SCHARP
Statistical Center for HIV/AIDS Research and Prevention

STATISTICAL ANALYSIS PLAN

A Phase 1 Open Label Safety and Pharmacokinetic Study of Rectal Administration of a Tenofovir Alafenamide/Elvitegravir Insert at Two Dose Levels

MTN-039

Effective Date: October 8, 2021

Version: 2.0

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Protocol Name:	*A Phase 1 Open Label Safety and Pharmacokinetic Study of Rectal Administration of a Tenofovir Alafenamide/Elvitegravir Insert at Two Dose Levels*
Protocol Number:	*MTN-039*
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Version:	*2.0*

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1. LIST OF ABBREVIATIONS AND ACRONYMS

A list of abbreviations used in the SAP.

Term/Abbreviation	Definition
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
CASI	computer assisted self-interviews
C_{last}	last observed concentration
C_{max}	peak concentration
CRS	Clinical Research Site
EVG	elvitegravir
h	hour
k_e	terminal elimination rate constant
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetics
RF	rectal fluid
RT	rectal mucosal tissue
SAP	statistical analysis plan
SSP	study specific procedures
t1/2	terminal concentration half-life
TAF	tenofovir alafenamide
T_{max}	time to peak concentration

2. INTRODUCTION

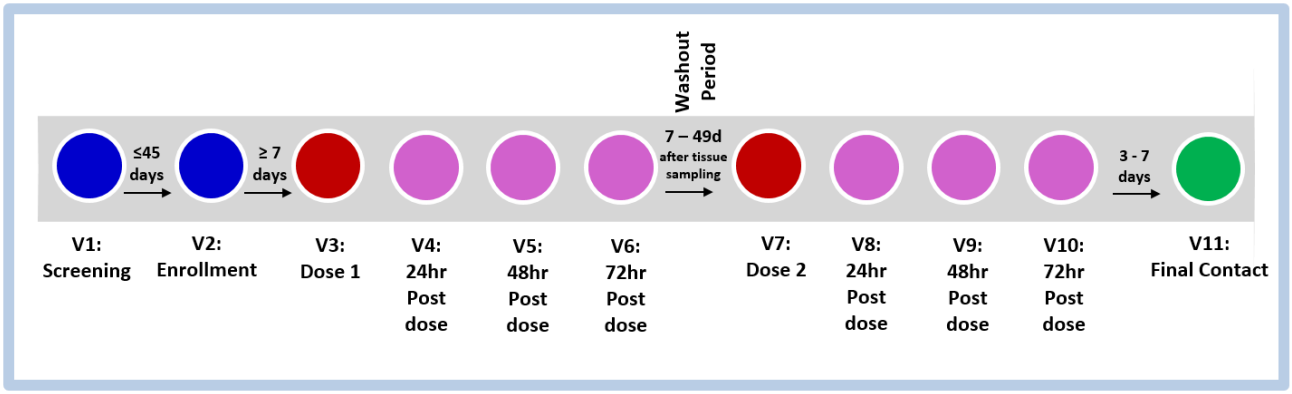
This Statistical Analysis Plan (SAP) describes the plan for the final analysis of data regarding the safety, pharmacokinetics, and acceptability among HIV-uninfected individuals 18 years of age or older in a Phase I, multi-site, open-label, single arm, two-period study of rectal administration of one Tenofovir Alafenamide/Elvitegravir Insert, 20/16 mg, and then two TAF/EVG Inserts.

2.1 General Design Considerations

PROTOCOL SUMMARY

Short Title:	Safety and PK Study of TAF/EVG Administered Rectally
Clinical Phase:	Phase 1
IND Sponsor:	DAIDS
Protocol Chair:	Sharon Riddler, MD, MPH
Sample Size:	MTN-039 will enroll approximately 20 participants.
Study Population:	HIV-uninfected individuals 18 years of age or older
Study Sites:	Alabama CRS and University of Pittsburgh CRS
Study Design:	Phase 1, multi-site, open-label, single arm, two-period study of rectal administration of one Tenofovir Alafenamide/Elvitegravir Insert, 20/16 mg and then two TAF/EVG Inserts
Study Duration:	Approximately 6-13 weeks 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 months.
Study Products:	TAF/EVG Insert, 20/16 mg
Study Regimen:	Participants will apply a single TAF/EVG Insert rectally and samples will be collected over a 3-day period. After a washout period of at least 7 days, participants will apply two TAF/EVG Inserts rectally and samples will be taken over a 3-day period.

