD). Administration of study product during the 7-day period will be performed either by participants or by study staff, depending upon site and/or participant preference. Study staff who apply gel rectally are not to be the same staff who assess the participant's safety. If a participant is not able to attend a clinic visit, the participant will be instructed to administer a dose at home at approximately the same time of day as all other daily doses, unless the next dose is due within 6 hours. If the next dose is due within 6 hours, the dose will be skipped and the next dose will be administered as originally scheduled. Participants who miss more than one application of the product will be instructed to contact the site for further direction. Participants will receive one pre-filled applicator of dapivirine gel (0.05%) or placebo gel at Visit 7 in the event that they cannot attend one of their seven daily dosing clinic visits. Participants will be informed of the ideal storage conditions for this single dose. Participants will also be instructed on how to properly dispose of the used applicator at home in the event they insert a dose at home.

Additional detail on administration and participant education will be provided in the MTN-026 SSP Manual.

6.3 Study Product Formulation

Dapivirine Gel (0.05%)
Dapivirine gel (0.05%) is formulated as an aqueous semi-solid (gel). The excipients in the drug product formula are pharmacopoeia grade components that have a history of use in currently approved vaginal products. Dapivirine gel has a pH of 4.7. Each pre-filled applicator will contain approximately 2.5 g (2.5 mL) of 0.05% dapivirine gel.

Dapivirine gel should be stored at room temperature 25°C (77°F). Excursions are permitted between 15°C to 30°C (59°F to 86°F).

Universal Placebo Gel
The Universal Placebo gel contains HEC as the gel thickener, purified water, sodium chloride, sorbic acid and sodium hydroxide. The gel is isotonic and formulated at a pH of 4.4. HEC, the gelling agent, is used to approximate the viscosity of other microbicide gel candidates. Each pre-filled applicator will contain approximately 2.5 g (2.5 mL).[4]

Universal Placebo gel should be stored at room temperature 25°C (77°F). Excursions are permitted between 15°C to 30°C (59°F to 86°F).

6.4 Study Applicator

MTN-026 will use the HTI pre-filled applicator, the same applicator that has been utilized in other rectal studies, including RMP02/MTN-006, MTN-007, Project GEL and

CHARM 01, and is currently being used in MTN-017 and CHARM 03. The applicator is manufactured by HTI Plastics, Lincoln NE, USA, in accordance with HTI's quality assurance procedures and the Good Manufacturing Practices as established by the Food and Drug Administration. Participants will be advised on proper storage conditions while at home.

6.5 Study Product Supply and Accountability

6.5.1 Study Product Supply

MTN (Pittsburgh, PA) will supply the 0.05% dapivirine gel and Universal Placebo gel prefilled applicators. MTN will ensure the manufacture of dapivirine gel (0.05%) and Universal Placebo gel and analyze/release the gels under Good Manufacturing Practices (GMP). Study product will ship directly to the Pharmacist of Record (PoR) at each study site.

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.

6.6 Study Product Dispensing

Following receipt of a written prescription from an authorized prescriber, one pre-filled applicator of study product (0.05% dapivirine gel or Universal Placebo gel) will be dispensed to enrolled study participants or to study staff on behalf of the participant at each study product administration visit for DOD. 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.

Additionally, participants will receive one pre-filled applicator of 0.05% dapivirine gel or Universal Placebo gel for at home use in the event that they are unable to attend a scheduled observed dosing visit at the clinic. This dose will be dispensed and provided to the participant at the first administration of the 7 consecutive daily doses, Visit 7.

6.7 Retrieval of Unused Study Products

Study participants will be instructed to return the unused applicator of dapivirine gel (0.05%) or Universal Placebo gel at Visit 14: 24 hour PK Visit. In the event that unused study products are not returned at Visit 14: 24 hour PK Visit, site staff members will make every effort to encourage participants to return study product as soon as possible. Attempts by study staff to retrieve unused study product from the participant must be documented. If study product is not returned within the time frames outlined below the MTN-026 PSRT must be notified.

Study product must be retrieved (optimally within 24 hours) and returned to the study site pharmacy when study product use is permanently discontinued. If the study product(s) is not retrieved within 24 hours, the MTN-026 PSRT must be informed.

It is expected that participants will return any unused study product not previously returned at their Final Clinic Visit (Visit 16). If a participant does not bring his/her unused study product to the Final Clinic Visit (Visit 16), study staff must attempt to retrieve the unused study product within 7 days. If the study product(s) are not retrieved within that timeframe, the MTN-026 PSRT must be informed.

6.8 Ancillary Study Supplies

All participants will be offered study-provided lubricant to facilitate the insertion of the applicator. Lubricant will be dispensed by the clinic staff and made available in the clinic.

Study provided condoms will be offered to participants at Visit 6.

6.9 Concomitant Medications

With the exception of those not permitted under inclusion and exclusion criteria, and listed below, concomitant medications will be permitted. Throughout the course of the study, all concomitant medications, including those used to treat AEs, will be recorded on forms designed for that purpose. Prescription medications, over-the-counter preparations, vitamins and nutritional supplements, and herbal preparations all will be recorded as concomitant medications. Sexual lubricants may be recorded on a separate form.

6.10 Prohibited Medications and Practices

Use of Heparin, including Lovenox®, Warfarin, Plavix® (clopidogrel bisulfate), hormone-replacement therapy in tablet, injectable or gel form is prohibited during study participation. See Section 9.3 for additional details regarding permanent discontinuation for reported use of these medications.

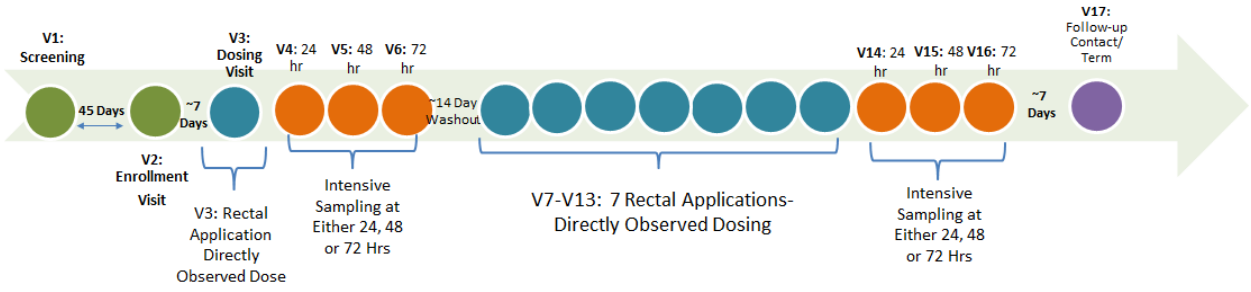
Participants will be counseled to abstain from using aspirin (greater than 81 mg) and other non-steroidal anti-inflammatory drugs (NSAIDS), CYP3A inducer(s) and/or inhibitor(s) and any other drugs that are associated with increased likelihood of bleeding. Should a participant report the use of such drugs within 72 hours prior to a PK sample collection visit, collection of biopsies at that visit would be performed at IoR discretion. Participants will be appropriately counseled regarding the potential risks associated with biopsy collection and documentation of the decision process will be included in the participants' study documents. Rapid PSRT consultation can be requested at IoR discretion, if needed. Participants who report use of prohibited products and/or products to avoid during study product use period will be counseled regarding the use of alternative methods.

Participants are to abstain from inserting any non-study products into the rectum or vagina for 72 hours prior to clinic visits and during the study product use periods. Male participants are to abstain from the following sexual activities for 72 hours after biopsy collection: receptive anal intercourse (RAI), receptive oral anogenital stimulation, rectal stimulation via fingers, and rectal insertion of sex toys. Further, female participants are to abstain from inserting anything into their vagina and rectum for 7 days following biopsy collection, including the following sexual activities: RAI, penile-vaginal intercourse, receptive oral anogenital stimulation, vaginal or rectal stimulation via fingers, and vaginal or rectal insertion of sex toys. Participants will be appropriately counseled regarding the potential risks associated with biopsy collection and documentation of the decision process will be included in the participants' study documents. Rapid PSRT consultation can be requested at IoR discretion, if needed.

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 across sites are provided in the MTN-026 SSP Manual available at www.mtnstopshiv.org.

Figure 2: MTN-026 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 in a directly observed fashion, 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 the study site 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/EC. Procedures and documentation will comply with local IRB/EC requirements.

7.2 Visit 1: 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 7: Visit 1: Screening Visit

Visit 1: Screening Visit		
Component		**Procedures**
Administrative and Regulatory		• Obtain written informed consent • Assess consent form comprehension • Assign participant ID (PTID) • Collect locator information • Collect demographic information • Assess eligibility • Provide reimbursement for study visit • Schedule next visit*
Behavioral		• Provide counseling – HIV pre- and post-test – HIV/STI risk reduction – Protocol requirements
Clinical		• Collect medical history • Collect menstrual history♀ • Collect concomitant medications • Perform physical examinationϴ • Perform pelvic examinationϴ ♀ • Perform rectal examinationϴ • Provide available test results • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*
Laboratory	**Urine**	• Collect urine – Qualitative hCG♀ – Dipstick urinary analysis (UA)* – Urine culture* – NAAT for GC/CT
	Blood	• Collect blood – Complete blood count (CBC) with differential and platelets – Chemistries (AST, ALT, Creatinine) – Syphilis serology – HIV-1/2 test – HSV-1/2 serology – HBsAg – HCV serology – Coagulation (PT/INR)
	Pelvic Samples	• Collect pelvic specimens – Vaginal NAAT for GC/CT♀ – Pap test♀*
	Anorectal Samples	• Collect rectal specimens – Rectal NAAT for GC/CT – Anal HSV-1/2 detection*

♀Female participants *if indicated ϴ See Section 7.13 for examination details

7.3 Visit 2: Enrollment (Day 0)

Menses must not coincide with Study Visits 2-6, therefore participant's menstrual cycle must be considered when scheduling the Enrollment Visit (Visit 2).

