Protocol DR-OVP-001

Safety and Acceptability Study of a Non-Hormonal Ring

Statistical Analysis Plan

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STATISTICAL ANALYSIS PLAN APPROVAL

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
BMI	Body Mass Index
BV	Bacterial Vaginosis
CRF	Case Report Form
CSR	Clinical Study Report
CVF	Cervicovaginal Fluid
EVMS	Eastern Virginia Medical School
FDA	Food and Drug Administration
FG	Ferrous Gluconate
HIV	Human Immunodeficiency Virus
HPF	High Power Field
IQR	Interquartile Range
MedDRA	Medical Dictionary for Regulatory Activities
OPK	Ovulation Predictor Kit
OVP	Ovaprene®
PCT	Postcoital Test
PMA	Premarket Approval – Food and Drug Administration
PMS	Progressively Motile Sperm
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
UTI	Urinary Tract Infection
WHO	World Health Organization

1.0 INTRODUCTION

This statistical analysis plan (SAP) was developed after review of the DR-OPV-001 study protocol V06.00 (13 June 2019) and case report forms (CRFs) V7.00 (13 May 2019), but before any analysis of the data had begun. Detailed information is given to aid in the production of the statistical outputs and the statistical section of the final clinical study report (CSR). This document gives a summary of the protocol and describes the populations that will be analyzed. All subject characteristics, efficacy, safety, acceptability, and device fit parameters that will be evaluated, along with the specific statistical methods, are described. If the actual analysis is deviated, but not that significantly different, from this document, no amendment to SAP will be done, and the changes will be described in the final CSR.

2.0 PROTOCOL SUMMARY

2.1 Background

Ovaprene® (OVP) is a single use, hormone-free contraceptive device for female contraception. It consists of a flexible ring combined with a knitted polymer barrier insert. The ring component is comprised of a liquid silicone rubber matrix that is combined with a proprietary mixture of ferrous gluconate (FG), ascorbic acid (Vitamin C), glycine, and polyglycolide microparticles. Historically, the PCT was developed to evaluate couples with infertility, but it has been used in the initial evaluation of vaginal chemical and mechanical contraceptive barriers. If PCT testing of Ovaprene® were to show results similar to the results from Food and Drug Administration (FDA)-approved diaphragms, such as Lea's Shield, FemCap®, and the SILCS diaphragm (also known as Caya®), it is likely that Ovaprene® would also show similar results in a contraceptive effectiveness study. An Ovaprene® postcoital test (PCT) study in 20 women was published in 2009.[1] It demonstrated proof of concept in terms of demonstrating no progressively motile sperm (PMS) seen in cervical mucus with the device in place. This new study is designed to provide more evidence of changes in the PCT results with and without the OVP in place, as well as safety and acceptability.

2.2 Objectives

The primary objective of the study is to look at the changes in PCT results due to device use. An average of fewer than 5 progressively motile sperm in the cervical mucus per high powered field (HPF) is considered indicative of acceptable barrier function.

The secondary and tertiary objectives include the release of ferrous gluconate from device, safety, acceptability, and fit.

2.3 Study Design

This is a multi-center, open-label, non-significant risk device feasibility study recruiting up to approximately 45 healthy, sexually active women who are not at risk for pregnancy due to previous female tubal sterilization, and their male partners, with the goal of approximately 25 couples completing the study. Each woman will be seen for a screening visit and in 5 scheduled menstrual cycles:

- One Baseline PCT cycle (no device) with one act of intercourse at the time of ovulation to collect baseline information on the female and male subjects (enrollment will take place at the successful completion of this cycle);
- One Caya® PCT cycle using the Caya® diaphragm with spermicide during one act of intercourse at the time of ovulation;
- One Ovaprene® safety, release, acceptability, and fit assessment cycle with no acts of intercourse (abbreviated as "Ovaprene® safety cycle"); and
- Two Ovaprene® PCT cycles using Ovaprene® during one act of intercourse at the time of ovulation in each cycle.

The purpose of the Caya® PCT cycle is to ensure that in this study population and at these sites, results that are expected to be observed in a PCT cycle with an approved vaginal barrier can be replicated.

Subjects will be seen in 21 scheduled visits over a period of up to 6-7 months, as shown below, and will be contacted 7-10 days after the final visit. Additional visits may take place if certain procedures must be repeated.

