SCHARP
Statistical Center for HIV/AIDS Research and Prevention

STATISTICAL ANALYSIS PLAN

A Phase 1, Randomized Pharmacokinetic and Safety Study of a 90 Day Intravaginal Ring Containing Tenofovir

MTN 038

Effective Date: December 30, 2020

Version: 1.0

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STATISTICAL ANALYSIS PLAN

Protocol Name:	*A Phase 1, Randomized Pharmacokinetic and Safety Study of a 90 Day Intravaginal Ring Containing Tenofovir*
Protocol Number:	*MTN-038*
Author(s):	*Barbra Richardson, PhD, Holly Gundacker, MS, SRA*
Version:	*1.0*

Author(s):

Barbra Richardson, PhD *Lead Statistician*	*< see email signature below >* Signature	*< see email below>* Date: DD/MM/YYYY
Holly Gundacker, MS *Statistical Research Associate*	*< see email signature below >* Signature	< see email below> Date: DD/MM/YYYY

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From: Barbra Richardson
To: Gundacker, Holly M
Subject: RE: MTN=038 SAP approval
Date: Wednesday, December 30, 2020 9:56:07 AM

I, Barbra Richardson, Faculty Statistician, approve. This email is a substitute for a wet signature approval of the MTN-038 Statistical Analysis Plan, dated December 30, 2020.

From: Gundacker, Holly M <hgundack@scharp.org>
Sent: Tuesday, December 29, 2020 10:22 PM **To:** Barbra Richardson <barbrar@uw.edu> **Subject:** MTN=038 SAP approval

Dear Barb,

At your earliest convenience, we will need to document your approval of the MTN-038 SAP dated December 30, 2020. During this time of working-from-home mandate we are allowed to collect approvals by email.

If you have reviewed and approve of the attached MTN-038 Statistical Analysis Plan (SAP), please respond to this email with the following statement:

I, <name and title>, approve. This email is a substitute for a wet signature approval of the MTN-038 Statistical Analysis Plan, dated December 30, 2020.

Thank you very much, holly

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From: Gundacker, Holly M
To: Gundacker, Holly M
Subject: RE: MTN-038 SAP approval
Date: Wednesday, December 30, 2020 9:57:48 AM

I, Holly Gundacker, Statistical Research Associate, approve. This email is a substitute for a wet signature approval of the MTN-038 Statistical Analysis Plan, dated December 30, 2020.

From: Gundacker, Holly M <hgundack@scharp.org>
Sent: Tuesday, December 29, 2020 10:20 PM
To: Gundacker, Holly M <hgundack@scharp.org>
Subject: MTN-038 SAP approval

Dear Holly,
During this time of working-from-home mandate we are allowed to collect approvals by email.
If you have reviewed and approve of the attached MTN-038 Statistical Analysis Plan (SAP), please respond to this email with the following statement:

I, <name and title>, approve. This email is a substitute for a wet signature approval of the MTN-038 Statistical Analysis Plan, dated December 30, 2020.

Thank you,
holly

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1. LIST OF ABBREVIATIONS AND ACRONYMS

A list of abbreviations used in the SAP.

Term/Abbreviation	Definition
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the concentration Curve
CASI	Computer assisted self-interview
CBC	Complete Blood Count
CI	Confidence Interval
C_{max}	Maximum Concentration
CRF	Case Report Form
CV	Coefficient of Variation
CVF	Cervicovaginal Fluid
DAIDS	Division of AIDS
EAE	Expedited Adverse Event
eCRF	Electronic Case Report Form
GM	Geometric Mean
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
IQR	Interquartile Range
IRB/EC	Institutional Review Board
IVR	Intravaginal Ring
LLOQ	Lower limit of quantification
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
MTN	Microbicide Trials Network
PD	Pharmacodynamics
PEP	Post-exposure prophylaxis
PK	Pharmacokinetics
PrEP	Pre-exposure prophylaxis
PUEV	Product use end visit
SAP	Statistical Analysis Plan

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SD	Standard Deviation
SDMC	Statistical Data Management Center
SMC	Study Monitoring Committee
SRA	Statistical Research Associate
TFV	Tenofovir
TFV-DP	Tenofovir diphosphate
T_{max}	Time to Reach the Maximum Concentration
WBC	White blood cell

2. INTRODUCTION

2.1 General Design Considerations

The following is a protocol summary of the study.