Table 8: Visit 2: Enrollment (Day 0)

Visit 2: Enrollment		
Component		**Procedures**
Administrative and Regulatory		• Review informed consent and confirm participant's willingness to continue in the study • Confirm eligibility • Review/update locator information • Randomization • Provide reimbursement for study visit • Schedule next visit*
Behavioral		• Behavioral assessment • Provide counseling – HIV pre- and post-test – HIV/STI risk reduction – Protocol requirements
Clinical		• Review/update medical history • Review/update menstrual history♀ • Review/update concomitant medications • Perform targeted physical examination • Perform pelvic examination♀ • Perform rectal examination • Provide available test results • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*
Laboratory	**Urine**	• Collect urine – Qualitative hCG ♀ – Dipstick UA* – Urine culture* – Urine NAAT for GC/CT*
	Blood	• Collect blood – CBC with differential and platelets* – Chemistries (AST, ALT, Creatinine)* – Syphilis serology* – HIV-1/2 test – Plasma for archive
	Pelvic Samples	• Cervicovaginal lavage (CVL) for PD baseline prior to biopsy collection♀
	Anorectal Samples	• Rectal NAAT for GC/CT* • Anal HSV-1/2 detection* • Rectal enema effluent for PD baseline prior to biopsy collection • Rectal tissue for PD baseline • Rectal tissue for mucosal safety baseline • Rectal fluid for mucosal safety baseline

♀Female participants *If indicated

7.4 Visit 3: Single Dose Administration Visit

Table 9: Visit 3: Single Dose Administration Visit

Visit 3: Single Dose Administration Visit		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement for study visit • Schedule next visit
Behavioral		• Behavioral assessment • In-depth interview (IDI) • Provide counseling – Protocol requirements – Product use
Clinical		• Review/update medical history • Review/update menstrual history♀ • Review/update concomitant medications • Perform targeted physical examination* • Perform pelvic examination♀* • Perform rectal examination • Provide available test results • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings* • Record/update AEs
Laboratory	**Urine**	• Collect urine – Dipstick UA* – Urine culture* – Urine NAAT for GC/CT*
	Blood	• Collect blood – CBC with differential and platelets* – Chemistries (AST, ALT, Creatinine)* – Syphilis Serology* – PK levels ●
	Anorectal Samples	• Collect rectal specimens – Rectal NAAT for GC/CT* – Anal HSV-1/2 detection* – Rectal fluid for PK levels ● – Rectal fluid for mucosal safety ● – Rectal tissue for PD ● – Rectal tissue for PK ● – Rectal tissue for mucosal safety ●
Study Product Supply		• Provision of study product • Provision of lubricant • Observe dose application

♀Female participants *if indicated ● = Participants will be assigned to provide samples at either 30-60 or 120 minutes. In addition, all participants will provide blood for PK at hr 0. Blood collection times are matched to fluid/tissue sample collection times.

7.5 Visits 4-6 (~24, 48, 72 Hours After Application of Study Product)

All participants attend Visits 4, 5, and 6. Participants will only provide intensive PK samples at Visit 4, 5 or 6**.**

Table 10: Visits 4-6: PK Visits (~24, 48, 72 Hours After Application of Study Product)

Visits 4-6 (~24, 48, 72 Hours After Application of Study Product)		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement for study visit • Schedule next visit/contact
Behavioral		• Provide counseling – Protocol requirements
Clinical		• Review/update medical history • Review/update menstrual history♀ • Review/update concomitant medications • Perform targeted physical examination * • Perform pelvic examination ●♀ • Perform rectal examination ● • Provide available test results • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings* • Record/update AEs
Laboratory	**Urine**	• Collect urine – Dipstick UA* – Urine culture* – Urine NAAT for GC/CT*
	Blood	• Collect blood – CBC with differential and platelets* – Chemistries (AST, ALT, Creatinine)* – Syphilis Serology* – PK levels
	Pelvic Samples	• Collect pelvic specimens – Cervicovaginal fluid for PK levels ●♀ – CVL for PK and PD prior to biopsy collection ●♀ – Cervical tissue for PK levels ●♀
	Anorectal Samples	• Collect rectal specimens – Rectal NAAT for GC/CT* – Anal HSV-1/2 detection* – Rectal fluid for PK levels ● – Rectal enema effluent for PK and PD prior to biopsy collection ● – Rectal tissue for PK levels ● – Rectal tissue for PD ●
Study Product Supply		• Offer condoms□

♀Female participants *If indicated ● Participants will be assigned to provide intensive PK samples at either Visit 4, 5 or 6 □Visit 6 only

7.6 Visits 7-12: Study Product Administration Visits

After a minimum 14 day washout period, participants will return to the clinic to initiate the application of 7 daily doses.

Note: The washout period should be timed to coincide with female participants' menses.

Table 11: Visits 7-12: Study Product Administration Visits

Visits 7-12: Study Product Administration Visits		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement for study visit • Schedule next visit
Behavioral		• Provide counseling – Protocol requirements – Product use – HIV pre- and post-test (Required at Visit 7)* – HIV/STI risk reduction (Required at Visit 7)*
Clinical		• Review/update medical history • Review/update menstrual history♀ • Review/update concomitant medications • Perform targeted physical examination* • Perform pelvic examination♀* • Perform rectal examination (Required at Visit 7 & 8)* • Provide available test results • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings* • Record/update AEs
Laboratory	**Urine**	• Collect urine – Qualitative hCG (Required at Visit 7)♀* – Dipstick UA* – Urine culture* – Urine NAAT for GC/CT*
	Blood	• Collect blood – CBC with differential and platelets* – Chemistries (AST, ALT, Creatinine)* – HIV-1/2 test (Required at Visit 7)* – Plasma for storage (Visit 7 only) – Syphilis serology* – PK levels (Visits 7 & 8 only)
	Anorectal Samples	• Collect rectal specimens – Rectal NAAT for GC/CT* – Anal HSV 1/2 detection* – Rectal fluid for PK levels (Visits 7 & 8 only)
Study Product Supply		• Provision of study product *Note: At Visit 7 one additional pre-filled applicator of study product will be dispensed in the event a participant cannot attend one of their seven daily dosing visits, See Section 6.2* • Provision of lubricant • Observe dose application

♀Female participants *if indicated

7.7 Visit 13: Last Study Product Administration Visit/Early Termination Visit

Table 12: Visit 13: Last Study Product Administration Visit/Early Termination Visit

Visit 13: Last Study Product Administration Visit		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement for study visit • Schedule next visit/contact
Behavioral		• Behavioral assessment□ • In-Depth Interview□ • Provide counseling – Protocol requirements – Product use
Clinical		• Review/update medical history • Review/update menstrual history♀ • Review/update concomitant medications • Perform targeted physical examination* • Perform pelvic examination♀ • Perform rectal examination • Provide available test results • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings* • Record/update AEs
Laboratory	**Urine**	• Collect urine – Dipstick UA* – Urine culture* – Urine NAAT for GC/CT*
	Blood	• Collect blood – CBC with differential and platelets* – Chemistries (AST, ALT, Creatinine)* – Syphilis Serology* – PK levels ●
	Pelvic Samples	• Collect pelvic specimens – Cervicovaginal fluid for PK levels ●♀ – CVL for PK and PD prior to biopsy collection for PD ●♀ – Cervical tissue for PK levels ●♀
	Anorectal Samples	• Collect rectal specimens – Rectal NAAT for GC/CT* – Anal HSV 1/2 detection* – Rectal enema effluent for PK and PD prior to biopsy collection ● – Rectal fluid for PK levels ● – Rectal fluid for mucosal safety ● – Rectal tissue for PK levels ● – Rectal tissue for PD ● – Rectal tissue for mucosal safety ●
Study Product Supply		• Provision of study product Θ • Provision of lubricant Θ • Observe dose application Θ • Collect unused study product

♀Female participants *if indicated ● Participants will be assigned to provide samples at either 30-60 or 120 minutes. In addition, all participants will provide blood for PK at hr 0. Blood collection times are matched to fluid/tissue sample collection times. □Required at Early Termination only Θ Omit at Early Termination

Note: If Visit 13 is serving as the Early Termination Visit- PK and PD sample collection will be at the discretion of the MTN-026 Management Team.

7.8 Visits 14-16: PK Visits (~24, 48, 72 Hours After Last Application of Study Product)

All participants attend Visits 14, 15, 16. Participants only provide intensive PK samples at Visit 14, 15 or 16.

Table 13: Visits 14-16: PK Visits (~24, 48, 72 Hours After Last Application of Study Product)

Visits 14-16: PK Visits (~24, 48, 72 Hours After Last Application of Study Product)		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement for study visit • Schedule next visit/contact
Behavioral		• Behavioral assessment∞ • IDI∞ • Provide counseling – HIV pre- and post-test (Required at Visit 16)* – HIV/STI risk reduction (Required at Visit 16)* – Protocol requirements
Clinical		• Review/update medical history • Review/update menstrual history♀ • Review/update concomitant medications • Perform targeted physical examination* • Perform pelvic examination●♀ • Perform rectal examination● • Provide available test results • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings* • Record/update AEs
Laboratory	**Urine**	• Collect urine – Qualitative hCG ♀∞ – Dipstick UA* – Urine culture* – Urine NAAT for GC/CT*
	Blood	• Collect blood – PK levels – CBC with differential and platelets* – Chemistries (AST, ALT, Creatinine) (Required at Visit 16)* – HIV-1/2 test (Required at Visit 16)* – Syphilis serology* – Plasma for archive/storage (Visit 16 only)
	Pelvic Samples	• Collect pelvic specimens – Cervicovaginal fluid for PK levels●♀ – Cervical tissue for PK levels●♀ – CVL for PK and PD prior to biopsy collection●♀
	Anorectal Samples	• Collect rectal specimens – Anal HSV 1/2 detection* – Rectal NAAT for GC/CT* – Rectal enema effluent for PK and PD prior to biopsy collection ● – Rectal fluid for PK levels● – Rectal tissue for PD● – Rectal tissue for PK levels●

♀Female participants *if indicated ● Participants will be assigned to provide intensive PK samples at either Visit 14, 15 or 16 ∞Visit 14 only

7.9 Visit 17: Follow-Up Safety Contact and Termination Visit

Approximately one week following Visit 16, study staff will contact participants (clinic visit or via phone) to inquire about AEs that they might have experienced as a result of the study product or procedures performed. This contact will also serve as the participant's study termination.

Table 14: Visit 17: Follow-up Safety Contact and Termination Visit

Visit 17: Follow-up Safety Contact/Termination Visit	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Provide reimbursement (if required)~ • Schedule next visit/contact*
Clinical	• Record/update AEs • Provide available test results • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*

* if indicated; ~ Sites to reference SOPs regarding participant reimbursement

7.10 Follow-up Procedures for Participants Who Permanently Discontinue Study Product

7.10.1 Participants Who Become Infected with HIV-1

If a participant tests positive for HIV-1 after the Enrollment Visit, they 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 will occur. Participants who seroconvert after randomization may be offered additional laboratory testing (such as HIV RNA and HIV drug resistance testing), as clinically indicated per discussions between IoR and LC. Please reference the MTN-026 SSP Manual for additional details (www.mtnstopshiv.org).

7.10.2 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 and procedures will be discontinued and the participant will be considered terminated from the study. An Early Termination Visit will occur. A participant who is pregnant at study termination will continue to be followed until the pregnancy outcome is ascertained, see Section 9.5 for additional details.

Participants who become pregnant while on study product may be offered enrollment in MTN-016 (www.mtnstopshiv.org), provided their study site is taking part in MTN-016.

For additional details regarding obtaining pregnancy outcome, please reference the MTN-026 SSP Manual (www.mtnstopshiv.org).

7.10.3 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. Continued study participation would be of no added benefit. An Early Termination Visit will occur. 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.

7.11 Interim Visits

Interim visits may be performed at any time during the study and any procedures may be conducted. All interim contacts and visits will be documented in participants' study records and on applicable CRFs.

7.12 Study Product Use / Adherence Counseling

Study staff will document administration of study product. Product adherence counseling will be provided to study participants upon enrollment into the study. Counseling will be provided in accordance with standard study methods. Participants will be counseled to return to the clinic daily during the product use periods for directly observed gel administration. Strategies to ensure the availability and use of the study product when participants are not able to present to the clinic for direct observation will be provided. Counseling also will include reminders to contact study staff with questions about study product use.

