STATISTICAL ANALYSIS PLAN

MTN-037

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

Microbicide Trials Network

Statistical Center for HIV/AIDS Research and Prevention

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Approval Signature Page

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Statistical Analysis Plan

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I have read this Statistical Analysis Plan and approve its contents.

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TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$\%AUC_{ex}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation, calculated as $[(C_{last} / k_e) / AUC_{0-\infty} * 100]$
AUC	area under the concentration-time curve
AUC_{0-t}	AUC from time zero to the time of the last measurable concentration
$AUC_{0-\infty}$	AUC from time zero extrapolated to infinity, equal to AUC_{0-t} plus $AUC_{t-\infty} = (C_{last} / k_e)$
BMI	body mass index
BLOQ	below the limit of quantitation
BP	blood plasma
C_{last}	last observed concentration
C_{max}	peak concentration
CG	carrageenan
CrCl	creatinine clearance
h	hour
k_e	terminal elimination rate constant
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MIV-150	Urea, *N*-(5-cyano-2-pyridinyl)-*N*'-[(1*S*,2*S*)-2-[6-fluoro-2-hydroxy-3-(1-oxopropyl)phenyl]cyclopropyl]-; an NNRTI
mL	milliliter
PC-1005	0.002% MIV-150/0.3% zinc acetate [ZA] in 3.0% carrageenan [CG] gel
PK	pharmacokinetics
RAI	receptive anal intercourse
RF	rectal fluid
RT	rectal mucosal tissue homogenates
SAP	statistical analysis plan
SSP	study specific procedures
$t_{1/2}$	half-life of drug elimination in the terminal phase
t_{max}	time to peak concentration
WSI	web-based self-interviews
ZA	zinc acetate

2. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the plan for analyzing data regarding the safety, pharmacokinetics, and acceptability among men and women after using a single dose of PC-1005 (0.002% MIV-150/0.3% zinc acetate [ZA] in 3.0% carrageenan [CG] gel) applied rectally in three sequential dose/volumes of 4mL, 16mL, and 32mL.

2.1 Study Objectives and Endpoints

Primary Objectives:

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

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

Primary Endpoints:

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

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

Secondary Objectives:

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

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

Secondary Endpoints:

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

Pharmacokinetics
MIV-150 concentrations in vaginal fluid

Exploratory Objectives:

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

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

Exploratory Endpoints:

Biomarkers of Mucosal Safety
- Rectal histology
- Tissue archive

Ex Vivo Antiviral Activity
- Changes in HIV-1 p24 levels in colorectal explant culture supernatant
- Anti-HIV activity in rectal fluid

2.2 Primary Study Hypothesis

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

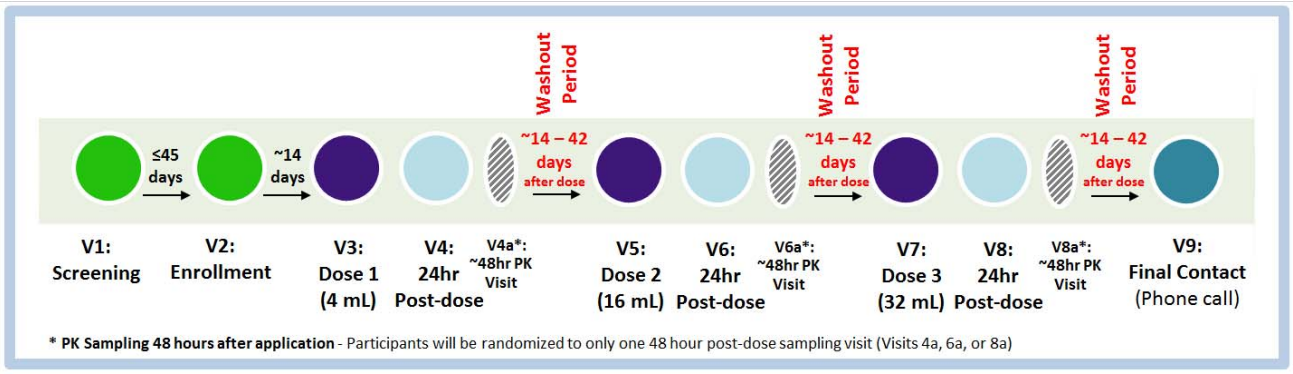
2.3 General Design Considerations

This section summarizes the protocol and objectives covered in this Statistical Analysis Plan (SAP).

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

to six weeks (to accommodate scheduling around the menstrual cycles of female participants) following each dosing visit, dosing with the next sequential escalating volume will be administered. A final study contact will occur after the third dosing visit and associated washout period.