Protocol title: A Phase 1, Randomized Pharmacokinetic and Safety of a 90 Day Intravaginal Ring Containing Tenofovir
Short Title: PK and Safety Study of a 90 Day Vaginal Ring Containing Tenofovir
Clinical Phase: Phase 1
IND Sponsor: DAIDS
Protocol Chair: Albert Liu, MD, MPH
Sample Size: Approximately 48 participants
Study Population: Healthy, HIV-uninfected individuals assigned female sex at birth, 18-45 (inclusive) years old
Study Sites: Three US sites: Birmingham, AL; San Francisco, CA; Pittsburgh, PA
Study Design: Phase 1, two-arm, multi-site, randomized (2:1), placebo controlled trial
Study Duration: Approximately 92 days per participant, with approximately 6-9 months planned for accrual
Study Products: Tenofovir (TFV) intravaginal ring (IVR)
Placebo IVR
Study Regimen: Participants will be randomized to the study products in a 2:1 TFV: placebo ratio and will not be told their group assignment. Participants will insert one IVR to be used for a period of approximately 91 days, followed by approximately 1 day of no product use

2.2 Study Objectives and Endpoints

Primary Objectives:

Pharmacokinetics

To characterize the local and systemic pharmacokinetics of one TFV IVR used continuously for 91 days

Safety

To evaluate the safety of one TFV IVR used continuously for 91 days

Secondary Objectives:

Adherence

To evaluate participant adherence to one TFV IVR used continuously for 91 days

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Acceptability
To evaluate the overall acceptability of one TFV IVR used continuously for 91 days

Exploratory Objectives:

Adherence
To evaluate markers of ring use for the TFV IVR

Acceptability
To evaluate components of acceptability of ring use for the TFV IVR

Vaginal Microenvironment
To describe the genital microenvironment in HIV-uninfected participants during 91 days of continuous IVR use

Pharmacokinetics
To determine the anti-HIV activity in CVF and cervical tissue
To determine the anti-HSV-2 activity in CVF.

Primary Endpoints:

Pharmacokinetics
TFV levels in:
- o Plasma
- o Cervicovaginal fluid (CVF)
- o Rectal fluid
- o Cervical tissue

Tenofovir diphosphate (TFV-DP) levels in:
- o Cervical tissue

Safety
The proportion of participants with Grade 2 or higher genitourinary adverse event as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, and/or Addendum 1 (Female Genital [Dated November 2007] Grading Table for Use in Microbicide Studies)
The proportion of participants with Grade 3 or higher adverse event as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017

Secondary Endpoints:

Adherence
Frequency of study IVR removal/expulsions (voluntary and involuntary) and duration without IVR in vagina (by self-report)
IVR use initiation and persistence (whether the IVR is in place when participants come to the clinic for their study visits)

Acceptability
Degree to which study participants liked or disliked using the IVR (by self-report)

Exploratory Endpoints:

Adherence
Plasma and CVF TFV levels
Residual drug levels in returned IVRs

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Biomarkers of ring use

Acceptability
Self-reported attitudes about ring attributes, including dosing regimen and willingness to use IVR in the future
Interest/preference in a single vs. dual-purpose indication
The proportion of participants who find the study IVR to be at least as acceptable as other HIV prevention methods

Vaginal Microenvironment
Changes in microbiota and biomarkers
Impact of microbiota on TFV levels in tissue and plasma

Pharmacodynamics
Measures of HIV inhibition in CVF and cervical tissue
Measures of HSV-2 inhibition in CVF

2.3 Randomization

Participants were randomized in a 2:1 ratio to the active and placebo arms of the study. Study arm randomization was stratified by site to ensure balanced assignment of products at each site. In addition, biopsy collection was randomized to one of two biopsy schedule assignments. This schedule assignment was randomized and approximately balanced across sites and study product arms in a 1:1 ratio of Day 14 and Day 56 to Day 28 and Day 91. The randomization scheme has been generated and maintained by the MTN SDMC.