For participants who have adherence problems and/or issues presenting to the clinic for the administration of study product, every effort will be made to identify adherence strategies to increase their rates of study product use and attendance to daily clinic visits throughout the course of the study.

7.13 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 the Screening Visit

Pelvic Examination

The pelvic examination may include the following:

- Visual exam
- Speculum exam
- Bimanual exam

Anorectal Examination

The anorectal examination may include the following:

- Visual exam
- Digital exam
- Anoscopy
- Flexible sigmoidoscopy

Detailed information regarding the pelvic and rectal examinations, as well as the associated procedures required for collecting cervical/vaginal/rectal specimens at each visit can be found in the MTN-026 SSP Manual.

Mucosal Safety

Mucosal safety will be assessed by visual appearances of the rectal mucosa at the time of both anoscopy and flexible sigmoidoscopy, and quantified with reference to the DAIDS toxicity tables. Safety assessment procedures are consistent with RMP02/MTN-006, MTN-007 and MTN-017.

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.

7.14 Behavioral Assessments

Participants will respond to brief computer administered self-interviews (CASI) at the Enrollment visit (Visit 2), after the single dose (Visit 3) and a follow-up assessment will occur after the 7 daily doses are applied (Visit 14). The baseline assessment, done at enrollment, 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 follow-up assessments will explore reactions to product, applicator, and administration method. These assessments will allow us to identify product attributes likely to challenge and facilitate future sustained use of dapivirine gel when applied rectally by participants (secondary objective: acceptability). Suggestions for product improvement will also be collected. Survey assessments have been used in prior rectal microbicide trials (e.g., MTN-006, MTN-007, MTN-017, Project Gel).[30-32] Using validated measures allows us to compare and contrast findings across these trials.

An in-depth interview is planned after the application of a single dose (Visit 3) and following the application of 7 daily doses (Visit 14). 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 with the direct observation administration method.[33] These interviews will be triangulated with the behavioral data to understand participants' experiences in greater depth.

7.15 Pharmacokinetics, Pharmacodynamics and Mucosal Safety

Table 15: PK, PD, and Mucosal Safety Sampling Table

Visit	Specimens Collected to Assess Drug Concentrations (PK)	Specimens Collected for Anti-HIV Activity (PD)	Specimens Collected for Mucosal Safety
Visit 2: Enrollment (Baseline Samples)		• CVL • Rectal tissue • Rectal enema effluent prior to biopsy collection	• Rectal fluid • Rectal tissue
Visit 3: SINGLE Dosing Visit	• Blood (Hours: 0 min., 30-60 or 120 minutes matched to fluid/tissue sample collection) • Rectal fluid (30-60 or 120 minutes) • Rectal tissue (30-60 or 120 minutes)	• Rectal tissue (30-60 or 120 minutes)	• Rectal fluid (30-60 or 120 minutes) • Rectal tissue (30-60 or 120 minutes)
Visits 4, 5 and 6	• Blood collected at each visit • Cervicovaginal fluid♀* • CVL prior to biopsy collection♀* • Cervical tissue♀* • Rectal fluid* • Rectal enema effluent prior to biopsy collection* • Rectal tissue*	• CVL prior to biopsy collection♀* • Rectal tissue* • Rectal enema effluent prior to biopsy collection*	
Visit 7 Initial Dosing Visit	• Blood (0 hour) • Rectal fluid (0 hour)		
Visit 8 (~24 hours after the initial application of product)	• Blood (24 hour) • Rectal fluid (24 hour)		
Visit 13 (Final Dose)	• Blood (Hours: 0 minutes and 30-60 or 120 minutes, matched to fluid/tissue sample collection) • Rectal fluid (30-60 or 120 minutes) • Rectal tissue (30-60 or 120 minutes) • Rectal enema effluent prior to biopsy collection • Cervicovaginal fluid ♀ • CVL prior to biopsy collection♀ • Cervical tissue♀	• Rectal tissue (30-60 or 120 minutes) • CVL prior to biopsy collection♀ • Rectal enema effluent prior to biopsy collection	• Rectal fluid (30-60 or 120 minutes) • Rectal tissue (30-60 or 120 minutes)

Visit	Specimens Collected to Assess Drug Concentrations (PK)	Specimens Collected for Anti-HIV Activity (PD)	Specimens Collected for Mucosal Safety
Visits 14, 15, 16	• Blood collected at each visit • Cervicovaginal fluid♀* • CVL prior to biopsy collection♀* • Cervical tissue♀* • Rectal fluid* • Rectal enema effluent prior to biopsy collection • Rectal tissue*	• CVL prior to biopsy collection♀* • Rectal tissue* • Rectal enema effluent prior to biopsy collection	

♀Females only *Participants will be assigned to provide intensive PK samples at either 24, 48, or 72 hrs after the final administered dose

7.16 Laboratory Evaluations

Local Laboratory

The local laboratory will run the following, as indicated:

- Urine specimens
    - Urine GC/CT by NAAT
    - Qualitative hCG
    - Urine dipstick/culture

- Anorectal specimens
    - Rectal fluids for:
        - Rectal GC/CT by NAAT
        - HSV 1/2 detection
    - Rectal tissue for:
        - PD

- Pelvic specimens
    - HSV 1/2 detection

- Blood specimens
    - HIV-1/2 serology, with confirmatory testing as needed
    - CBC with differential and platelets
    - Syphilis serology
    - Creatinine, AST, ALT
    - Hepatitis B surface antigen
    - HCV serology
    - HSV 1/2 serology
    - Coagulation (PT/INR)

- Cervicovaginal specimens
    - Vaginal GC/CT by NAAT

Laboratory Center (LC)

- Blood specimens
    - PK (Pharmacology Core)
    - Plasma archive/storage

- Rectal specimens
    - Rectal fluids and/or lavage for:
        - PK (Pharmacology Core)
        - PD (Protocol Support Core)
        - Mucosal safety
    - Rectal tissue for:
        - PK (Pharmacology Core)
        - Mucosal safety

- Cervicovaginal specimens
    - Cervicovaginal fluid and/or lavage for:
        - PK (Pharmacology Core)
    - Cervical tissue for:
        - PK (Pharmacology Core)
    - Cervicovaginal lavage for:
        - PD (Protocol Support Core)

7.17 Specimen Collection and Processing

The study site will adhere to the standards of good clinical laboratory practice (https://www.niaid.nih.gov/sites/default/files/gclp.pdf) in accordance with current DAIDS Laboratory Requirements and the MTN-026 SSP Manual (www.mtnstopshiv.org) for proper collection, processing, labeling, transport, and storage of specimens at the local laboratory. Specimen collection, testing, and storage at the site laboratories will be documented 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.

7.18 Specimen Handling

Specimens will be handled in accordance with current requirements for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials.
(https://www.niaid.nih.gov/research/daids-clinical-research-policies-us-labs)

7.19 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

The site IoR is 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, and Protocol Safety Physicians will serve as the PSRT. The MTN Statistical Data Management Center (SDMC) prepares routine AE and clinical data reports (blinded to treatment assignment) for review by the PSRT, which meets via conference call approximately once per month or as needed throughout the period of study implementation 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. Adverse event reports submitted in an expedited manner to the DAIDS Safety Office will be forwarded to the DAIDS Medical Officer and SDMC 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 10.8.1), since no Data and Safety Monitoring Board oversight is planned for MTN-026. 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 the Site IoR will notify the responsible IRB/EC 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. The SMC will meet approximately once during study implementation, but not less than once a year. These reviews will take place 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 (i.e., once a participant is randomized). The term “investigational product” for this study refers to all study products.

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 recorded on study CRFs. Given the differences in appearance and viscosity between the two study products, study staff who apply a participant's gel are not to be the same clinic staff who assess his/her safety. 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 the appropriate AE Log CRF 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, 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 that asymptomatic BV and asymptomatic candidiasis will not be reportable AEs. In addition, fetal losses (e.g., spontaneous abortions, spontaneous fetal deaths, stillbirths) will not be reported as AEs. However, untoward maternal conditions that either result in or result from fetal losses are reported as reproductive system AEs. Further, changes in genital bleeding judged to be related to a woman's contraceptive use or return of menstruation postpartum will not be considered an AE, nor will a pelvic exam be required for follow-up.

Bleeding at the time of speculum, anoscope, or flexible sigmoidoscope insertion/removal and/or biopsy collection that is judged by the clinician to be within the range of normally anticipated will not be reportable as an AE. Bleeding of greater quantity or longer duration than typical will still be reported. Fecal urgency, bloating and flatulence associated with rectal procedures deemed to be within the range of normally expected will also not be reportable as AEs.

In cases where a genital or anorectal AE is covered in multiple tables, the Rectal Grading Table for Use in Microbicide Studies (Addendum 3 clarification dated May 2012) will take first priority followed by the Female or Male Genital Grading Tables (Addendum 1 [dated November 2007] and Addendum 2 [dated November 2007], respectively).

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 Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS Expedited Adverse Event (EAE) Manual, which is available on the Regulatory Support Center (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 AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at CRMSSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

Where DAERS has not been implemented, sites will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website, http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com) or call 1-800-537-9979 or 301-897-1709; or fax 1-800-275-7619 or 301-897-1710.

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 agents for which expedited reporting are required are: 0.05% dapivirine gel, Universal Placebo gel and the applicator.

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 2017and 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 expedited AE reporting period for this study begins at enrollment (i.e., randomization) 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 Pregnancy Outcomes

Pregnant women are excluded from this study.

A participant who is pregnant at study termination will continue to be followed until the pregnancy outcome is ascertained, see Section 9.5 for additional details. Pregnancy outcomes will not be expeditiously reported to 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.

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 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/ECs 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 s/he feels that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary. The IoR/designee 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.

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:

- Reported use of the following prohibited medications:
  - Heparin
  - Lovenox®
  - Warfarin
  - Plavix® (clopidogrel bisulfate)
  - Hormone-replacement therapy in tablet, injectable or gel form
- Acquisition of HIV infection; for those who acquire HIV study product should be held beginning immediately upon recognition of the first reactive rapid HIV test
- Pregnancy
- Breastfeeding
- Anorectal 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.

9.4 Follow-up in Response to Observed Adverse Events

Grade 1 or 2
In general, a participant who develops a Grade 1 or 2 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 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. If the IoR/designee opts to discontinue study product, the PSRT must be notified.

Grade 3 Unrelated
For participants who develop a Grade 3 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 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), determined to be unrelated to study product, the IoR must consult with PSRT regarding continued study product use. Pending a response from the PSRT, study product use may continue.

Grade 3 Related or Grade 4

For participants who develop a Grade 3 related or any Grade 4 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 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, study product must be permanently discontinued.

9.5 Pregnancy

For female participants, pregnancy testing will be performed at scheduled study visits and 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 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. 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 outcomes will be reported on relevant CRFs; outcomes meeting criteria for EAE reporting also will be reported on EAE forms. Participants who become pregnant may take part in observational studies, including pregnancy registries.

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 7.10.2, and may be offered enrollment in MTN-016 (www.mtnstopshiv.org), provided their study site is taking part in MTN-016.