Figure 1: MTN-039 Study Visit Schedule



As displayed in Figure 1, participants will receive a rectally administered dose of one TAF/EVG insert at Visit 3 and have safety laboratory tests, PK and PD assessments performed over the next three days (Visits 4, 5, and 6). Participants will self-administer a saline enema at home the evening prior to a clinic dosing visit (Visits 3 and 7). After a washout period of one to seven weeks following the last tissue sampling associated with one TAF/EVG insert dosing, participants will receive dosing of two TAF/EVG inserts at Visit 7 and have safety laboratory tests, PK and PD assessments performed over the next three days (Visits 8, 9, and 10). A final study contact will occur approximately 3-7 days after Visit 10 and may be conducted over the phone.

2.2 Study Objectives and Endpoints

The primary, secondary and exploratory objectives and endpoints of this study are described below. This SAP will describe the plan for the statistical analyses of the primary and secondary endpoints only.

Primary Objectives:

Safety

- To evaluate the safety of the TAF/EVG Insert, 20/16 mg administered rectally at two dose levels: 1 insert and 2 inserts

Pharmacokinetics

- To characterize the systemic and rectal pharmacokinetics of the TAF/EVG Insert, 20/16 mg applied rectally at two dose levels: 1 insert and 2 inserts

Primary Endpoints:

Safety

- All Grade 2 and higher AEs

Pharmacokinetics

- EVG concentrations in:
  - Blood
  - Rectal fluid
  - Rectal mucosal tissue homogenates

- TAF and TFV concentrations in
  - Blood

  - Rectal fluid
  - Rectal mucosal tissue homogenates

- TFV-DP concentration in:
  - Rectal mucosal tissue cell isolates

Secondary Objective:

Acceptability

- To identify product attributes considered likely to challenge and/or facilitate future sustained use of the TAF/EVG Insert applied rectally

Secondary Endpoints:

Acceptability

- Participant report of overall acceptability of the TAF/EVG Insert applied rectally

Exploratory Objectives:

Ex Vivo Efficacy

- To assess the preliminary (ex vivo) efficacy of TAF/EVG after product is inserted rectally

Pharmacokinetics

- To characterize the cervicovaginal pharmacokinetics of the TAF/EVG Insert, 20/16 mg applied rectally at two dose levels: 1 insert and 2 inserts

Mucosal Safety

- To evaluate mucosal safety of the TAF/EVG Insert, 20/16 mg applied rectally at two dose levels: 1 insert and 2 inserts

Exploratory Endpoints:

***Ex Vivo* Efficacy**

- Changes in HIV-1 replication in colorectal explant culture supernatant
- Anti-HIV activity in rectal fluid
- Anti-HIV activity in cervicovaginal fluid

Pharmacokinetics

- EVG, TAF and TFV concentrations in cervicovaginal fluid

Mucosal Safety

- Rectal histology
- Rectal proteomics
- Rectal metabolomics
- Rectal immunophenotype
- Rectal microbiome
- Cervicovaginal microflora

2.3 Randomization

There will be no randomization to dose of TAF and EVG (one or two inserts) in this open-label, single arm, and two-period trial.

At study randomization upon enrollment, participants will be assigned to one of two sampling group schedules for collection of rectal tissue (collected with flexible sigmoidoscopy), rectal fluid, and cervicovaginal fluid (if applicable):

Group 1:	Visits 3, 5, 7, and 9
Group 2:	Visits 4, 6, 8, and 10
Notes:	Both sampling groups 1 and 2 will provide blood at Visits 3-10. At Visits 3 and 7, both sampling groups will provide rectal fluid and cervicovaginal fluid (if applicable) – Group 1 at 2- and 6-hours post-dose, and Group 2 at 4-hours post-dose. At Visits 3 and 7, rectal tissue sampling will be conducted in Group 1 participants at 2-hours post-dose. All sampling times are approximate; allowable windows and detailed instructions are provided in the MTN-039 SSP Manual.