2.4 Blinding

This is not a blinded study. However, participants are not told their study product assignment.

2.5 Sample Size and Power

The proposed total sample size is approximately N=48 adult participants. The sample size is based upon the size of similar Phase 1 studies of vaginal microbicide products.
The statistical properties of the study are described using the probability of detecting pharmacokinetic (PK) concentrations among participants assigned to the active study product arm and the power to detect safety event differences between the study arms. For example, if the true rate of detection of PK concentrations among the 32 participants in the active arm is 99%, then the probability we will see 31 or more participants with detectable PK concentrations is 98%. Furthermore, if the true rate of a given safety event in the placebo arm is 12.5%, the sample size provides 90% power to exclude safety event rates greater than 57.5%.
Further details of the statistical properties for this study are described in section 10.4.1 of the protocol.

3. GENERAL DATA ANALYSIS CONSIDERATIONS

3.1 Analysis Set(s)

For the primary PK endpoint, all participants with concentration results from at least two sample collection timepoints will be included in the PK analysis set. For the primary safety endpoint and secondary

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adherence endpoint, all participants with a study IVR inserted at any time during the trial will be included in the analysis set. For the secondary acceptability endpoint, all participants who completed question J2 of the product use end visit computer assisted self-interview (PUEV CASI) behavioral questionnaire will be included in the analysis set.

3.2 Statistical Analysis Issues

Based on previous MTN trials, minimal missing data is expected for the primary PK and safety endpoints. Any missing data will be tabulated as a separate category when reporting data summaries.

If missing data rates are higher than anticipated (over 10%), secondary sensitivity analyses will be conducted to assess the impact of the missing data on the study endpoints. These analyses will include imputing the data under the most extreme scenarios of information missingness, such as assuming everyone missing has an extreme value of the missing variable, and less informative imputation approaches.

4. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE

No interim statistical analysis was planned or performed for the MTN-038 study.

One study monitoring committee (SMC) review was conducted for MTN-038 with a report date of May 17, 2019. Evaluation of safety was based on descriptive tables of adverse events, with no formal statistical testing.

5. GENERAL ANALYSIS METHODS

Descriptive statistics will be used to assess group characteristics or difference by study arm. Continuous variables will be summarized using the number of non-missing values, mean, standard deviation, median, interquartile range (IQR), and range (minimum and maximum). Categorical variables will be summarized using the number of missing values, frequencies, and percentages. The Pearson-Clopper method[1] will be used to obtain 95% confidence intervals on the proportion of binary variables where applicable.

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 arms is required, the following methods will be used: Fisher's exact test or logistic linear regression for categorical response variables; t-test or linear regression for continuous outcomes. Hypothesis tests for the primary and secondary endpoints comparing the two study arms (active and placebo IVR arms) will have a two-sided significance level of 5%.

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.

In any situation with missing data, appropriate secondary analyses will be performed to adjust for variables that may be related to the missingness mechanism. If missing data rates are higher than 10%, covariates that are related to missingness in likelihood-based regression models will be included. A sensitivity analysis to assess the potential impact of the missing data will also be performed. These analyses will include imputing the data under the most extreme scenarios of information missingness,

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such as assuming everyone missing has an extreme value of the missing variable, and less informative imputation approaches.

6. TRIAL PARTICIPANT DISPOSITION

6.1 Disposition of Participants

Enrollment of participants took place at three study sites in the U.S: San Francisco, CA, Pittsburgh, PA, and Birmingham, AL. The participants screened and the reasons for those not enrolled will be summarized in a table by study site. The participants screened and enrolled by month will be summarized by study site. In addition, a consort diagram will describe the screening, eligibility, enrollment, randomization, and follow-up for the participants in this study.