9.6 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. The IoR/designee 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/ECs 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 Section 7.10.3 for details regarding the Early Termination Visit). Study staff members will record the reason(s) for all withdrawals in participants' study records.

10 STATISTICAL CONSIDERATIONS

10.1 Overview and Summary of Design

MTN-026 is a Phase I, multi-site, double-blind, two arm, randomized trial (2:1) that assesses the PK of 0.05% dapivirine gel exposure when applied once and then used daily for 7 days by healthy, HIV-uninfected, men and women under direct observation in the clinic. Approximately 27 individuals will be randomized.

10.2 Study Endpoints

Primary Endpoints
Consistent with the primary study objectives to (1) evaluate the safety of dapivirine gel formulation when applied rectally and (2) characterize the systemic and compartmental pharmacokinetics of dapivirine 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**
  Dapivirine concentrations
  - Plasma
  - Rectal fluid
  - Rectal mucosal tissue homogenates

10.3 Primary Study Hypotheses

MTN-026 hypothesizes that the gel containing dapivirine will be as safe and as well-tolerated as the gel containing placebo.

10.4 Sample Size and Power Calculations

10.4.1 Safety Endpoints

The proposed total sample size for assessing safety in the randomized portion of the study is approximately N=27 participants randomized into 2 arms in a 2:1 (active:control) ratio, giving 18 participants in the active arm and 9 participants in the control arm. 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, the table below presents the probability of observing zero, at least one, and two or more safety endpoints among the 18 participants in the active arm for various "true" event rates:

Table 16: Analysis of Safety Event Frequency

Event Rate	P (0 events | n=18)	P (≥1 event | n=18)	P (≥2 events | n=18)
1%	83.5	16.5	1.4
5%	39.7	60.3	22.6
10%	15.0	85.0	55.0
15%	5.4	94.6	77.6
25%	0.6	99.4	96.1
35%	0.0	100.0	100.0

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. The table 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 27 participants receiving a treatment regimen experience a safety event, the 95% exact 2-sided upper confidence bound for the true rate of such events in a particular arm of the study is 18.5%.

Table 17: Exact 2-sided 95% Confidence Intervals Based on Observing a Particular Rate of Safety Endpoints for Arms of Size 18

Observed event rate	Confidence interval (%)
0/18	0.0, 18.5
1/18	0.1, 27.3
2/18	1.4, 34.7
3/18	3.6, 41.4

An additional aim of the study is to compare the safety between the active and placebo products. Assuming a two-sided test with α=0.05 or α=0.10 and 80% power, the table below provides the difference in the rates of safety events (proportion of participants experiencing the safety event of interest) between the active and placebo arms that is detectable with 80% power for a given rate in the placebo arm. For example, if the true rate of a given toxicity endpoint in the placebo gel arm is 11.1% (1 of 9 participants experiencing a safety event), the proposed sample size provides 85% power to exclude safety endpoint rates greater than 67% (61% with α=0.10) which translates to at least 12 of 18 participants in the active arm. Hence, while comparisons will be made between the drug containing VR arm of the study and the placebo VR arm, the study will only have power to detect very large differences in safety event rates.

Table 18: Difference in the Rates of Safety Events

Rate in Placebo Gel Arm	Rate in a Drug Containing Gel Arm Detectable with at least 80% Power	
	α=0.05	α=0.10
11.1% (1 of 9)	67% (12 of 18)	61% (11 of 18)
22.2% (2 of 9)	78% (14 of 18)	72% (13 of 18)

10.5 Participant Accrual, Follow-up and Retention

Based on previous studies of rectal products with similar eligibility requirements, the accrual of approximately 27 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 their regularly scheduled safety evaluations. The site will target retention of 95% of enrolled participants over the follow-up period.

10.6 Randomization

Participants will be randomized in a 2:1 ratio to the two arms of the study stratified by study site. The randomization scheme will be generated and maintained by the MTN SDMC.

10.7 Blinding

Study staff and participants will be blinded to the random treatment assignment of all study participants. The study products will be packaged in individual identical wrappers. Blinding will be maintained until all data are entered into the study database, all study endpoint data and other data included in the final analysis have been cleaned and verified, and the data are ready for final analysis. This will be explained to participants as part of the study. See Section 8.3.1 for additional information.

There are no circumstances under which it is expected that unblinding will be necessary for the provision of medical treatment or to otherwise protect the safety of study participants. As described in Section 7.10.3, study product use may be discontinued for any reason by the Investigator or the participant. Knowledge of the specific product to which the participant was assigned should not be necessary to guide further follow-up and/or treatment. If an Investigator feels that specific product knowledge is necessary to protect participant safety, the Investigator will notify the PSRT to review and approve the request.

10.8 Data and Safety Monitoring and Analysis

10.8.1 Study Monitoring Committee

No Data and Safety Monitoring Board oversight is planned for this study. The MTN SMC will conduct interim reviews of study progress, including rates of participant accrual, retention, completion of primary and main secondary endpoint assessments, study or lab issues, and, in a closed report, safety data by arm of the study. These reviews will take place approximately once during study implementation, but not less than once a year. Reviews may also be conducted on an as needed basis. 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.

10.8.2 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). When use of formal testing to assess differences between users of the placebo gel and users of the gel containing dapivirine is required, the following methods will be used: for binomial response variables, chi-square tests and logistic regression (or exact testing methods); for continuous variables, t-tests and linear regression or nonparametric methods if data are non-Normal.

To assess the adequacy of the randomization, participants in each of the two arms will be compared for baseline characteristics including demographics and laboratory measurements using descriptive statistics. Due to the small sample size, formal comparisons will not be done.

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 study arm. Each participant will contribute once in each category (i.e., only for highest severity AE for each participant) for the calculation of event rates. Exact binomial confidence intervals will be calculated for each safety endpoint for each arm and Fisher's Exact test used to test for differences in event rates between the arms.

Pharmacokinetic Analysis

We will use descriptive statistics such as the mean and median and corresponding 95% confidence intervals to describe the dapivirine concentrations in all biological matrices assessed at all visits. Pre-dose concentrations during visits 4-7 will be used to assess approach to steady-state. The 30-60 minute sample will be used to describe the concentrations soon after a gel dose, and the 2 hour sample roughly approximates the time to peak concentrations among different matrices. Composite concentrations from the 2 hour sample (Visit 3 single dose, Visit 13 multiple dose) and concentrations from Visit 4-6 and Visits 14-16, respectively, for the single and multiple dose periods will be used to estimate terminal elimination half-life from each matrix sampled. The single dose Visit 3 and multiple dose Visit 7 will be compared to provide an estimate of concentration accumulation with multiple dosing.

10.8.3 Missing Data

A retention rate of 95% is targeted. Based on previous MTN trials, minimal missing data is expected. If missing data rates are higher than anticipated (over 10%), robust methods such as nonparametric tests and generalized estimating equations (GEE) using all available baseline predictors of the missing outcomes as covariates will be used to obtain less biased estimates of the treatment effect.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Study CRFs will be developed by the MTN SDMC in conjunction with the protocol team. Quality control reports and queries routinely will be generated and distributed by the SDMC to the study sites for verification and resolution. As part of the study activation process, the study sites must 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 regarding testing investigational products, the IoR/designee will maintain all study documentation for at least two years following the date of marketing approval for the study products being tested 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

All 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 the site 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

The IoR/designee 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. The IoR/designee also will allow inspection of all study-related documentation by authorized representatives of the MTN LOC, SDMC, LC, NIAID, FDA, OHRP, IRBs/ECs and other local and US regulatory authorities. A site visit log will be maintained at the study site 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, the IoR/designee will have obtained IRB/EC approval and the protocol will have been submitted to the FDA. The IoR/designee will permit audits by the NIH, the FDA, OHRP, MTN LOC, IRBs/ECs, SDMC, and other local and US regulatory authorities or any of their appointed agents.

13.1 Institutional Review Boards/Ethics Committees

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

Subsequent to the initial review and approval, the responsible IRBs/ECs must review the study at least annually. Each IoR/designee will make safety and progress reports to the IRBs/ECs 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/ECs. The study site will submit documentation of continuing review to the DAIDS Protocol Registration Office 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, each site must have the protocol and the protocol consent forms approved, as appropriate, by their local IRB/EC and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (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 when the DAIDS PRO receives a complete registration packet. Receipt of an Initial Registration Notification 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/EC 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 the site's 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.

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 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 all 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, documentation, and information-sharing across sites. 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.

Phlebotomy
Phlebotomy may lead to excessive bleeding, discomfort, feelings of dizziness or faintness, bruising, swelling, venous thrombosis, and/or infection.

Pelvic Exam & Cervical Biopsy Collection
Pelvic examination and vaginal fluid collection may cause mild discomfort and/or vaginal bleeding or spotting. Cervical biopsies carry the risk of discomfort or pain during the procedure and for a few hours afterwards. Participants may have mild vaginal spotting (bleeding) for one or two days, and will be instructed to avoid sexual intercourse for 7 days following biopsy collection.

Participants will be instructed not to use NSAIDs, aspirin (over 81 mg per day) and/or other drugs that are associated with the increased likelihood of bleeding for 3 days before and after the collection of the rectal biopsies. Female participants are to refrain from penile-vaginal intercourse for 3 days before and for 7 days following cervical biopsy collection. 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 (soaking through a pad in an hour or less) or if the participant develops any abnormal odor or discharge from the vagina.

Rectal Enema
An enema will be 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. 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 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.[34] 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.[35]

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 3 days before and after the flexible sigmoidoscopy. If participants engage in sexual intercourse before the biopsy has healed they may experience some temporary discomfort.

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.

Participants at sites requiring partner notification in response to diagnosed STI or HIV infection could have problems in their relationships with their sexual partners. Participants also could have problems in their partner relationships associated with maintenance of study-required abstinence.

Site staff will make every effort to protect participant privacy while in the study. Although study sites 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.

Adverse events among participants who dosed vaginally with the gel included:

- Metrorrhagia
- Headache
- Vaginitis bacterial
- Vaginal candidiasis
- Vulvovaginal pruritus
- Upper respiratory tract infection

These side effects may or may not be associated with rectal use of dapivirine 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

These side effects may or may not be associated with the use of dapivirine 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 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, pelvic 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, the IoR 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 informed consent form if they are willing to receive them.

In addition to informed consent form, 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 the study site, which will be detailed in the MTN-026 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 products
- The need to abstain from sexual intercourse for protocol defined periods, regardless of study treatment group
- The importance of participants in both study groups 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. The study site 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. In addition to local considerations, the protections described below will be implemented at the study site.

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 collection, 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' ID 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 and US regulatory authorities
- PPD
- Representatives of the MTN LOC, SDMC, and/or LC
- Study staff
- Site IRBs/ECs

The MTN has a Certificate of Confidentiality from the US Department of Health and Human Services that is applicable to the US sites participating in 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. Thus it serves to protect the identity and privacy of study participants.

13.7 Special Populations

13.7.1 Pregnant Women

Women who test positive for pregnancy at Screening or Enrollment Visits will not be eligible to participate in this study. Should a woman test positive for pregnancy after Enrollment, study product will be permanently discontinued and participants will be withdrawn from the study, per Section 7.10.2. During the informed consent process,

women will be informed that the study product is not a method of contraception and the effects of the study product on a developing human fetus are unknown.