Each participant will have a total of 5 flexible sigmoidoscopies for rectal tissue sampling:

- at baseline (both sampling groups, 1 set of biopsies)
- at 2- and 48-hours post-dose for each dose (Group 1 only, 4 sets of biopsies)
- at 24- and 72-hours post-dose for each dose (Group 2 only, 4 sets of biopsies).

Randomization will be stratified by sex at birth to incorporate at least three participants assigned female sex at birth in each sampling group.

2.4 Blinding

There is no blinding in this open-label study.

2.5 Sample Size and Power

The study is designed for a total accrual of twenty (20) participants, which gives sufficient power for the detection of adverse events 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 a TAF/EVG insert at any dosing visit (Visit 3 or 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 regimen (one or two inserts) based on the doses administered at a dosing visit (Visit 3 and 7). If a participant was not administered a particular dose, then the participant will be excluded from analyses describing that particular dose regimen.

For the primary pharmacokinetics analyses, timing of drug concentration results will be based on the time the specimen was actually collected, and not based on time points as planned for each sampling group

per randomization. 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-039 study.

One study monitoring committee (SMC) review was conducted for MTN-039, on December 7, 2020, 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 dosing regimen 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 dosing regimens: "One Insert" and "Two Inserts".

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 enrolled participants administered the one insert dosing regimen at Visit 3 and then number of participants administered the two inserts dosing regimen at visit 7 will be displayed overall and by site. Participants will be classified into groups by dosing regimen based on the time from dosing up until just before the next higher dosing regimen is administered (e.g., for the one insert dosing regimen, any safety endpoints which occur between the time of one insert administration at Visit 3 up until, but not including, the time of the two insert administration at Visit 7.)

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-039 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, gender, sexual orientation, 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, race, gender, and sexual orientation. No formal comparisons are planned.

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

8. SAFETY ANALYSES

All participants enrolled and administered any TAF/EVG insert will be assessed for safety.

8.1 Primary Safety Analyses

The primary safety endpoint is defined as follows:

All Grade 2 and higher AEs

The number and the percentage of participants experiencing each safety endpoint will be tabulated by dosing regimen (one insert or two inserts). 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 dosing regimen. Exact binomial confidence intervals (Clopper-Pearson) will be calculated for each safety endpoint, even if no events occur for an endpoint for a particular dosing regimen.

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 dosing regimen, and listings will include the dosing regimen 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 site: hCG for pregnancy and HIV. A listing of participants with positive results of STI testing (syphilis, trichomonas, gonorrhea, chlamydia) after dose administration will be presented.

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

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

8.4 Other Safety Measures

Additional safety summaries include:

A listing of participants with abnormal findings on pelvic examination or rectal examination after dose administration (with dosing regimen 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 administration) for blood, rectal fluid, rectal tissue, and cervicovaginal fluid samples, and these summaries will be provided by site and overall.

For each dosing regimen, blood samples are expected to be collected from all participants at baseline and at 1h, 2h, 4h, 6h, 24h, 48h, and 72h after dose administration. Samples of rectal fluid and cervicovaginal fluid (if applicable) are expected to be collected at the following study time points after dose administration: 2h, 4h, 6h, 24h, 48h, and 72h with samples collected for each participant only at specific time points based upon their group status (see table below). Similarly, samples of rectal tissue are expected to be collected at the following study time points after dose administration: 2h, 24h, 48h, and 72h with samples collected for each participant only at specific time points based upon their group status (see Table 1 below).