6.2 Retention

For each visit, a participant is expected to have returned to the site clinic within a protocol-specified visit window based on the date of her enrollment visit. The proportion of participants retained at a scheduled visit is obtained by dividing the number of participants who have completed the visit by the number of participants expected for that visit. Tables will be presented that show by visit the number and percentage of expected, retained, and missed visits in addition to participants lost-to-follow-up or terminated early from the study by site and by arm. No formal statistical testing will be conducted.

6.3 Study and Study Product Discontinuation

The number and percentage of participants who completed the study, along with the number and percentages of participants who did not complete the study for the reasons collected on the Study Termination eCRF will be presented in tables by site and by arm. Reasons for not completing the study include the following: death, participant refusal of further participation, unwilling to comply with study procedures, lost to follow-up, investigator decision, participant refusal of further study product use, unable to contact participant, early study closure, pregnancy, HIV infection, adverse event, protocol deviation, allergic reaction to IVR, breastfeeding, non-therapeutic drug use, and other. No formal statistical testing will be conducted.

The number and percentage of participants who completed the study product regimen, along with the number and percentages of participants who did not complete the study product as specified per protocol for the reasons collected on the Discontinuation of Study Product eCRF will be presented in tables by site and by arm. Reasons for not completing the study product regimen per protocol include the following: death, participant refusal of further participation, unwilling to comply with study procedures, lost to follow-up, investigator decision, participant refusal of further study product use, unable to contact participant, early study closure, study terminated by sponsor, withdrawal of consent by participant, pregnancy, HIV infection, one or more reactive HIV test results or acute HIV infection suspected, adverse event, protocol deviation, allergic reaction to IVR, breastfeeding, non-therapeutic drug use, reported use of PEP, reported use of PrEP, use of anticoagulant, and other. No formal statistical testing will be conducted.

6.4 Visit Adherence: Completion of procedures

Completion of the following required and expected procedures will be evaluated: 1) physical exams; 2) vital signs; 3) pelvic exams; 4) pregnancy tests; 5) HIV tests; 6) plasma archive; 7) chemistries; 8) CBC with differential and platelets; 9) creatinine; 10) plasma for PK; 11) vaginal swabs for microbiota; 12) vaginal gram stain; 13) cervicovaginal fluid for anti-HSV-2 activity; 14) cervicovaginal fluid for PK; 15) cervicovaginal fluid for biomarkers; 16) cervicovaginal lavage for PK, PD or biomarkers; 17) cervical biopsy for PK; 18) cervical biopsy for PD; 19) rectal fluid for PK; 20) returned IVRs; 21) behavioral assessment; 22) In-depth interview. Tables displaying the number and percentages of participant-visits in

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which these procedures were completed, by arm and by site, will be presented. No formal statistical testing will be conducted.

6.5 Protocol Deviations

Protocol deviations, as collected in the protocol deviations log eCRF will be reported. The number and percentage of participants with protocol deviations, along with the number and percentage of participants experiencing each type of protocol deviation, will be tabulated by site and by arm. Type of deviations include: inappropriate enrollment, failure to follow randomization or blinding procedures, study product management deviation, study product dispensing error, study product use/non-use deviation, study product sharing, study product not returned, conduct of non-protocol procedure, improper AE/EAE follow-up, unreported AE, unreported EAE, breach of confidentiality, physical assessment deviation, lab assessment deviation, mishandled lab specimen, staff performing duties that they are not qualified to perform, questionnaire administration deviation, counseling deviation, use of non-IRB/EC-approved materials, use of excluded concomitant medications, devices, or non-study products, informed consent process deviation, visit completed outside of window, other.

Additionally, a listing with all the recorded protocol deviations will be presented, including the description of the deviation, the steps taken to address the deviation and the steps taken to prevent future occurrences.

7. BASELINE DATA

Baseline characteristics of all enrolled participants will be compared by their treatment assignment as randomized and by site. No formal statistical comparisons will be performed for any of the baseline results below.