All potential participants are required by the eligibility criteria for Screening and Enrollment to be sexually abstinent for the protocol defined periods and using effective contraception as defined by the protocol.

13.7.2 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/EC 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 informed consent forms.

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 each site and additionally will emphasize the unknown efficacy of the study products in preventing HIV-1 infection. In accordance with the policies of the NIH, participants must receive their HIV-1/2 test results to take part in this study.

13.11 Study Discontinuation

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

14 PUBLICATION POLICY

DAIDS/NIAID and MTN policies 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 IPM for review prior to submission.

15 APPENDICES

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

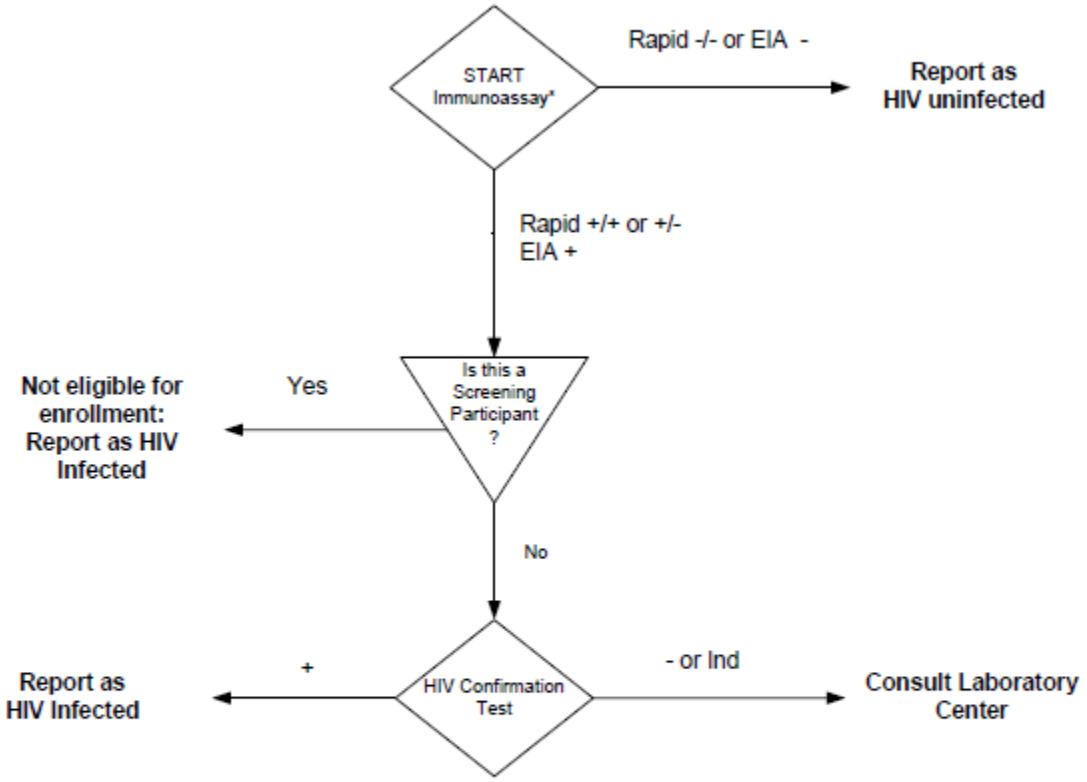
	Visit 1 SCR	Visit 2 ENR	Visit 3 Dosing Visit	Visit 4, 5, 6 (Sampling Assigned 4, 5, or 6)	Visit 7, 8, 9, 10, 11, 12: Dosing Visits*	Visit 13 (Final Dose)/ Early Term	Visit 14, 15, 16, (Sampling Assigned 14, 15 or 16)	Visit 17 F/U Contact
ADMINISTRATIVE AND REGULATORY								
Informed consent (SCR/ENR)	X							
Assess consent form comprehension	X							
Review informed consent/Confirm participant willingness to participate in study		X						
Assign PTID	X							
Collect demographic data	X							
Locator information	X	X	X	X	X	X	X	X
Assess eligibility	X							
Confirm participant eligibility		X						
Provide reimbursement	X	X	X	X	X	X	X	~
Schedule next study visit/contact	▲	▲	X	X	X	X	X	▲
Randomization		X						
BEHAVIORAL/COUNSELING								
HIV pre-/post-test and HIV/STI risk reduction counseling	X	X			▲ (Required at Visit 7)		▲ (Required at Visit 16)	
Protocol counseling (Adherence counseling and product use instructions)	X	X	X	X	X	X	X	
Behavioral assessment		X	X			□	X (Visit 14 only)	
In-depth interview			X			□	X (Visit 14 only)	
CLINICAL								
Medical history	X	X	X	X	X	X	X	
Menstrual history	♀	♀	♀	♀	♀	♀	♀	
General/Targeted physical exam	X	X	▲	▲	▲	▲	▲	
Perform pelvic examination	♀	♀	♀▲	♀ Φ (Visit 4, 5 or 6)	♀▲	♀	♀ Φ (Visit 14, 15 or 16)	
Perform rectal examination	X	X	X	Φ (Visit 4, 5 or 6)	▲ (Visits 7 & 8 only)	X	Φ (Visit 14,15 or 15)	
Concomitant medications	X	X	X	X	X	X	X	
Treat for UTI/RTI/STI or refer	▲	▲	▲	▲	▲	▲	▲	▲
Provide available test results	X	X	X	X	X	X	X	X
Record/update AEs			X	X	X	X	X	X
LABORATORY								
URINE								
Qualitative hCG	♀	♀			▲♀ (Required at Visit 7)		♀ (Visit 14 only)	
Dipstick UA	▲	▲	▲	▲	▲	▲	▲	
Urine Culture	▲	▲	▲	▲	▲	▲	▲	
NAAT for GC/CT	X	▲	▲	▲	▲	▲	▲	
BLOOD								
CBC with differential and platelets	X	▲	▲	▲	▲	▲	▲	
Chemistries (AST/ALT/Creatinine)	X	▲	▲	▲	▲	▲	▲ (Required at Visit 16)	
Plasma for archive/storage		X			X (Visit 7 only)		X (Visit 16 only)	
Plasma PK (Visits 3 and 13 at hour 0 and either 30-60 or 120 minutes; single time point at all			Φ	X	X (Visits 7 & 8 only)	Φ	X	

	Visit 1 SCR	Visit 2 ENR	Visit 3 Dosing Visit	Visit 4, 5, 6 (Sampling Assigned 4, 5, or 6)	Visit 7, 8, 9, 10, 11, 12: Dosing Visits*	Visit 13 (Final Dose)/ Early Term	Visit 14, 15, 16, (Sampling Assigned 14, 15 or 16)	Visit 17 F/U Contact
other visits)								
Syphilis Serology	X	▲	▲	▲	▲	▲	▲	
HIV-1/2 test	X	X			▲ (Required at Visit 7)		▲ (Required at Visit 16)	
HSV 1/2 serology	X							
HBsAg	X							
HCV serology	X							
Coagulation (PT/INR)	X							
PELVIC SAMPLES								
Vaginal NAAT for GC/CT	♀							
Cervicovaginal lavage for PK and PD (prior to biopsy collection)		♀		♀ Φ (Visit 4, 5 or 6)		♀	♀ Φ (Visit 14, 15 or 16)	
Cervicovaginal fluid for PK				♀ Φ (Visit 4, 5 or 6)		♀	♀ Φ (Visit 14, 15 or 16)	
Cervical tissue for PK				♀ Φ (Visit 4, 5 or 6)		♀	♀ Φ (Visit 14, 15 or 16)	
Pap test	♀▲							
ANORECTAL SAMPLES								
HSV 1/2 detection	▲	▲	▲	▲	▲	▲	▲	
Rectal fluid for adherence PK (Visits 3 and 13 at either 30-60 or 120 minutes)			Φ	Φ (Visit 4, 5 or 6)	X (Visits 7 & 8 only)	Φ	Φ (Visit 14, 15 or 16)	
Rectal tissue for PK (Visits 3 and 13 at either 30-60 or 120 minutes)			Φ	Φ (Visit 4, 5 or 6)		Φ	Φ (Visit 14, 15 or 16)	
Rectal fluid for mucosal safety (Visits 3 and 13 at either 30-60 or 120 minutes)		X	Φ			Φ		
Rectal tissue for mucosal safety (Visits 3 and 13 at 30-60 min or 120 minutes)		X	Φ			Φ		
Rectal tissue for PD (Visits 3 and 13 at either 30-60 or 120 minutes)		X	Φ	Φ (Visit 4, 5 or 6)		Φ	Φ (Visit 14, 15 or 16)	
Rectal enema effluent for PK and PD prior to biopsy collection		X		Φ (Visit 4, 5 or 6)		Φ	Φ (Visit 14, 15 or 16)	
NAAT for GC/CT	X	▲	▲	▲	▲	▲	▲	
STUDY PRODUCT/SUPPLIES								
Provision of study product			X		X	X Θ		
Provision of lubricant			X		X	X Θ		
Observe dose application(s)			X		X	X Θ		
Collect unused study product						X		
Offer condoms				X (Visit 6 only)				

X = Required, ▲ = As Indicated, ♀ = Female participants, Φ = Participants will be assigned to provide samples at specific dates and/or times, ~ Sites to reference SOPs regarding participant reimbursement , □= Required if Early Termination only, Θ= Omit at Early Termination

** The washout period should coincide with female participants' menses.*

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



*CLIA certified labs may perform 1 rapid test
Ind: Indeterminate test results
EIA: Enzyme Immunoassay

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

DIVISION OF AIDS, NIAID, NIH

MTN-026

A Randomized, Double Blind, Placebo-Controlled, Phase 1 Safety and Pharmacokinetic Study of Dapivirine Gel (0.05%) Administered Rectally to HIV-1 Seronegative Adults

Version 2.0

July 21, 2017

PRINCIPAL INVESTIGATOR: ***[Sites to insert]***
PHONE: ***[Sites to insert]***
Short Title for the Study: Dapivirine Gel Rectal Safety and PK Study

INFORMED CONSENT

You are being asked to take part in this research study because you are a healthy, HIV-negative man or woman between the ages of 18 and 45 years old and reported at least one experience of receptive anal sex in the last year. Approximately 27 people will participate in this study. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH). The products being used in this study include dapivirine gel and placebo gel; these products will be explained later in this document. The study products are supplied by the MTN. The study gel is inserted with an applicator into the rectum. Participants are asked to apply one dose of study gel 8 times over the course of 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.

It is important to know that your participation in this research is your decision and taking part in this study is completely voluntary (see Your Rights as a Research Participant/Volunteer for more information).

WHAT IS THE PURPOSE OF THIS STUDY?
The main purpose of this research study is to find out if gel containing the study drug dapivirine is safe when inserted into the rectum after a single dose, followed by 7 daily doses. Another purpose of this study is to better understand how dapivirine is absorbed by and eliminated from the body.