Study Visits and Cycles (following Visit 1 - Screening):

	Cycle 1 Baseline PCT			Cycle 2 Caya® PCT		Cycle 3 Ovaprene® safety cycle					Cycle 4 Ovaprene® PCT					Cycle 5 Ovaprene® PCT				
Visit	2 BP1	3 BP2	4 BP3	5 CP1	6 CP2	7 OS1	8 OS2	9 OS3	10 OS4	11 OS5	12 OP1 A	13 OP2 A	14 OP3 A	15 OP4 A	16 OP5 A	17 OP1 B	18 OP2 B	19 OP3 B	20 OP4 B	21 OP5 B

2.4 Study Endpoints

Objective	Endpoint	Cycle(s) or visits in which endpoint is assessed
Primary: 1. Changes in PCT results due to device use	a) Proportion of women and cycles with an average of fewer than 5 progressively motile sperm per HPF in cervical mucus, after sex at ovulation in the *absence* of the device.	Baseline PCT cycle
	b) Mean, median, standard deviation and interquartile range (IQR) for the average number (across 9 HPFs) of progressively motile sperm per HPF in cervical mucus, across all subjects, in the *absence* of the device.	Baseline PCT cycle
	c) Proportion of women and cycles with an average of fewer than 5 progressively motile sperm per HPF in cervical mucus, in the *presence* of the Ovaprene® device.	Ovaprene® PCT cycles
	d) Mean, median, standard deviation and interquartile range (IQR) for the average number (across 9 HPFs) of progressively motile sperm per HPF in cervical mucus, across all women and cycles, in the *presence* of the Ovaprene® device.	Ovaprene® PCT cycles
	e) Mean, median, standard deviation and interquartile range (IQR) for change from baseline in the number of progressively motile sperm per MPF in cervical mucus during each Ovaprene® test cycle, across all women.	Ovaprene® PCT cycles vs. baseline PCT cycle
Secondary: 2. Release of active	a) Levels of ferrous gluconate in CVF before sex that are associated with fewer than 5 progressively motile sperm per HPF in the cervical mucus after sex (i.e. success), during ovulation.	Ovaprene® PCT cycles

component from device	b) Levels of ferrous gluconate in CVF at multiple time points in the cycle in the absence of coitus. (Allows estimation of how long after insertion it takes to reach levels associated with "success" and whether levels associated with "success" are still present 27-29 days after insertion.)	Ovaprene® safety cycles
	c) Levels of ferrous gluconate in CVF before and at multiple time points after sex at ovulation with the device in place. (Allows determination of whether they are different from before sex and, if so, how much time is needed to return to pre-sex levels.)	Ovaprene® PCT cycles
	d) Cervicovaginal pH before and after sex in the absence and presence of the device	Baseline PCT cycle, Ovaprene® PCT cycles
	e) Residual amount of ferrous gluconate in Ovaprene devices that have been worn over a cycle of use.	Ovaprene® safety cycle and Ovaprene® PCT cycles
3. Safety	a) Treatment-emergent AEs among female subjects during Ovaprene® use.	Ovaprene® safety cycle & Ovaprene® PCT cycles
	b) Urogenital, product-related, and/or serious AEs among female and male subjects during Ovaprene® use.	Ovaprene® safety cycle & Ovaprene® PCT cycles
	c) Changes from baseline in complete blood count, serum chemistries, and serum ferritin	Ovaprene® safety cycle
	d) Changes from baseline in findings on pelvic exam, including colposcopy.	Ovaprene® safety cycle & Ovaprene® PCT cycles
	e) Changes from baseline in: ▪ Nugent score and microflora ▪ Antibacterial (anti-E. coli) activity in CVF ▪ Soluble markers of inflammation in CVF	Ovaprene® safety cycle & Ovaprene® PCT cycles
	f) Presence of *Staphylococcus aureus* or group A *Streptococcus* on Ovaprene® devices that have been worn over a cycle of use	Ovaprene® safety cycle & Ovaprene® PCT cycles
Tertiary: 4. Acceptability	a) Response on acceptability questionnaire/diary: ▪ Problems with insertion, including confirmation of placement ▪ Aspects liked most and least by the female partner ▪ Dislodgements reported by the female partner ▪ Comfort reported by both partners during intercourse and whether discomfort, if reported, was bothersome and would keep the person from using the device again	Ovaprene® safety cycle & Ovaprene® PCT cycles
5. Fit	a) Proportion of subjects who can be fitted with Ovaprene®.	Baseline PCT cycle
	b) Proportion of subjects who can correctly insert, position, and remove the device using written instructions only.	Baseline PCT cycle, Ovaprene® safety cycle & Ovaprene® PCT cycles
	c) Proportion of subjects who require assistance to correctly insert, position, and remove the device.	Baseline PCT cycle, Ovaprene®