7.1 Demographics

Baseline demographic characteristics will include race/ethnicity, age and age category, sex at birth, gender identity, and gender of sex partners. Summary statistics appropriate for the measurement scale will be presented in tables by site and by arm.

7.2 Baseline Medical History

The number and percentage of participants reporting a medical history, as collected on the Medical History CRF, will be tabulated by site and by arm. A listing of all the medical history events will be presented, including whether the event is gradable, severity (if applicable), whether the condition is ongoing, and the beginning and end dates of the events.

7.3 Vital Signs

Baseline vital signs as collected on the Vital Signs eCRF at Screening and Enrollment will be presented for each visit, by arm and by site. Summary statistics appropriate for continuous outcomes will be used to describe distribution of height (at Screening only), weight, body temperature, systolic blood pressure, diastolic blood pressure, pulse, and rate of respiration.

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7.4 Physical Exam

Baseline physical exam results as collected on the Physical Exam eCRF at Screening and Enrollment will be presented for each visit in tables by arm and by site. Number and percentage of participants experiencing any abnormal physical findings at each visit will be presented as well as the number and proportions of participants with findings for the following organ systems and body parts: general appearance; head, eye, ear, nose, and throat; neck; lymph nodes; heart/cardiovascular; lung/respiratory; abdomen; extremities; neurological; skin; and other system.

7.5 Pelvic Exam

Baseline results from the pelvic exam as collected on the Pelvic Exam eCRF at Screening and Enrollment will be presented in tables by arm and by site. Number and percentage of participant-visits for which any abnormal finding was reported will be presented, as well as the number and percentage of specific types of pelvic exam findings.

8. PRIMARY ENDPOINT ANALYSES

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 Mann-Whitney U test (for continuous variables).

To assess the adequacy of the randomization, participant's baseline characteristics including demographics and laboratory measurements will be compared between the two study arms using descriptive statistics. Due to the small sample size, formal comparisons will not be done.

8.1 Pharmacokinetic Primary Endpoint

The proportion of participants with detectable drug levels in the active arm and the measured drug concentration levels will be summarized using descriptive statistics and graphics. Concentration of TFV will be summarized for plasma, cervicovaginal fluid (CVF), rectal fluid, and cervical tissue (biopsy) biological sample types and of TFV-DP concentrations in cervical tissue. Cervical tissue is collected at two time points: Participants are randomized to biopsy collection either at Visits 5 and 8 or Visits 6 and 9. Because of the limited time points per participant, not all the following described analyses will be possible for cervical tissue concentrations.

For concentrations of TFV that fall below the corresponding assay's lower limit of quantification (LLOQ), we will use a value equivalent to half the LLOQ. For CVF, rectal fluid and cervical tissue, the assay-level LLOQ will be adjusted for the sample weight to derive a weight-normalized LLOQ for each specimen sample.

The time to each sample collection will be calculated using the time of insertion of the first IVR at Enrollment, as recorded in the Ring Insertion and Removal eCRF, and the time of sample collection, as recorded in the PK results dataset from the Lab Data Management group.

TFV concentration in the sample types will be described using the following PK parameters: maximum observed concentration (C_{max}), area under the concentration-time curve ($AUC_{0\text{-}92days}$) from enrollment until the last collected sample (Day 92), and time to maximum observed concentration (T_{max}). AUC will be calculated using the trapezoidal method[2] on the observed times to sample collection. The geometric

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mean, geometric coefficient of variation (CV%), median, interquartile range (IQR), minimum, and maximum will be reported for these PK parameters. The CV% will be calculated as $100 \times \sqrt{\exp(s^2) - 1}$, where s is the SD of the natural log-transformed values. The natural log transformation of the concentration values will be used. In addition, these same summary statistics will be used to describe TFV concentrations at each sample collection time-point.