Figure 1: MTN-037 Study Visit Schedule



As displayed in Figure 1, participants will receive the 4mL dose of PC-1005 at Visit 3 and have safety laboratory tests, PK and PD assessments performed within 24 hours. After a washout period of two to six weeks (to accommodate scheduling around the menstrual cycles of female participants) following the 4mL dosing visit, participants will receive the 16mL dose of PC-1005 at Visit 5 and have safety laboratory tests, PK and PD assessments performed within 24 hours. After a washout period of two to six weeks (to accommodate scheduling around the menstrual cycles of female participants) following the 16mL dosing visit, participants will receive the 32mL dose of PC-1005 at Visit 7 and have safety laboratory tests, PK and PD assessments performed within 24 hours. Participants will be randomized to only one 48-hour post-dose sampling visit (Visits 4a, 6a, or 8a). A final study contact will occur after the third dosing visit and associated washout period (Visit 9).

2.3.1 Randomization

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

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

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

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

- All 12 participants will have flexible sigmoidoscopy at enrollment.
- For the 4 mL, 16 mL, and 32 mL dose/volumes, participants will be randomly assigned 1:1:1:1 to one of the following 4 time-frames to provide samples of rectal tissue, rectal fluid, vaginal fluid (if applicable), and effluent from rectal lavage: 0.5-1 hour, 1.5-3 hours, 3.5-5 hours, and 24 hours following PC-1005 gel application.

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

2.3.2 Blinding

There is no blinding in this open-label study.

2.3.3 Sample Size and Power

The study is designed for a total accrual of twelve (12) participants, which gives sufficient power for the detection of events (adverse events or detection of drug) as described in the protocol. Descriptive safety analyses and pharmacokinetic analyses are planned with no formal statistical testing.

3. GENERAL DATA ANALYSIS CONSIDERATIONS

3.1 Analysis Set(s)

The analysis set consists of all participants enrolled in the study who are administered PC-1005 at any dosing visit (Visit 3, Visit 5, or Visit 7). All available safety, PK, and acceptability data will be analyzed on this set of participants, as described below.

3.2 Statistical Analysis Issues

For the primary safety analyses, safety endpoints will be classified into groups by dose/volume of gel based on the amount of gel administered at a dosing visit (Visit 3, Visit 5, and Visit 7). If a participant was not administered a particular dose/volume of gel, then the participant will be excluded from analyses describing that particular dose/volume group.

For the primary pharmacokinetics analyses, timing of drug concentration results will be based on the time the specimen was actually taken, and not based on timing group as randomized. Time points may still be grouped into categories based the average or targeted time point for specimen collection. The handling of missing data and concentration data below the limit of quantitation (BLOQ) are described in the section on pharmacokinetic analyses below.

4. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE

No interim statistical analysis was planned or performed for the MTN-037 study.

One study monitoring committee (SMC) review was conducted for MTN-037, on December 10, 2018, for which a closed report was produced. Evaluation of safety was based on descriptive tables of adverse events, with no formal statistical testing.

5. GENERAL ANALYSIS METHODS

When the use of descriptive statistics to assess dose/volume 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).

The following descriptions may be used to distinguish the dose/volume groups: "4 mL Volume", "16mL Volume", and "32 mL Volume".

6. TRIAL PARTICIPANT DISPOSITION

Enrollment will take place at two sites: Birmingham and Pittsburgh, USA.

6.1 Disposition of Participants

6.1.1 Screening and Enrollment

Dates of site activation, first enrollment, and last enrollment, as well as the number or participants screened, number and percentage of participants enrolled, and the screening-to-enrollment ratio will be displayed in a table overall and by site.

6.1.2 Retention

A table will display for each visit the number and percentage of participants who are expected, retained, missing, and lost-to-follow-up or terminated with respect to that visit, overall and by site.

6.1.3 Treatment Discontinuation

The number and percentage of participants who ended product use early, as well as the reasons for terminating product use early, will be presented in a table overall and by site.

6.1.4 Study Discontinuation

The number and percentage of participants who completed the study, as well as the reasons for non-completion, will be displayed in a table overall and by site.

6.1.5 Completion of Procedures

The completion of required and expected procedures will be displayed in a table overall and by site. The table will display the number and percentages of participant-visits for each procedure.

6.2 Treatment Exposure

The number and percentage of participants administered each of the three (3) dose/volumes of gel at Visits 3, 5, and 7 will be displayed overall and by site. Participants will be classified into groups by dose/volume of gel based on the time from dosing up until just before the next higher dose/volume is administered (e.g., for the 4 mL dose/volume group, any safety endpoints which occur between the time of gel insertion at Visit 3 up until (but not including) the time the 16 mL dose/volume is administered at Visit 5.)