		safety cycle & Ovaprene® PCT cycles
	d) Location of Ovaprene® in relation to the cervix as determined by clinical exam; relationship of position to PCT results, safety, and acceptability.	Ovaprene® safety cycle & Ovaprene® PCT cycles

2.5 Sample Size Consideration

Approximately 45 women will be enrolled, with the intent that approximately 25 will complete the study. Statistical considerations were not used to determine the size of the study population; rather, the study size was determined according to the maximum number of subjects who could feasibly be enrolled and complete this rigorous protocol in a reasonable time frame.

3.0 STATISTICAL METHODS

3.1 Statistical Handling Policy

3.1.1 Safety Monitoring and Interim Analysis

No formal Data Safety and Monitoring Board (DSMB) has been established, but all safety related data, such as adverse events (AEs), including urogenital, product-related, and/or serious adverse events (SAEs) among female and male subjects, will be reviewed periodically by qualified medical personnel. A completed SAE form must be faxed or emailed to Daré Bioscience or designee within 24 hours of its discovery. The Investigator must complete, sign and date the SAE pages, verifying the accuracy of the information recorded on the SAE pages with the corresponding source documents.

The first interim analysis will take place after at least 10 women have completed one Ovaprene® PCT cycle, and then another interim analysis will take place when at least 20 women have completed one Ovaprene® PCT cycle. An additional pre-database lock analysis will take place when approximately 20 women have completed the study. For this analysis all PCT data used will have been monitored and therefore be considered clean. There are no cleaning requirements for the first 2 interim analyses. The purpose of the interim analyses is to evaluate all primary endpoints as well as to evaluate the proportion of Ovaprene® PCT cycles with an average of fewer than 5 progressively motile sperm per HPF in cervical mucus, across all women, in the presence of the Ovaprene® device.

3.1.2 Electronic Diary Data

All study participants are to use an electronic device daily diary, answering both closed-ended questions and open-ended questions while in the study. Those data will be presented in by-subject data listings at the end of the study.

3.1.3 Analysis Conventions

This section details general policies used for the statistical analyses. Departures from these general policies may be given in the specific detailed sections of this statistical analysis plan. When this situation occurs, the rules set forth in the specific section take precedence over the general policies. The following policies will be applied to all data presentations and analyses.

- Discrete variables' summary statistics will consist of the number and percent of responses in each category
- Continuous variables' summary statistics will include the sample size (number of non-missing observations), mean, median, standard deviation (SD), minimum and maximum, abbreviated as "6-number summary statistics", where minimum and maximum may be replaced with 25th and 75th percentiles, i.e., interquartile range (IQR), if desired.
- All mean values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Median values will be formatted to same decimal place as the measured values when that is possible without losing accuracy; otherwise, they will be formatted to one more decimal place than the measured values.
- All percentages will be rounded to one decimal place. The number and percent of responses will be presented in the form XX (XX.X), where the percentage is in the parentheses. The decimal of the percentage may be dropped due to space constraints when creating a table. The denominator for percentage calculations will be the number of non-missing observations, or the analysis population's sample size – if no such number of non-missing observations is presented along with the categorical values.
- All by-subject data listings will be sorted for presentation in order of site number, subject number, and date of procedure or event.
- When necessary for analysis purposes, partial dates will be completed (i.e., turned into complete dates) using the most conservative approach: for example, if a concomitant medication start date had Month and Year parts only, it's assumed to be the first day of that month; while if the stop date had Month and Year parts only, it's assumed to be the last day of that month.
- All analysis and summary tables will have the population sample size in the column heading.
- Calculating change from Baseline to a visit will be done as follows:

  Change = Observed value at a Visit – Observed value at Baseline.
- Version 9.4 of SAS® or higher will be the statistical software package used to produce all summary tables, data listings, and statistical analyses.