The following tables and figures will be generated:

- Summary table of PK parameters by site and overall
- Summary table(s) of PK concentrations for each sample collection time point and sample type by site and overall
- Spaghetti plot of PK concentrations with all participants over time for each sample type.
- Plot of geometric mean PK concentrations with bars to indicate the exponentiated mean +/- SD of the log values over time for each sample type.

8.2 Safety Primary Endpoint

For the analysis of the primary safety endpoints, two tables summarizing the number and the proportion (in percentage) of participants experiencing (i) a grade 2 or higher genitourinary adverse event and (ii) a grade 3 or higher adverse event, will be produced. Each participant will contribute once in each category (i.e., only the highest severity AE for each participant) for the calculation of the proportions. Exact 95% binomial confidence intervals for the proportion of participants experiencing each safety endpoint, using the Pearson-Clopper method, will be provided for each arm. The Fisher's exact test will be used to test for differences in event rates between the TFV IVR arm and the placebo IVR arm.

Additionally, the following listings and tables of AEs will be presented. No formal statistical testing will be conducted:

- A cumulative listing of AE sorted by arm, site, and participant ID.
- Number and percentages of adverse experiences by body system/MedDRA preferred term and severity overall and by arm, and by site.
- Number and percentages of adverse experiences by body system/MedDRA preferred term and relationship to study product overall and by arm, and by site.
- AE summary: the total number of adverse experiences by severity and relationship to study product, overall and for each arm and each site separately.

9. SECONDARY ENDPOINT ANALYSES

9.1 Adherence Secondary Endpoint

To assess participant adherence to the IVR, the proportion of participants who reported keeping the study IVR inserted at all times during the 91 days will be calculated along with a 95% confidence interval, using the exact Pearson-Clopper method, and these proportions will be formally compared using Fisher's exact test. Adherence will be calculated using the self-reported IVR outages from the Ring Adherence eCRF and clinician-reported outages reported on the Study Termination, the Discontinuation of Study Product, the Product Hold Log, and the Ring Insertion and Removal eCRFs. Clinician-initiated IVR removals for the purpose of clinical examination will be excluded from consideration during product adherence analysis.

For participants who were not fully adherent, the number, median, and IQR of the duration of self-reported removal/expulsion events will be reported. Additionally, the median and IQR of the cumulative time during the study period when the study IVR was outside the vagina will be calculated. No formal statistical comparisons will be performed.

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Additional summaries of the number and proportion of participants who had the vaginal ring in place at the start of the visit, who had the ring removed at the visit, who had a ring inserted at the visit, and the reasons for removals from the Ring Insertion and Removal eCRF will be tabulated by arm. The following information collected on the Ring Adherence eCRF will be tabulated for all follow-up visits, overall and by arm: the total number of times that the participant had the vaginal ring out; the number of times that the participant had the vaginal ring out for more than 12 hours continuously (grouped in following categories: 0, 1, 2, 3 or more), the longest number of days in a row the vaginal ring was out; the number and proportion of participant visits where the ring was removed; the number and proportion of participant visits where the ring came out on its own; the number and proportion of participant visits reporting the different reasons why the vaginal ring was removed and the reasons why the vaginal ring came out on its own. No formal statistical comparisons will be performed.

9.2 Acceptability Secondary Endpoint

To assess acceptability of the study IVR, the participants' answers to questions J2 ("Overall, how much do you like the ring?"), based on the participants' self-report by CASI at the Product Use End Visit (PUEV) or Early Termination Visit, will be used for this the primary endpoint analysis. The acceptability response is on the 10-point Likert scale and will be summarized by calculating the mean, standard deviation, median, IQR, minimum, and maximum values and 95% CI overall, and by study arm. A bar plot of scores reported for question J2, by arm, will be presented. In addition, acceptability between the active and placebo arms will be compared using the t-test or Mann-Whitney U test depending on the distribution of the data.

10. SAFETY ANALYSES

All participants enrolled will be assessed for safety and tolerability. See section 8.2 for the description of the analyses on the Safety Primary Endpoint Adverse Events. For the additional safety results below, no formal statistical testing will be performed.