If applicable, the number and percentage of participants who had study product held during follow-up will be displayed overall and by site (along with the reasons why product was held).

6.3 Protocol Deviations

Protocol deviations occurring in MTN-037 will be summarized in a table of each type of deviation by site and overall, and in a listing of deviation events.

These data will be reviewed prior to the analysis of the primary and secondary endpoints to determine if any protocol deviations in this study impact participant eligibility or treatment administration and subsequently necessitate adjustments to the analysis set.

7. BASELINE DATA

Baseline participant demographic characteristics such as age, sex at birth, ethnicity, race, height, weight, and body mass index (BMI) will be summarized and displayed in tables overall and by site, and in tables overall and by sex at birth. Descriptive statistics will be presented for age, height, weight, and BMI. Frequency counts and percentages will be presented for sex at birth, ethnicity, and race. No formal comparisons are planned.

Individual participant baseline characteristics (medical history and results from baseline anorectal exam findings, pelvic exam findings, STI results, hematology, and local laboratory results) will be presented in listings.

8. SAFETY ANALYSES

All participants enrolled and administered a dose of PC-1005 will be assessed for safety.

8.1 Primary Safety Analyses

The primary safety endpoint is defined as follows:

> 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).

The number and the percentage of participants experiencing each safety endpoint will be tabulated by dose/volume of gel. This table will display a summary for any primary safety endpoint and for each individual safety endpoint. Each participant will contribute once in each category (i.e., only for highest severity AE for each participant) for the calculation of event rates for each dose/volume of gel. Exact binomial confidence intervals (Clopper-Pearson) will be calculated for each safety endpoint, even if no events occur for an endpoint for a particular dose/volume.

8.2 Adverse Events

Summaries of adverse events will include a cumulative listing of adverse events, a table displaying the total number of adverse events by severity grade and relationship to study product, a table of the incidence of adverse events by MedDRA organ system class/preferred term and severity, and a table of incidence of adverse events by MedDRA organ system class/preferred term and relationship to study product. Tables will be displayed by dose/volume, and listings will include the dose/volume period when the AE occurred.

8.3 Laboratory Evaluations

The number and percentage of participants with a positive result for the following laboratory tests will be displayed in a table overall and by sex at birth: hCG for pregnancy and HIV. A listing of participants with positive results of STI testing (syphilis, trichomonas, gonorrhea, chlamydia) after dose insertion will be presented.

Hematology results after dosing with each dose/volume, including hemogram (hemoglobin, hematocrit, MCV, platelets, WBC) and differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) results will be tabulated by dose/volume using descriptive statistics.

Serum chemistries (AST, ALT, and creatinine) after dosing with each dose/volume will be tabulated by dose/volume using descriptive statistics.

8.4 Other Safety Measures

Additional safety summaries include:

A listing of participants with abnormal findings on rectal examination after dose insertion (with dose/volume period when finding occurred) will be presented.

Concomitant medications are defined as any medication taken during the study. A participant listing of all concomitant medications will be presented.

9. PHARMACOKINETIC ANALYSES

Descriptive statistics will be used to summarize actual PK sample collection times (from dose insertion) for plasma, rectal fluid, rectal tissue, and vaginal fluid samples, and these summaries will be provided by site and overall. Plasma samples are expected to be collected pre-dose and at 1h, 2h, 3h, 4h, 5-6h, and 24h after dose administration. Samples of rectal fluid, rectal tissue, and vaginal fluid (if applicable) are expected to be collected at one of the following time points, 0.5-1h, 1.5-3h, 3.5-5h, or 24h during each dose/volume administration (chosen randomly 1:1:1:1). These samples are also expected to be collected at 48h after dose administration for one of the three dose/volume levels (4 mL, 16 mL, or 32 mL; chosen randomly 1:1:1).

A table summarizing the number and percentage of plasma, rectal fluid, rectal tissue, and vaginal fluid samples collected outside of the windows of the expected time points will be provided overall and by site. For samples collected outside of the window, a listing of sample collection times along with the amount of time before (-) the window or after (+) the window will be provided. Allowable windows for the collection of plasma, rectal fluid, rectal tissue, and vaginal fluid are detailed in section 5.4.2 and Table 5-1 of the MTN-037 SSP Manual.