3.2 Subject Disposition

Subject disposition will be summarized for the All Screened population (see Section 3.4 for Analysis Population definitions). The following data will be presented:

- The number and percent of subjects who consented, screen failed, enrolled, treated with Caya®, treated with Ovaprene®, completed or discontinued prematurely from the study. The number and percent of subjects who discontinued for each reason will be presented. Reasons for screen fails will also be summarized categorically.
- The number and percent of subjects at each scheduled visit.
- The number of subjects at each scheduled visit and time point (at hour 0, 0.5, 1, 2, 4, and 6) in the study site at Eastern Virginia Medical School (EVMS).

- The number of subjects who were consented, screen failed, enrolled, treated with Caya®, treated with Ovaprene®, completed, or discontinued at each study site will be presented.

The End of Trial CRF will be used to determine who discontinued prematurely from the study.

3.3 Protocol Deviations

The number and percent of subjects in the Treated with Caya and Treated with Ovaprene populations with each type of protocol deviation (Subject not consented properly, Subject does not meet eligibility criteria, Scheduled visit completed out of specified window, Deviation from protocol-defined procedure, Clinical assessment not done, Visit not done, Lab processing error, Lab assessment not completed, etc.) will be summarized by study cycle, i.e., Baseline, Caya®, Ovaprene®. Subjects who have more than one deviation event in the same type/cycle are only counted once to that type/cycle.

3.4 Analysis Populations

All Screened: All subjects who were consented and screened for the study.

All Enrolled: All Screened subjects except for screen failures (who haven't met study eligibility criteria).

Treated with Caya: All Enrolled subjects who have used the Caya® in the study.

Treated with Ovaprene: All Enrolled subjects who have used the Ovaprene® in the study.

Treated with Ovaprene with at Least One PCT Cycle: All Enrolled subjects who have used the Ovaprene® and completed one or two PCT cycles in the study.

"Treated with Ovaprene" is a sub-set of "Treated with Caya", whereas all used Ovaprene® device subjects also used Caya® device, but not vice versa. Since Ovaprene® is the target study device, most analyses will be using "Treated with Ovaprene" and "Ovaprene with at Least One PCT Cycle" populations. In the summary tables, "Treated with Caya" and "Treated with Ovaprene" analysis populations will be simply labeled as "Caya Population" and "Ovaprene Population", respectively.

3.5 Subject Demographics and Pre-Treatment Characteristics

Subject demographics and pre-treatment characteristics, including medical histories, will be summarized for the All Enrolled, also will be repeated for Ovaprene and Caya populations.

3.5.1 Demographics

The summary of demographics will include:

- The number and percent of subjects within each category of age (18-35 inclusive, 36+), race, ethnicity.
- The sample size, mean, median, SD, minimum, and maximum values for age, weight, height, and body mass index (BMI). BMI will also be summarized categorically with 4 categories: Underweight, Normal, Overweight, and Obese.

3.5.2 Medical History

The number and percent of subjects reporting a medical history will be summarized for each category by the status ("Ongoing", "Resolved") of the medical history:

- Cardiovascular
- Congenital
- Dermatological
- Gastrointestinal
- Genitourinary/Reproductive
- H.E.E.N.T.
- Hematological
- Hepatic/Biliary
- Immunological/Allergies
- Metabolic
- Musculoskeletal
- Neurological/Psychological
- Prior Surgery
- Recent Trauma (past 3 months)
- Renal
- Respiratory

Subjects reporting more than one medical history in the same body area, same status ("Ongoing", "Resolved") are counted only once to that body system and that status.

3.5.3 Gynecological History

The number and percent of subjects in each of the following gynecological history conditions will be presented along with the number and percent of subjects with their condition currently ongoing and resolved:

- Heaviest Volume of Flow (Light, Moderate, Heavy),
- Any History of Irregular Periods (Yes, No)
- Symptoms of Menstruation (Check all that apply: Cramps, Backache, Headache, Nausea, Vomiting, Diarrhea, Acne, Mood Changes, Breast Tenderness, Appetite Changes, Bloating, Other)
- Urinary Tract Infection History (Never, Once in the past year, Twice in the past year, Yes, but not in the past year, More than twice in the past year, Don't know/Uncertain)
- Yeast Infection History (Never, Once in the past year, Twice in the past year, Yes, but not in the past year, More than twice in the past year, Don't know/Uncertain)
- Bacterial Vaginosis (BV) (Never, Once in the past year, Twice in the past year, Yes, but not in the past year, More than twice in the past year, Don't know/Uncertain)
- Breasts (Normal History, Abnormal History, Not Done)
- Vulva (Normal History, Abnormal History, Not Done)
- Vaginal Wall (Normal History, Abnormal History, Not Done)
- Cervix (Normal History, Abnormal History, Not Done)
- Uterus (Normal History, Abnormal History, Not Done)
- Adnexae (Normal History, Abnormal History, Not Done)
- Rectal (Normal History, Abnormal History, Not Done)

The 6-number summary statistics will be provided for the following 2 questions:

- Average Cycle Length (# of days)
- Usual Flow Duration (# of days)

3.5.4 Contraceptive History

Contraceptive history will be summarized for the all questions collected in the CRF with the number and percent of subjects in questions of:

- Male Condom
- Female Condom
- Diaphragm
- Oral Contraceptive Pill
- Spermicides
- Vaginal Ring
- Contraceptive Patch
- Sponge
- Natural Family Planning/Rhythm Method
- Withdrawal
- IUD
- Injectable
- Implant
- Abstinence
- Subject Surgically Sterile
- Sexual Partner Surgically Sterile
- Emergency Contraception
- Other Method

The 6-number summary statistics will be provided for the “Length of Abstinence”, after converting the one Year to 12 months.

3.5.5 Pregnancy History

Contraceptive history will be summarized with 6-number statistics, as well as categorically, for the questions:

- Number of times the subject has been pregnant
- Number of pregnancies that resulted in preterm deliveries
- Number of full-term pregnancies (at least 37 weeks)
- Number of ectopic pregnancies
- Number of spontaneously aborted pregnancies
- Number of therapeutically aborted pregnancies
- Number of living children

The following questions will be summarized categorically:

- Is the subject currently breastfeeding? (Yes, No)
- Has the subject stopped breastfeeding in the last 30 days? (Yes, No)

3.5.6 Prior and Concomitant Medications

All medications (prior and concomitant) taken by subjects during the study (from screening through recovery) will be coded to the therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug classifications. The WHO Drug 2017 March dictionary will be used for this study.

- Prior Medications – There will be 2 types Prior Medications: Prior to Caya medications are any medication that was used prior to the date of Caya® device placement; Prior to Ovaprene Medications are any medication that was used prior to the date Ovaprene® device placement.
- Concomitant Medications – There will also be 2 types Concomitant Medications: Concomitant with Caya medications are any medication that was taken on or after the date of Caya® device placement, and Concomitant with Ovaprene medications are any medication that was taken on or after the date of Ovaprene® device placement.

Prior and Concomitant medications will be summarized for the Treated with Caya population and Treated with Ovaprene population, respectively. Summaries will provide the number and percent of subjects who took medications that were coded to each generic drug name and therapeutic drug class, as well as the number and percent of subjects who took at least one medication. Subjects reporting more than one medication in the same drug class/generic name are counted only once to that drug class/generic name.

3.6 Efficacy Analysis

All efficacy analyses will be done for the Ovaprene with at Least One PCT Cycle population, and may be repeated for Treated with Caya population when necessary. The primary efficacy analysis will be the changes in PCT results due to Ovaprene® device use, and consists of the following 6 endpoints:

a) The proportion (and 95% exact binomial confidence interval [2]) of subjects with an average of fewer than 5 progressively motile sperm per HPF in cervical mucus, after sex at ovulation in the absence of the device. This needs to use the "Average number of progressively motile sperm" (SAS variable name MUAVPMS) in Cervical Mucus CRF, and count the number of subjects with MUAVPMS < 5.0 at the Visit 3 (BP2); then divided by the total number of subjects with PMS measurements at this visit, and finally converted to a percentage (multiplied by 100). In the data listing of PMS data, the data that occur in a cycle after a dislodgement in the e-diary, and clinician noted dislodgement, will be flagged.