10.1 Product Holds

Instances of product hold as collected in the Product Hold Log eCRF will be described. The number and percentages of women who had a product hold at least once, the number of product holds, reasons for product holds, resolution of product hold and duration of product hold (for those who were instructed to resume product use) will be presented in tables by arm and by site.

10.2 Laboratory Evaluations

Boxplots and tables with summary statistics (see Section 5) will be reported for laboratory evaluations performed at the Screening and PUEV (Day 91) Visit, by arm and visit and by site and visit. The following tests will be included: hemogram (hemoglobin, hematocrit, MCV, platelets, WBC, neutrophils, lymphocytes, monocytes, eosinophils, and basophils) test results as collected on the Hematology eCRF and chemistries (AST, ALT, and creatinine) test results as collected on the Chemistry Panel eCRF.

10.3 Pelvic Exam Findings

The summary of abnormal pelvic exam findings will include any findings reported on the Pelvic Exam eCRF at any visit after the Enrollment Visit. The numbers and proportion of participant-visits with any abnormal pelvic exam findings and with specific types of findings will be presented in tables by arm and by site.

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10.4 Pregnancy

If any pregnancies are reported during the study, as collected from the Pregnancy Report eCRF, these will be listed, along with the information from the Pregnancy History and Pregnancy Outcome Log eCRFs.

10.5 HIV Testing

If any positive Rapid HIV test results are reported, the number and proportion of participants with positive results as collected in the HIV Test Results eCRF will be summarized in a table by arm. For any positive results, a listing from the HIV Confirmatory Test Results eCRF will be presented.

11. EXPLORATORY ANALYSES

In this section, we describe some analyses related to exploratory endpoints for Adherence, and Acceptability that are considered of special interest.

11.1 Residual TFV levels in used rings

Residual TFV levels in returned IVRs will be reported. Tables with summary statistics appropriate for continuous measurements will be presented, by arm. Box plots and histograms for the residual TFV levels, by arm, will be produced.

11.2 Total TFV released

The amount of TFV released for each ring will be estimated by subtracting the residual level measures from average TFV load level of the corresponding manufacturing batch. Tables with summary statistics, by arm, will be produced and box plots will be used to compare the distribution of the total TFV released.

11.3 Exploratory Acceptability Analyses

As an exploratory endpoint, the number and proportion of participants who reported a score of 9 or higher to question J2 (“Overall, how much do you like the ring?”) will be tabulated by arm, along with 95% confidence intervals calculated using the Pearson-Clopper method. A second cut-off point will also be explored by tabulating the number and proportion of participants who reported a score of 5 or higher to question J2 by arm, along with the 95 confidence intervals.

A composite from answers to questions J1 (“Overall, how much do you like male condoms?”) and J2 will be presented. Answers to both questions are recorded as Likert scales from 1 to 10. Additionally, the number and proportion of participants who reported a score as high or higher to question J2 than to question J1 will be tabulated by arm, with 95% confidence intervals.

For these endpoints, the proportions will be formally compared between the TFV IVR arm and the comparator placebo IVR arm using Fisher’s exact test. A bar plot of scores reported for question J2, by arm, will be presented.

A bar plot of scores reported for question JJ4 “If the ring is found to be effective for HIV prevention, how likely would you be to use it in the future if it were available?” will be presented. The number and proportion of participants who reported a score of 9 or 10 to question JJ4 will be tabulated by arm, along with 95% confidence intervals calculated using the Pearson-Clopper method.

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12. REFERENCES

1. C.J.Clopper and E.S. Pearson, *The use of confidence or fiducial limits illustrated in the case of the binomial*, Biometrika, vol. 26, 404-413.
2. Jaki T, Wolfsegger MJ. *Non-compartmental estimation of pharmacokinetic parameters for flexible sampling designs.* Statistics in Medicine. 2012; 31 (11):1059-1073.

13. CHANGE HISTORY

Identify major changes. Only changes after version 1.0 approval need to be recorded.

Version		Affected Section(s)	Activity Description
Number	Effective Date		

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