9.1 Methods for Handling Missing and BLOQ Data

Each bioanalytical assay for plasma, rectal fluid, rectal tissue, and vaginal fluid has an assay sensitivity described by a lower limit of quantitation (LLOQ). These LLOQs will be reported for each matrix. Concentration values assayed below the LLOQ, as well as those classified as “Not Detected”, are identified as below the limit of quantitation (BLOQ).

In individual participant data listings, actual concentration values below the LLOQ will be displayed, if provided from the lab, along with the LLOQ for the assay. For values identified as BLOQ in the data, a listing will be provided displaying the assay and time point(s) of the BLOQ values.

Pre-dose samples that are BLOQ or missing will be assigned a numerical value of zero for the calculation of area under the concentration-time curve (AUC). Pre-dose samples that are missing will be excluded from the concentration summary calculations at pre-dose. Any anomalous quantifiable concentration values (at or above the LLOQ) observed at pre-dose will be identified in the study report and used for the computation of AUC.

Any other BLOQ concentrations that precede quantifiable samples in the initial portion of the profile or a BLOQ value that occurs between quantifiable data points, especially prior to C_{max}, will be evaluated to determine if an assigned concentration of zero makes sense, or if reanalysis or exclusion of the data is warranted. Following C_{max}, BLOQ values embedded between two quantifiable data points will be treated as missing when calculating AUC. If BLOQ values occur at the end of the collection interval (after the last quantifiable concentration), these will be treated as missing data. If consecutive BLOQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by assigning them a value of missing, unless otherwise warranted by the concentration-time profile.

Drug concentration-time data will be listed for each participant and summarized by descriptive statistics at each nominal collection time. BLOQ concentrations will be treated as zero for computation of descriptive statistics. Concentrations assigned a value of missing will be omitted from the calculation of descriptive statistics. If the calculated mean concentration is BLOQ, the mean value will be reported as BLOQ, and SD will be reported as ND (not determined). Median, quartiles, minimum and maximum may be reported, and if any of these values are BLOQ, they will be reported as BLOQ.

9.2 Primary PK Analyses

The primary PK analyses describe the concentrations of MIV-150 in the following matrices: 1) blood plasma (BP), 2) rectal fluid (RF), and 3) rectal mucosal tissue homogenates (RT) during each of three sequential dose/volumes of 4mL, 16mL, and 32mL.

As BP samples are collected among all participants at seven time points and RF and RT samples are collected among three participants at each time point up to 24 hours and among four participants at 48 hours for each dose/volume, there are differences between how the concentration data for these matrices will be analyzed and summarized.

In general, due to the small number of concentrations available at sampling time points, a log transformation of the concentrations will be considered if the data suggest strong skewness. In this case, figures and tables will report medians with 95% C.I. at each sampling time point and figures will be presented on a semi-logarithmic scale (y-axis: logarithmic concentration; x-axis: linear time (h)). If no log transformation of concentration is needed, then figures and tables will report the mean (with 95% confidence interval based on a Student's t-distribution approximation) at each sampling time point and figures will be presented on a linear scale.

Blood Plasma Concentrations

For blood plasma, MIV-150 concentrations can be plotted over time for each individual participant and PK parameters (defined below) may be calculated for each participant and then summarized across all participants.

Displays of blood plasma concentration data include:

- Tables summarizing the distribution of concentrations at each sampling time point for each dose/volume (3 tables, or 1 table with a column for each dose/volume).
- Plots of individual participant concentration-time data presented in a panel for each dose/volume (3 panels of plots (1 panel for each dose/volume)).

- Individual participant concentration-time data will also be overlaid on a single plot for each dose/volume (3 plots).
- Plots of mean/median concentration at each time point (with 95% C.I.) for each dose/volume (3 plots, or 1 panel with 3 plots (1 for each dose/volume)).
- Listings of individual participant PK parameters for each dose/volume (3 listings).
- Tables summarizing the distributions of PK parameters across all participants for each dose/volume (3 tables).

Rectal Fluid and Rectal Tissue Concentrations

For rectal fluid and rectal tissue, the concentration-time profile will consist of data from different participants at different sampling time points. Individual participant PK parameters will not be calculated for concentration data from rectal fluid and rectal tissue since data were not collected at each time point for each participant.

Displays of rectal fluid and rectal tissue concentration data include:

- For each matrix (RF, RT), tables summarizing the distribution of concentrations at each sampling time point for each dose/volume (3 tables per matrix, or 1 table per matrix with a column for each dose/volume).
- For each matrix (RF, RT), scatter plots of MIV-150 concentration-time data for each dose/volume (3 plots per matrix, or 1 panel per matrix with 3 plots (1 for each dose/volume)).
- For each matrix (RF, RT), plots of mean/median concentration at each time point (with 95% C.I.) for each dose/volume (3 plots per matrix, or 1 panel per matrix with 3 plots (1 for each dose/volume)).
- For each matrix (RF, RT), tables of PK parameters calculated from mean/median concentrations at each sampling time point for each dose/volume (3 tables per matrix).