   This primary efficacy analysis will be repeated by subgroups for:

   (1) Had vaginal ring use before enrolling in the study vs. Never had

   (2) Had vaginal delivery vs. caesarean birth

   (3) BMI ≥30 (Obese) vs. <30 at Baseline

   (4) Study site EVMS vs. Non-EVMS study sites

   (5) Device position at the time PCT: Over cervical os, Not over cervical os - on anterior vaginal wall, Not over cervical os and not on anterior vaginal wall

(6) Dislodgments (dislodgement reported in cycle before the PCT visit vs. no dislodgements reported in cycle before PCT).

b) The sample size, mean, median, standard deviation, and interquartile range (IQR, i.e., 25th and 75th percentiles), for the average number (across 9 HPFs) of progressively motile sperm per HPF in cervical mucus, across all treated subjects, in the absence of the device. This is to summarize the same field (MUAVPMS) in the above Bullet a) as a continuous variable at Visit BP2.

c) The proportion of subjects (and 95% exact binomial confidence interval) with an average of fewer than 5 progressively motile sperm per HPF in cervical mucus, in the presence of the Ovaprene® device. This is similar to that in Bullet a), but will be done at Visit OP3A, and at Visit OP3B, by sub-setting the CRF data at VISIT_ID = 14, and at VISIT_ID = 19, respectively.

d) The sample size, mean, median, and standard deviation for the average number (across 9 HPFs) of progressively motile sperm per HPF in cervical mucus, across all treated subjects, in the presence of the Ovaprene® device. This is similar to that in Bullet b), but will be done at Visit OP3A, and also at Visit OP3B, by sub-setting the CRF MU data at VISIT_ID = 14, and at VISIT_ID = 19, respectively.

e) The change from Baseline for the average number (across 9 HPFs) of progressively motile sperm per HPF in cervical mucus, across all Ovaprene® subjects. The change from Visit BP2 to Visit OP3A will be calculated by the value of MUAVPMS at Visit OP3A – the value of MUAVPMS at Visit BP2. Then this change will be summarized by the sample size, mean, and median, and standard deviation across all treated subjects. Similarly, the changes from Visit BP2 to Visit OP3B will be calculated by replacing the Visit OP3A with OP3B.

f) Overall percent of cycles with fewer than 5 PMS in the presence of Ovaprene® device. The numerator for this percentage will be the sum of all Ovaprene® device use cycles in the above Bullet c), and the denominator will be the total number of cycles from all treated with Ovaprene® and with MUAVPMS values.

g) The sample size, mean, median, and standard deviation for the average number (across 9 HPFs) of progressively motile sperm per HPF in cervical mucus, across all Ovaprene® device cycles. This is similar to that in Bullet d), but will be inclusive of Visit OP3A and Visit OP3B.

Note that if a PCT cycle met the following 2 criteria that made the cycle invalid for the analysis, that cycle will be excluded from the efficacy analysis, but all safety data in that cycle will still be included in safety analysis:

- There is No, or Insufficient, material for sperm present in the vaginal pool, and
- Sperm at 100x and 400x also equals ‘No’.

The secondary efficacy analysis will focus on the release of active component from the device in vaginal and cervix samples, and consists of the following endpoints:

a) Determine the concentration release curve of ferrous gluconate in cervicovaginal fluid (CVF) over the first 4-6 hours after Ovaprene® insertion at one clinical site

b) Determine whether the minimum target level of 8.2 µg/mL is achieved in the first 4-6 hours after Ovaprene® insertion at one clinical site.

c) Levels of ferrous gluconate in CVF before sex that are associated with fewer than 5 progressively motile sperm per HPF in the cervical mucus after sex (i.e. success), during ovulation. Summary statistics of sample size, mean, median, standard deviation, and IQR will be presented by visit.

d) Levels of ferrous gluconate in CVF at multiple time points in the safety cycle in the absence of coitus. This will allow the estimation of how long after insertion it takes to reach the target concentration levels associated with success and whether target levels are still present up to 29 days after insertion. Summary statistics of sample size, mean, median, standard deviation, and IQR will be presented by visit and assessment time-point.

e) Levels of ferrous gluconate in CVF before and at multiple time points after sex at ovulation with the device in place. This will allow determination of whether they are different from before sex and, if so, how much time is needed to return to pre-sex levels at all visits in Ovaprene® PCT cycles in both vaginal and cervical fluid. Summary statistics of sample size, mean, median, standard deviation, and IQR will be presented by visit and assessment time-point.