STUDY PRODUCT
Dapivirine has been previously tested for safety, acceptability, and HIV prevention. HIV is the virus that causes AIDS. Now researchers would like to know more about the safety of dapivirine gel applied rectally and how it is processed within the body. To do this, they first need to better understand what effect this drug has on the body, including in and around the rectum and anus.

Dapivirine works in a specific way to potentially prevent HIV; it is thought to prevent HIV from making copies of itself, thereby stopping the spread of HIV in the body.

This study is <u>not</u> testing to see if dapivirine prevents HIV infection. Researchers do not yet know if this drug will work in humans to protect against HIV. There are only two known effective ways to prevent HIV: condoms and/or the use of pre-exposure prophylaxis (PrEP). PrEP is a new 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.

While dapivirine has been tested before in humans, this is the first time it has been tested as a rectal gel.

STUDY GROUPS
All of the eligible participants will be randomized to one of two rectal gel study groups:

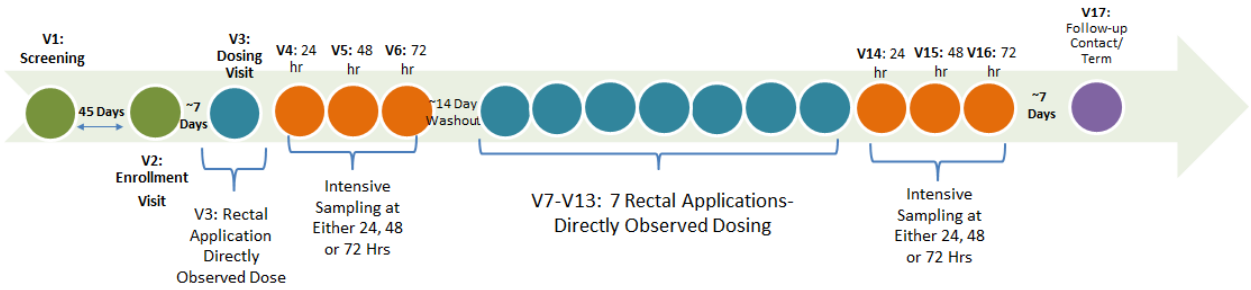
- Dapivirine gel, or
- Placebo gel (which has no dapivirine or any other active ingredient(s) in it).

Approximately 18 people will be in the dapivirine gel study group and 9 people will be in the placebo gel group. You will be assigned to a group by random chance (the equivalent of throwing dice). It is important that you know that you will receive a gel that may or may not contain dapivirine. This study is double-blind, which means neither you nor the study clinician will know which group you are in until the study is completed. You will be asked to apply the study gel in your rectum once daily 8 times over the course of the study.

Both study groups are important to this study. No matter which study group you are in, you must remember that we do not know if the drug contained within the gel will work to protect men and women from getting HIV. Participants in each study group will have the same study visit schedule.

WHAT WILL HAPPEN DURING THE MTN-026 STUDY VISITS?
The MTN-026 study includes a total of 16 clinic visits and one contact (via phone or in person) including the Screening Visit which is taking place today, if you decide to sign this informed consent form. Visits will take place here, at this study clinic.

[SITES TO UPDATE THE STUDY VISIT/PROCEDURE DESCRIPTIONS TO ALIGN WITH THE FLOW OF STUDY VISITS.]



Screening Visit:

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

- Study staff will ask you where you live and other questions about you, your medical health (including what medications you are taking), menstrual history (for females), your sexual practices and your understanding of the study requirements.
- You will be asked to provide and/or update study staff with your contact information (i.e. about how we can contact you).
- Ask you to abstain from some medications at certain timepoints during the study:

Medication:	*Abstain For How Long?*
• NSAIDs (nonsteroidal anti-inflammatory drugs) • Aspirin (over 81 mg per day) • Any other drug that is associated with an increased likelihood of bleeding	• 72 hours (3 days) prior to study visits at which tissue samples are scheduled to be collected • 72 hours (3 days) after each visit at which tissue samples were collected

- Study staff will:
  - Perform a physical exam.
  - Talk with you about sexually transmitted infections (STIs), HIV, HIV/STI testing, and ways to avoid HIV and other infections passed through sex.
  - Talk with you about the requirements of the study including, but not limited to, restrictions on sexual practices:

(**I AM MALE**) For men, sex for this study is defined as anal intercourse, receptive oral anogenital stimulation (e.g., partner placing their mouth on your anogenital area), finger stimulation, and the use of sex toys. *Males will be asked to abstain from the following activities at these timepoints during the study*:

Activity:	*Abstain For How Long?*

• Receptive anal intercourse
• Receptive oral anogenital stimulation (e.g., partner placing their mouth on your anogenital area)
• Inserting any non-study products or objects into your rectum, including:
  ○ Rectal medications
  ○ Enemas
  ○ Lubricants
  ○ Sex toys (dildos, anal plugs, etc.)
  ○ Fingers
	• 72 hours (3 days) prior to each study visit
	• On the day(s) you dose with gel
	• 72 hours (3 days) following biopsy collection

(I AM FEMALE) For women, sex for this study is defined as receptive penile-vaginal intercourse, anal intercourse, receptive oral intercourse, finger stimulation, and the use of sex toys. *Females will be asked to abstain from the following activities at these timepoints during the study*:

Activity:	*Abstain For How Long?*

• Anal intercourse
• Receptive penile-vaginal intercourse
• Receptive oral anogenital stimulation (e.g., partner placing their mouth on your anogenital area)
• Inserting any non-study products or objects into your **vagina**, including:
  ○ Vaginal medications
  ○ Douches
  ○ Lubricants
  ○ Sex toys (dildos, etc.)
  ○ Fingers
• Inserting any non-study products or objects into your **rectum**, including:
  ○ Rectal medications
  ○ Enemas
  ○ Lubricants
  ○ Sex toys (dildos, anal plugs, etc.)
  ○ Fingers
	• 72 hours (3 days) prior to each study visit
	• On the day(s) you dose with gel
	• 1 week (7 days) following biopsy collection

At your Screening Visit, study staff will also:

- Test your urine for sexually-transmitted diseases and other infections
- Take 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, herpes simplex virus (HSV), hepatitis B, hepatitis C, 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.

- Perform a rectal examination, during which rectal swabs will be taken. These will be used to test for infections passed through sex. To collect these samples, study staff will insert a short hollow tube called an anoscope into your rectum. The clinician will insert swabs and/or sponges through the hollow tube to collect the sample.
- (For females):
  - Test your urine for pregnancy
    - If you are pregnant you cannot join this study.
    - Study staff will talk with you about ways to avoid becoming pregnant.
- Perform a pelvic examination:
  - The study clinician will use a speculum, a plastic or metal instrument used to separate the walls of the vagina, to check your vagina and cervix (the tissue that attaches the vagina to the uterus) for signs of infection, and other problems. They will also take some fluids to test for sexually transmitted infections and diseases (commonly known as STIs or STDs) and other problems.
  - The study staff may also collect samples from your cervix for a "Pap test" or "Pap smear". Study staff will inform you of the results of your Pap test. It takes about ***[SITES TO INSERT AMOUNT OF TIME]*** before Pap test results are ready If you are less than 21 years of age, a Pap test is not needed to join the study. If you are 21 years of age or older and can provide a written report confirming either a normal Pap test in the past 3 years, or an abnormal Pap test for which no treatment was required, you will not need to have a Pap test taken at this screening visit. The results of your Pap test may affect whether or not you can join the study.
- Give you treatment or refer you for treatment of sexually transmitted infections, if needed.
- Inform you about other services, if needed.
- Provide you with the results of your tests, when available. It is expected that all of your results will be available by ***[SITES TO SPECIFY TIMEFRAME]***.
- Reimburse you 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-026, 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.]*** In addition to the procedures listed below, it is possible that study clinicians may need to perform additional tests if medically necessary (for example, you report having symptoms of a urinary, genital, or other infection and/or other issues).

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

- Answer questions to confirm you are able and willing to join the study
- Provide and/or update study staff with your contact information (i.e. about where you live and how we can contact you)
- Be assigned to one of two study groups:
    - This may affect how long some of your study visits will last. For example: At some of your study visits after the Enrollment Visit, the rectal fluid and rectal tissue samples may be collected one time after inserting the study gel, either between 30-60 minutes later or two hours later, depending on which group you have been assigned to. 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 for these visits.
- Talk with study staff about the following:
    - The rules of the study and how to follow the rules, including the sexual abstinence requirement. **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)
- You will be asked some questions about your experience and comfort using rectal products, as well as douching or other rectal hygiene practices, among other things. Some of these questions may be asked via computer.
- Study staff will also take 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:
        - At this visit and some other visits as noted below, your blood is tested for HIV. 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. If the test shows you have HIV, 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 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 and what effect the drug has. 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 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 (rectal lavage). 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. 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 study clinician will then collect approximately 20 tissue samples, each about the size of a grain of rice.
- (For females):
    - Update study staff about your menstrual history
    - Test your urine for pregnancy
    - Have a pelvic exam
        - The study clinician will use a speculum.
        - A vaginal wash will be performed. The study clinician will rinse your vagina and cervix with about 2 teaspoons of sterile (very clean) fluid, and then will collect the fluid in a tube for testing. The fluid collected will be used for research purposes only, to better understand how the study drug enters and exits the body. When these samples are collected at future visits, similar tests will be done.
- Receive treatment or be referred for treatment issues that the study staff may find
- Receive test results, if available
- Be reimbursed for your visit
- Schedule your next visit, if applicable.

Dosing Visit (Visit 3):

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. In addition to the procedures listed below, it is possible that study clinicians may need to perform additional tests if medically necessary (for example, you report having symptoms of a urinary, genital, or other infection and/or other issues).

You will:
- Update study staff with your contact information
- Review the rules of the study and how to follow the rules, 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)
- (For females) Update study staff about your menstrual history
- Have a computer-administered interview. This interview may take approximately 45-60 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 administering the gel in the clinic.

- Study staff will insert one dose of study gel using a lubricated applicator, perform a rectal examination and collect rectal fluid and tissue to help researchers better understand how the study drug enters and exits the body and what effect the drug has. These samples may be collected one time after inserting the study gel, either between 30-60 minutes later or two hours later, depending on which group you have been assigned to.
    - 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 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 (rectal lavage). 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. 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 study clinician will then collect approximately 20 tissue samples, each about the size of a grain of rice.
- You will be asked some questions about your experience using the study product. Some of these questions may be asked via computer.
- Study staff will:
    - Take blood samples ***[SITES TO INSERT AMOUNT]*** at several timepoints including prior to gel administration and either between 30-60 minutes later or two hours after gel administration, depending on which group you have been assigned to. An intravenous cannula (IV tube) may be placed for 1 to 2 hours after you apply the rectal gel for the blood draws.
    - Give you any available test results and provide you with treatment or refer you for treatment if your test results indicate that you require it.
    - Reimburse you for your visit
    - Schedule your next visit or contact.