Table 1: Expected PK Sample Collection by Study Time Point

PK Specimen Type	Baseline Visit 2	1h, Visits 3 & 7	2h, Visits 3 & 7	4h, Visits 3 & 7	6h, Visits 3 & 7	24h, Visits 4 & 8	48h, Visits 5 & 9	72h, Visits 6 & 10
Blood	G12	G12	G12	G12	G12	G12	G12	G12
Rectal fluid			G1	G2	G1	G2	G1	G2
Rectal tissue			G1			G2	G1	G2
Cervicovaginal fluid			G1	G2	G1	G2	G1	G2

NOTE: G1=Group 1, G2=Group 2, G12=Groups 1 and 2.

A table summarizing the number and percentage of blood, rectal fluid, rectal tissue, and cervicovaginal 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 blood, rectal fluid, rectal tissue, and cervicovaginal fluid are detailed in the MTN-039 SSP Manual in section 5.4.2 and Table 5-1 Sample Collection Time-Points Post-Insert Administration (and provided below).

Table 5-1: Sample Collection Time-Points Post-Insert Administration

Study Visit	Blood Samples (All time-points required for all participants)	Rectal/Pelvic Samples (per sample collection sequence assignment)
Enrollment	1 time during visit (no specified time; no dose administration)	1 time during visit (no specified time; no dose administration)
Dosing Visit (V3 and 7)	1 hours 2 hours 4 hours 6 hours (+/- 15-minute window permitted for hourly times)	Group 1: 2 and/or 6 hours Group 2: 4 hours (+/-30 minute window permitted)
24-Hr Post-Dose Visit (V4 and 8)	24 hours (+/- 2 hours window permitted)	Group 2 only (+/- 2 hours window permitted)
48-Hr Post-Dose Visit (V5 and 9)	48 hours (+/- 4 hours window permitted)	Group 1 only (+/- 4 hours window permitted)
72-Hr Post-Dose Visit (V6 and 10)	72 hours (+/- 6 hours window permitted)	Group 2 only (+/- 6 hours window permitted)

9.1 Methods for Handling Missing and BLOQ Data

Each bioanalytical assay for blood, rectal fluid, rectal tissue, and cervicovaginal 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.

Baseline 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). Baseline samples that are missing will be excluded from the concentration summary calculations at baseline. Any anomalous quantifiable concentration values (at or above the LLOQ) observed at baseline 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.

When a concentration of zero cannot be plotted, the concentration may be assigned the value of LLOQ divided by 2 so that it may be displayed.

9.2 Primary PK Analyses

The primary PK analyses describe the concentrations of EVG, TAF, TFV, and TFV-DP in some or all of the following matrices: 1) blood, 2) rectal fluid (RF), 3) rectal mucosal tissue (RT) homogenates, and 4) rectal mucosal tissue cell isolates during each dosing regimen, one insert or two inserts. For each dosing regimen (one insert and two inserts), Table 2 below displays the drug concentrations to be analyzed for each PK specimen type.

Table 2: Expected PK Drug Concentrations per PK Specimen Type

PK Specimen Type	EVG	TAF	TFV	TFV-DP
Blood	X	X	X	
Rectal fluid	X	X	X	
Rectal tissue homogenates	X	X	X	
Rectal tissue cell isolates				X

NOTE: X=Drug concentrations expected.

As blood samples are collected among all participants at the enrollment visit and at seven post-dose time points per dose, RF samples are collected at three time points per dose for Group 1 participants and three separate time points per dose for Group 2 participants, and RT samples are collected at two time points per dose for Group 1 and two time points per dose for Group 2 participants, 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 Concentrations

For blood, EVG, TAF, and TFV 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 concentration data include:

- Tables summarizing the distribution of concentrations at each sampling time point for each dose administration (3 tables, one for each drug, with a column for each dose administration).
- Plots of individual participant concentration-time data presented in a panel for each dose administration (6 panels of plots (1 panel for each dose administration and drug)).
- Individual participant concentration-time data will also be overlaid on a single plot for each dose administration and drug (6 plots).
- Plots of mean/median concentration at each time point (with 95% C.I.) for each dose administration and drug (3 panels, one for each drug, with 2 plots (1 for each dose administration)).
- Listings of individual participant PK parameters for each dose administration and drug (6 listings).
- Tables summarizing the distributions of PK parameters across all participants for each dose administration and drug (6 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 administration and drug (7 tables (3 for RF, 4 for RT) with a column for each dose administration).
- For each matrix (RF, RT), scatter plots of drug concentration-time data for each dose administration (7 panels (3 for RF, 4 for RT) with 2 plots (1 for each dose administration)).
- For each matrix (RF, RT), plots of mean/median concentration at each time point (with IQR or 95% C.I., as appropriate) for each dose administration (7 panels (3 for RF, 4 for RT) with 2 plots (1 for each dose administration)).