The PK parameters are:

C_{max}	Maximum observed MIV-150 concentration.
C_{last}	Last observed MIV-150 concentration.
t_{max}	Time of occurrence for C_{max}
AUC_{0-t}	Area under the MIV-150 concentration-time curve to the time of the last measurable concentration.
$AUC_{0-\infty}$	Area under the MIV-150 concentration-time curve to infinite time. Equal to AUC_{0-t} plus $AUC_{t-\infty} = (C_{last} / k_e)$.
k_e	Terminal elimination rate constant.
$t_{1/2}$	Half-life of drug elimination in the terminal phase.
$\%AUC_{ex}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation, calculated as $[(C_{last} / k_e) / AUC_{0-\infty} * 100]$

The time, in hours, to each sample collection time is calculated from the time of dose insertion. The area under the curve (AUC) is calculated for each participant using the trapezoidal method from the time of dose insertion to the time of the last sample collection (AUC_{0-t}), typically at 24h or 48h.

Concentrations after C_{max} are used to determine the terminal elimination rate constant (k_e) and associated half-life of MIV-150 elimination in the terminal phase ($t_{1/2}$), when at least three such concentration values are available, according to the following formulas:

$$k_e = \ln (C_1/C_2) / (t_2 - t_1)$$

$$t_{1/2} = \ln(2) / k_e$$

where ln is the natural logarithm, C_1 is the first MIV-150 concentration value in the elimination phase after C_{max}, C_2 is the last MIV-150 concentration in the elimination phase after C_{max}, and t_1 and t_2 are the time (hours) of the first and last MIV-150 concentration values in the elimination phase after C_{max}, respectively, as measured from the time of dose insertion.

The area under the plasma MIV-150 concentration-time curve to infinite time ($AUC_{0-\infty}$) is calculated by extrapolating the area of the curve after the last observed plasma MIV-150 concentration (C_{last}) by dividing C_{last} by the terminal elimination rate constant (k_e) and adding the result to AUC_{0-t}. The percentage of $AUC_{0-\infty}$ obtained by extrapolation ($\%AUC_{ex}$) is calculated as [($AUC_{t-\infty}$ / $AUC_{0-\infty}$)*100].

10. SECONDARY ANALYSES

10.1 Acceptability Analyses

Enrolled participants are administered web-based self-interviews (WSI) at Enrollment (Visit 2) and at the three dosing visits (Visits 3, 5, and 7). The WSI at dosing visits explore reactions to product, with an emphasis on identification of product attributes likely to challenge and/or facilitate future sustained use when applied rectally by participants.

To address the secondary endpoints of participant self-report of comfort with gel application, liking the product across doses, and perceived side-effects, responses to WSI questions in section B (Rectal Gel Acceptability) and section C (Experiences Using the Product) of the dosing visits (Visits 3, 5, and 7) will be summarized in a table by dose/volume.

10.2 Secondary PK Analyses

The secondary PK analyses describe the analyses of MIV-150 concentrations in vaginal fluid and are limited to participants identified as female sex at birth.

For these secondary PK analyses, the primary PK analyses for rectal fluid and/or rectal tissue will be repeated for MIV-150 concentrations in vaginal fluid.

11. REFERENCES

A Phase 1 Safety and Pharmacokinetic Study of PC-1005 (MIV-150/Zinc Acetate/Carrageenan Gel) Administered Rectally to HIV-1 Seronegative Adults (MTN-037). Microbicide Trials Network (MTN) clinical study protocol, Version 1.0, November 9, 2017.

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

Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Publish Date: December 2004, Addendum 1, Female Genital Grading Table for Use in Microbicide Studies, Version 1.0, November 2007.

Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Publish Date: December 2004, Addendum 2, Male Genital Grading Table for Use in Microbicide Studies, Version 1.0, November 2007.

Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Addendum 3, Rectal Grading Table for Use in Microbicide Studies, Clarification dated May 2012.

MTN-037 SSP Manual, Version 1.1, 05 October 2018, Section 5, Page 5-5 and Page 5-6 of 5-10, Section 5.4.2 Pharmacokinetics, Pharmacodynamics, and Mucosal Safety Assignment. Table 5-1: PK Sample Collection Time-Points following Study Gel Administration.