Sampling Visits (Visits 4-6):

Your Sampling Visits will take place approximately 24 hours (1 day), 48 hours (2 days), and 72 hours (3 days) after you receive your first dose of the study gel. Each of these visits will take between ***[SITES TO SPECIFY TIMEFRAME]*** to complete. Some procedures (noted below) will not take place at every visit, but rather will take place at one of the three sampling visits. In addition to the procedures listed below, it is possible that study clinicians may need to perform additional tests if medically necessary (for example, you report having symptoms of a urinary, genital, or other infection and/or other issues).

At these visits, you will:

- Update study staff with your contact information

- Review the rules of the study and how to follow the rules, 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)
- (For females) Update study staff about your menstrual history
- Study staff will:
    - Perform a rectal examination
    - Rectal samples (fluid and tissue) will be collected (Visit 4, Visit 5 or Visit 6 only). These samples will help researchers to better understand how the study drug enters and exits the body and what effect the drug has.
        - 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 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 (rectal lavage). 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. 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 study clinician will then collect approximately 20 tissue samples, each about the size of a grain of rice.
    - (For females) Perform a pelvic exam at Visit 4, Visit 5 or Visit 6 only. A speculum will be inserted and the following will be collected:
        - Pelvic samples including vaginal fluid and cervical tissue to measure the amount of the study drug in your body. A vaginal wash will be performed. The study clinician will rinse your vagina and cervix with about 2 teaspoons of sterile (very clean) fluid, and then will collect the fluid in a tube for testing. In addition, approximately 2 small tissue samples (biopsies), each about the size of a grain of rice, will then be taken from your cervix.
        - Take a blood sample [SITES TO INSERT AMOUNT]:
            - To help researchers to better understand how the study drug enters and exits the body
    - Give you any available test results
    - Be offered study condoms (Visit 6)
    - Reimburse you for your visit
    - Schedule your next visit or contact.

Dosing Visits (Visits 7-12):

Your Dosing Visits will take place starting approximately two weeks after Visit 6. They will be scheduled to take place approximately 24 hours (1 day) apart. These visits will take between ***[SITES TO SPECIFY TIMEFRAME]*** to complete. Some procedures (noted below) will not take place at every visit. In addition to the procedures listed below, it is possible that study clinicians

may need to perform additional tests if medically necessary (for example, you report having symptoms of a urinary, genital, or other infection and/or other issues).

At these visits, you will:

- Update study staff with your contact information
- Review the rules of the study and how to follow the rules, 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)
- (For females) Update study staff about your menstrual history
- Study staff will:
    - Perform a rectal examination (Visits 7 and 8), during which rectal swabs will be taken to help researchers to better understand how the study drug enters and exits the body.
        - To collect these samples, study staff will insert a short hollow tube called an anoscope into your rectum. The clinician will insert swabs and/or sponges through the hollow tube to collect the samples.
    - Take a blood sample [SITES TO INSERT AMOUNT]:
        - In case there's a question about your test results at a later time. (Visit 7)
        - To test your blood for HIV, the virus that causes AIDS. (Visit 7)
        - To help researchers to better understand how the study drug enters and exits the body (Visit 7 and 8)
    - (For females) Test your urine for pregnancy (Visit 7)
    - Give you one dose of the study gel. Study staff may help you insert the study gel if you cannot do it on your own. Study lubricant and an applicator pre-filled with the study gel will be provided. Study staff will observe you inserting the gel to help ensure the gel is inserted successfully and correctly. In addition, at Visit 7 you will receive an extra dose of gel and lubricant to take home with you to use in the event that you cannot attend your clinic visit. Study staff will tell you more about this later.
    - Talk with you (Visit 7) about sexually transmitted infections (STIs), HIV, HIV/STI testing, and ways to avoid HIV and other infections passed through sex
    - Give you any available test results
    - Reimburse you for your visit
    - Schedule your next visit or contact.

Final Dosing Visit (Visit 13):

Your Final Dosing Visit will take place approximately 24 hours (1 day) after Visit 12. This visit will take between ***[SITES TO SPECIFY TIMEFRAME]*** to complete. In addition to the procedures listed below, it is possible that study clinicians may need to perform additional tests if medically necessary (for example, you report having symptoms of a urinary, genital, or other infection and/or other issues).

At this visit, you will:

- Update study staff with your contact information
- Review the rules of the study and how to follow the rules, 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)
- (For females) Update study staff about your menstrual history
- Study staff will:
    - Give you one dose of the study gel. Study staff may help you insert the study gel if you cannot do it on your own. Study lubricant and an applicator pre-filled with the study gel will be provided. Study staff will observe you inserting the gel to help ensure the gel is inserted successfully and correctly.
    - Perform a rectal examination and collect rectal fluid and tissue to help researchers better understand how the study drug enters and exits the body and what effect the drug has. These samples may be collected one time after inserting the study gel, either between 30-60 minutes later or two hours later, depending on which group you have been assigned to.
        - 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 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 (rectal lavage). 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. 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 study clinician will then collect approximately 20 tissue samples, each about the size of a grain of rice.
    - (For females) Perform a pelvic examination and collect:
        - Pelvic samples including vaginal fluid and cervical tissue to measure the amount of the study drug in your body. A vaginal wash will be performed. The study clinician will rinse your vagina and cervix with about 2 teaspoons of sterile (very clean) fluid, and then will collect the fluid in a tube for testing. In addition, approximately 2 small tissue samples (biopsies), each about the size of a grain of rice, will then be taken from your cervix.
    - Take a blood sample ***[SITE TO INSERT AMOUNT]*** to help researchers to better understand how the study drug enters and exits the body at two timepoints, prior to gel administration and either between 30-60 minutes later or two hours later, depending on which group you have been assigned to. An intravenous cannula (IV tube) may be placed for 1 to 2 hours after you apply the rectal gel for the blood draws.
    - Collect any unused study gel, applicators or lubricant
    - Give you any available test results
    - Reimburse you for your visit
    - Schedule your next visit or contact.

Sampling Visits (Visits 14-16):

Your Sampling Visits will take place approximately 24 hours (1 day), 48 hours (2 days), and 72 hours (3 days) after you receive your last dose of the study gel. These visits will take between ***[SITES TO SPECIFY TIMEFRAME]*** to complete. Some procedures (as noted below) will not take place at every visit; but rather will take place at one of the 3 sampling visits. In addition to the procedures listed below, it is possible that study clinicians may need to perform additional tests if medically necessary (for example, you report having symptoms of a urinary, genital, or other infection and/or other issues).

At these visits, you will:

- Update study staff with your contact information
- Review the rules of the study and how to follow the rules, 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)
- (For females) Update study staff about your menstrual history
- You will be asked some questions about your experience using the study product (Visit 14). Some of these questions may be asked via computer.
- Have a computer-administered interview (Visit 14). This interview may take approximately 45-60 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 administering the gel in the clinic.
- Perform a rectal exam, during which time rectal samples (fluid and tissue) will be collected (Visit 14, Visit 15 or Visit 16 only). These samples will help researchers to better understand how the study drug enters and exits the body and what effect the drug has.
    - 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 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 (rectal lavage). 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. 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 study clinician will then collect approximately 20 tissue samples, each about the size of a grain of rice.
- (For females) Perform a pelvic examination and collect (Visit 14, Visit 15 or Visit 16 only):
    - Pelvic samples including vaginal fluid and cervical tissue to measure the amount of the study drug in your body. A vaginal wash will be performed. The study clinician will rinse your vagina and cervix with about 2 teaspoons of sterile (very clean) fluid, and then will collect the fluid in a tube for testing. In addition, approximately 2 small tissue samples (biopsies), each about the size of a grain of rice, will then be taken from your cervix.

- Provide a blood sample [SITE TO INSERT AMOUNT]:
    - In case there's a question about your test results at a later time. (Visit 16)
    - To measure the amount of study drug in your blood (Visits 14, 15, 16)
    - To check the health of your blood, liver and kidneys (Visit 16)
    - To test your blood for HIV (Visit 16)
- (For females) Test your urine for pregnancy (Visit 14)
- Talk with you (Visit 16) about sexually transmitted infections (STIs), HIV, HIV/STI testing, and ways to avoid HIV and other infections passed through sex
- Give you any available test results
- Reimburse you for your visit
- Schedule your next visit or contact.

Last Study Visit or Contact (Visit 17)

Your Last Study Visit or Contact will take place approximately one week after Visit 16. 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
- Be reimbursed for your visit
- Schedule your next visit or contact (if necessary)
- Be given any available test results
- Discuss any health or medical problems you may have had since your last visit (including what medications you are taking)

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.

Additional Visits and 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
- Rectal exam
- Test anal/rectal samples for sexually-transmitted diseases
- Test cervix/vaginal samples for sexually-transmitted diseases
- Test your urine for sexually-transmitted diseases or other infections
- Test your blood for sexually-transmitted diseases
- Test your blood to check the health of your blood, liver and kidneys
- Give you treatment or refer you for treatment of sexually transmitted infections 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.

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.

RISKS AND/OR DISCOMFORTS
Whenever your blood is drawn, you may have:
- Excessive bleeding
- Discomfort
- Feelings of dizziness or faintness
- Bruising, swelling and/or infection
- Development of a blood clot within a vein

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.

During rectal exams and collection of rectal fluid and tissue samples, insertion of a lubricated anoscope will likely cause mild discomfort. Insertion of rectal swabs and sponges may also cause mild discomfort, in addition to a slight risk of bleeding. A flexible sigmoidoscopy is a commonly practiced medical procedure where a flexible tube with a light source 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. 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, as well as flatulence following the procedure. Endoscopic biopsies 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 approximately once out of every 1,000 procedures. If this extremely rare complication occurs, antibiotics and surgery to repair the tear may be necessary.

(For females) During pelvic exams and vaginal fluid collection you may feel discomfort or pressure in your vagina and/or pelvis. Due to the pelvic exam you may also have vaginal bleeding or spotting, which will stop shortly after the examination. Cervical biopsies carry the risk of discomfort or pain during the procedure and for a few hours afterwards. Participants may have spotting (bleeding) for one or two days. With cervical biopsies there is also a small risk of infection and heavier bleeding. You may also be at increased risk for STIs and HIV acquisition,

if exposed. You will be encouraged to call the clinic to report any problems after the collection, especially if heavy bleeding is noted (soaking through a pad or tampon in an hour or less) or if you develop any abnormal vaginal odor or discharge.

Study Gels
The study rectal gel can cause some side effects for both males and females. We do not yet know all the side effects of the gels. Some, but not all, participants who used gels in other studies have had:

- Discharge from the rectum
- Irritation and discomfort
- Abdominal bloating, feeling full, or a sense of abdominal pressure
- 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

These side effects may or may not be associated with rectal use of dapivirine gel.

Study Drug
The following side effects have been associated with the use of dapivirine in male and female participants in other studies. These side effects may or may not be associated with the use of dapivirine when the drug is placed into a rectal gel:

- Headache
- Abdominal pain
- Hypophosphataemia (Abnormally low level of phosphates in the blood)
- Neutropenia (Abnormally low level of white blood cells in the blood)

(For females)

- Vaginal bleeding at irregular intervals, particularly between your expected menstrual periods
- Vaginal discharge
- Vaginal candidiasis, i.e. yeast infection
- Urinary tract infection
- Gynecological chlamydia infection
- Bacterial Vaginosis
- Upper respiratory tract infection, such as the common cold

For females, the most common side effects associated with dapivirine in previous studies (in which dapivirine was placed into a vaginally-applied gel or a vaginal ring):

- Vaginal discharge
- Irregular vaginal bleeding
- Bacterial vaginosis

(For both males and females)
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.