The PK parameters are:

C_{max}	Maximum observed drug concentration.
C_{last}	Last observed drug concentration.
t_{max}	Time of occurrence for C_{max}
AUC_{0-t}	Area under the drug concentration-time curve to the time of the last measurable concentration.
$AUC_{0-\infty}$	Area under the drug 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 administration. The area under the curve (AUC) is calculated for each participant using the trapezoidal method from the time of dose administration to the time of the last sample collection (AUC_{0-t}), typically at 72h.

Concentrations after C_{max} are used to determine the terminal elimination rate constant (k_e) and associated half-life of drug 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 drug concentration value in the elimination phase after C_{max}, C_2 is the last drug concentration in the elimination phase after C_{max}, and t_1 and t_2 are the time (hours) of the first and last drug concentration values in the elimination phase after C_{max}, respectively, as measured from the time of dose administration.

The area under the blood drug concentration-time curve to infinite time ($AUC_{0-\infty}$) is calculated by extrapolating the area of the curve after the last observed blood drug 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 ENDPOINTS

10.1 Acceptability Analyses

Enrolled participants are administered computer assisted self-interviews (CASI) questionnaires at Enrollment (Visit 2) and at 24 hours after the one-insert and two-insert dosing visits (Visits 4 and 8, respectively). The CASI questionnaires after dosing visits explore such topics as experiences with trial participation, rectal insert acceptability, experiences using the product, recommendations, etc.

To address the secondary endpoint of participant report of overall acceptability of the TAF/EVG insert applied rectally, responses to CASI questions in section B (Rectal Insert Acceptability) of the dosing visits (Visits 4 and 8) will be summarized in a table by insert dose (one inserts or two inserts).

11. REFERENCES

A Phase 1 Open Label Safety and Pharmacokinetic Study of Rectal Administration of a Tenofovir Alafenamide/Elvitegravir Insert at Two Dose Levels (MTN-039). Microbicide Trials Network (MTN) clinical study protocol, Version 1.0, March 6, 2019.

LETTER OF AMENDMENT #03 TO MTN-039 A Phase 1 Open Label Safety and Pharmacokinetic Study of Rectal Administration of a Tenofovir Alafenamide/Elvitegravir Insert at Two Dose Levels, Version 1.0, dated March 6, 2019; Date of Letter of Amendment: 24 July 2020.

LETTER OF AMENDMENT #04 TO MTN-039 A Phase 1 Open Label Safety and Pharmacokinetic Study of Rectal Administration of a Tenofovir Alafenamide/Elvitegravir Insert at Two Dose Levels, Version 1.0, dated March 6, 2019; Date of Letter of Amendment: 29 September 2021.

MTN-039 SSP Manual, Version 1.2, 17 August 2020, Section 5, Page 5-5 and 5-6 of 5-10, Section 5.4.2 Pharmacokinetics, Pharmacodynamics, and Biomarker Sample Collection. Table 5-1 Sample Collection Time-Points Post-Insert Administration.

12. CHANGE HISTORY

Version		Affected Section(s)	Activity Description
Number	Effective Date		
2.0	08OCT2021	2.2, 9.2, 11	Clarify sample testing for TAF and TFV-DP concentrations as primary endpoints in the protocol. This change adds rectal mucosal tissue homogenates to sample testing to measure TAF concentration and removes rectal mucosal tissue homogenates from sample testing to measure TFV-DP concentrations. Changes are documented in Letter of Amendment #04, which is added as a reference.