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.

We will make every effort to protect your privacy and confidentiality during the study visits. Your visits will take place in private. However, 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. 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.

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 should NOT identify anyone in the interviews and 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).

(For Females) Pregnancy and Breastfeeding
The study gel does not prevent pregnancy. 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 have been sexually abstinent for more than 90 days and plan to continue for the duration of the study.

We do not know what effect dapivirine has on pregnancy, including the effect of dapivirine 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. *[SITES*

TO INCLUDE/AMMEND THE FOLLOWING: We may also contact you about a study that collects information about pregnancy and children up to one year old.]

BENEFITS

You will receive no direct benefit from receiving study gel during your participation in this study. Information learned from this study may help in the development of ways to prevent the spread of HIV in the future. You will receive pelvic (females) and rectal exams and counseling and testing for HIV and STIs. You will also have tests to check the overall health of your liver, kidneys, and blood cells.

This study cannot provide you with general medical care, but study staff will refer you to other available sources of care.

You will receive free male condoms, if you need them. If you are infected with HIV, you will be referred for medical care, counseling, and other services available to you. Medical care for HIV infection will not be part of this study. You will need to receive care for HIV infection from your own health care provider or we will provide you with a referral. If you have an STI diagnosed, you will receive medicine or a referral, if needed, and study staff will discuss options available for counseling and treatment of your partner.

NEW INFORMATION

You will be told of any new information learned during this study that might affect your willingness to stay in the study. For example, if information becomes available that shows that the gel may be causing bad effects, you will be told about this. You will also be told when study results may be available, and how to learn about them.

WHY YOU MAY STOP TAKING THE STUDY DRUG EARLY OR BE WITHDRAWN FROM THE STUDY WITHOUT YOUR 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 US Office for Human Research Protections (OHRP), MTN, the local government or regulatory agency, or the Institutional Review Board (IRB)/ the Ethics Committee (EC). An IRB or EC 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
- (Females) You become pregnant or begin breastfeeding
- You are not able to keep appointments or follow study requirements
- Other reasons that may prevent you from completing the study successfully

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 Visit 13, 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.

ALTERNATIVE OPTIONS
We do not know if the drug contained within the gel works to protect men and women from getting HIV. Currently there are two known methods to reduce your risk of contracting HIV, the use of condoms and/or the use of oral pre-exposure prophylaxis (PrEP) medication, Truvada®. If you are interested in these alternative options you may want to discuss them with your doctor.

COSTS TO YOU
[Site to complete according to site capacity] There is no cost to you for study related visits, the rectal gel, physical/pelvic/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.

REIMBURSEMENT
[***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.

CONFIDENTIALITY
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. 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. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by:
- 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 and US regulatory authorities
- Study monitors
- Site IRB/EC
- Study staff

*[**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**].*

[US 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.

RESEARCH-RELATED INJURY

*[**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.

YOUR RIGHTS AS A RESEARCH PARTICIPANT/VOLUNTEER

*[**SITES 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. If you want the results of the study after the study is over, let the study staff members know.

PROBLEMS OR 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/EC 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, vaginal fluid, cervical tissue, cervical fluid, rectal tissue and rectal 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. 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. 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 these specimens. The specific 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 and control testing, ensuring that tests function correctly and supply accurate data. No genetic testing (limited or genome-wide) is planned on leftover samples that are stored for the purposes of future research. It is important that you know that any future testing/studies planned for these specimens must be approved by an Ethics Committee/Institutional Review Board before they can be done. You can withdraw your consent for the storage and future testing of specimens at any time by providing a request 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 take part in 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

Reference List

1. International Partnership for Microbicides (IPM). Investigator's Brochure: Dapivirine Vaginal Gel. Version 7.0. 8-28-2013.

2. Clark MR, Friend DR. Pharmacokinetics and topical vaginal effects of two tenofovir gels in rabbits. AIDS Res Hum Retroviruses 2012;28(11):1458-1466.

3. Fletcher P, Harman S, Azijn H et al. Inhibition of human immunodeficiency virus type 1 infection by the candidate microbicide dapivirine, a nonnucleoside reverse transcriptase inhibitor. Antimicrob Agents Chemother 2009;53(2):487-495.

4. Di FS, Van RJ, Giannini G et al. Inhibition of vaginal transmission of HIV-1 in hu-SCID mice by the non-nucleoside reverse transcriptase inhibitor TMC120 in a gel formulation. AIDS 2003;17(11):1597-1604.

5. CONRAD. Investigator's Brochure: Universal Placebo Gel. 2005.

6. Tien D, Schnaare RL, Kang F et al. In vitro and in vivo characterization of a potential universal placebo designed for use in vaginal microbicide clinical trials. AIDS Res Hum Retroviruses 2005;21(10):845-853.

7. Gilead Sciences. Investigator's Brochure: Tenofovir Gel (GS-1278). Second Edition. 3-31-2005.

8. Patton DL, Sweeney YT, Balkus JE et al. Preclinical safety assessments of UC781 anti-human immunodeficiency virus topical microbicide formulations. Antimicrob Agents Chemother 2007;51(5):1608-1615.

9. Guttner J, Klaus S, Heinecke H. [Embryotoxicity of intraperitoneally administered hydroxyethylcellulose in mice (author's transl)]. Anat Anz 1981;149(3):282-285.

10. International Partnership for Microbicides. Investigator's Brochure: Dapivirine Vaginal Gel, Including Rectal Gel (Version 8.0 Final). 1-178. 9-4-2015.

11. International Partnership for Microbicides (IPM). Investigator's Brochure: Dapivirine Vaginal Gel (Version 7.0 Final). Version 7.0. 8-28-2013.

12. Bunge KE, Dezzutti CS, Rohan LC et al. A Phase 1 trial to assess the safety, acceptability, pharmacokinetics, and pharmacodynamics of a novel dapivirine vaginal film. JAIDS 2016;71(5):498-505.

13. Robinson JA. FAME 02B Study: TEAEs (Personal Communication). Conser E, editor. 10-4-2016. 10-10-2016.

14. International Partnership for Microbicides. PK/PD of Single Dose Dapivirine Vaginal Film (FAME-02B). 8-29-2016. ClinicalTrials.gov. 10-7-2016.

15. Baeten JM, Palanee-Phillips T, Brown ER et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. N Engl J Med 2016;375(22):2121-2132.

16. International Partnership for Microbicides (IPM). Investigator's Brochure: Dapivirine Vaginal Ring (Version 10.0 Final). 3-9-2016.

17. Safety and efficacy of dapivirine vaginal ring for HIV-1 prevention in African women. 2016 Conference on Retroviruses and Opportunistic Infections (CROI); 16 Feb 22; 2016.

18. Safety, Pharmacokinetics and Pharmacodynamics of Two Daily Dapivirine Vaginal Microbicide Gels for HIV Prevention. International Microbicides Conference M2012, Sydney, 2012.; 2012.

19. CSR Reference. Final Clinical Study Report for IPM 014A - A double-blind, randomized, placebo-controlled Phase I/II trial to evaluate the safety and acceptability of dapivirine Gel 4759, 0.05% 2.5g, a vaginal microbicide, conducted using daily monitored adherence in healthy HIV-negative women. 4-18-2013.

20. Cranston RD, Hoesley C, Carballo-Dieguez A et al. A randomized male tolerance study of dapivirine gel following multiple topical penile exposures (MTN 012/IPM 010). AIDS Res Hum Retroviruses 2014;30(2):184-189.

21. Robinson JA, Marzinke MA, Bakshi RP et al. Comparison of dapivirine vaginal gel and film formulation pharmacokinetics and pharmacodynamics (FAME 02B) (Epub ahead of print). AIDS Research and Human Retroviruses 2016.

22. Nel AM, Smythe SC, Habibi S, Kaptur PE, Romano JW. Pharmacokinetics of 2 dapivirine vaginal microbicide gels and their safety vs. Hydroxyethyl cellulose-based universal placebo gel. J Acquir Immune Defic Syndr 2010;55(2):161-169.

23. Nel A SSHSRJ. Comparison of Safety and PK of Two Formulations of Dapivirine Vaginal Gel in Healthy, HIV-Negative Women [abstract]. 16th Conference on Retroviruses and Opportunistic Infections . 2-8-2009.

24. Dreisbach R. Handbook of Poisoning: diagnosis & treatment. 9th ed. ed. Los Altos, Calif.: Lange Medical Publications; 1977.

25. Schwartz JL, Ballagh SA, Kwok C et al. Fourteen-day safety and acceptability study of the universal placebo gel. Contraception 2007;75(2):136-141.

26. Anton PA, Saunders T, Elliott J et al. First phase 1 double-blind, placebo-controlled, randomized rectal microbicide trial using UC781 gel with a novel index of ex vivo efficacy. PLoS One 2011;6(9):e23243.

27. Anton PA, Cranston RD, Kashuba A et al. RMP-02/MTN-006: A phase 1 rectal safety, acceptability, pharmacokinetic, and pharmacodynamic study of tenofovir 1% gel compared with oral tenofovir disoproxil fumarate. AIDS Res Hum Retroviruses 2012;28(11):1412-1421.

28. McGowan I, Hoesley C, Cranston RD et al. A phase 1 randomized, double blind, placebo controlled rectal safety and acceptability study of tenofovir 1% gel (MTN-007). PLoS One 2013;8(4):e60147.

29. Safety and pharmacokinetics/pharmacodynamics of dapivirine and maraviroc vaginal rings. 21st Conference on Retroviruses and Opportunistic Infections; 14 Mar 3; 2014.

30. Carballo-Dieguez A, Dolezal C, Bauermeister JA, O'Brien W, Ventuneac A, Mayer K. Preference for gel over suppository as delivery vehicle for a rectal microbicide: results of a randomised, crossover acceptability trial among men who have sex with men. Sex Transm Infect 2008;84(6):483-487.

31. Carballo-Dieguez A, Giguere R, Dolezal C et al. Rectal-specific microbicide applicator: evaluation and comparison with a vaginal applicator used rectally. AIDS Behav 2014;18(9):1734-1745.

32. Ventuneac A, Carballo-Dieguez A, McGowan I et al. Acceptability of UC781 gel as a rectal microbicide among HIV-uninfected women and men. AIDS Behav 2010;14(3):618-628.

33. Morrow KM, Rosen RK, Salomon L et al. Using integrated mixed methods to develop behavioral measures of factors associated with microbicide acceptability. Qual Health Res 2011;21(7):987-999.

34. Gatto NM, Frucht H, Sundararajan V, Jacobson JS, Grann VR, Neugut AI. Risk of perforation after colonoscopy and sigmoidoscopy: a population-based study. J Natl Cancer Inst 2003;95(3):230-236.

35. The safety of multiple flexible sigmoidoscopies in clinical trial participants (Poster). HIV Research for Prevention (HIV R4P) 2016; 16 Oct 11; 2016.