f) Vaginal pH (from Vaginal Sample CRF) and cervical pH (from Cervical Mucus CRF) before and after sex in the absence and presence of the device. Six-number summary for the observed values and difference between pre-sex and after sex will be presented by visit. For the study site (EVMS only) with multiple timepoints at a visit, the summary will be done at each timepoint. The average of pH values within each visit over the multiple timepoints will be calculated for each subject, and then be summarized. The goal of these assessments during the Ovaprene® safety cycle is to look at the effect of study device in the absence of sex.

g) Residual amount of ferrous gluconate in Ovaprene® devices that have been worn over a cycle of use. Six-number summary statistics will be presented by visit and by duration of time the device was worn (1-7 days, 8-14 days, 15-21 days, 22-28 days and >28 days).

h) Cervical mucus score. Summary statistics mean, median, standard deviation, and IQR will be presented by visit. The number and percent of subjects with cervical mucus score ≥ 10 in each Ovaprene cycle will also be presented. For the summary of cervical mucus score ≥ 10, cervical mucus data will only be used from the cycle that occurs after the highest OPK result for that cycle.

3.7 Safety Analysis

All safety analyses will be performed descriptively, and done for the Treated with Caya (if data exists for Caya cycle) and Treated with Ovaprene population.

Except for adverse events and concomitant medication, all safety data summary tables will be based on scheduled visits data, but if an safety assessment was later done again in an unscheduled visit, the data in this unscheduled visit will be used for the summary table in place of the safety data collected at the originally scheduled visit.

3.7.1 Adverse Events

An adverse event is any symptom, sign, illness, or experience that develops or worsens in severity and/or frequency after the date of informed consent. Each AE incidence will be assigned to one of the 3 Study Periods:

(a) Baseline Cycle,
(b) Caya® Cycle,
(c) Ovaprene® Cycles,

depending on the AE start date within the time-frame of:

(a) from date of consent through Cycle 1,
(b) during Caya® cycle (Cycle 2),
(c) in Cycles 3 through 5, respectively.

All adverse events will be coded with MedDRA 20.0. Incidence of adverse events will be summarized by system organ class (SOC) and preferred term (i.e., MedDRA term). The number and percent of subjects with each SOC and preferred term will be presented by the following 2 analysis populations:

(i) Subject was treated Ovaprene, including AEs at Baseline and Ovaprene cycles

(ii) Subject was treated with Caya, including AEs at Baseline and Caya cycles

Tables to summarize the incidence rates among female subjects (from those with answer "Female" to the question "Affected person?" in AE CRF) will be created for each of the following groups:

- Overall number and percent of subjects with AEs without presenting SOC or preferred term
- AEs by SOC and preferred term
- Study product-related AEs (including Possibly Related, Probably Related, and Definitely Related) by SOC and preferred term
- AEs presented in descending order of frequency by preferred term (without showing SOC), in which the most frequent one appears at first, and least frequent one will appear in the last
- AEs by SOC and preferred term and by severity
- AEs by SOC and preferred term and by relationship to the study product
- AEs by SOC and preferred term for each Ovaprene cycle by subgroups of Ovaprene location (based on digital exam) where the following 2 subgroups are used: "Over cervical os", "Not over cervical os". If a subject has an assessment of "Not over cervical os" in the cycle then that will be the classification for that cycle. The "Not over cervical os" will be made up of the following 2 sub-categories: "Not over cervical os - on anterior vaginal wall", and "Not over cervical os and not on anterior vaginal wall".

If a subject reports the same AE (i.e., same preferred term) more than once, that subject is counted only once to each "Study Period", and also only once to the "Total", for the summary of that AE, using the highest severity. The only exception to this will be for the summary by relationship to study device. For that summary, if a subject reports the same AE more than once, that subject is counted only once for the summary of that AE, using the most likely relationship to study product. The same principle will be applied at the body system level summary.

An overall summary of AEs, without presenting SOC or preferred term, by severity and relationship to study product will be presented, where it counts the number of events, not number of subjects, at each and every combination of severity level with relationship level.

AEs that led to premature discontinuation from the study will be listed. Subjects who developed a UTI during the study, as well as SAEs and urogenital system AEs in subjects and male partners will also be listed. These 4 listings will contain the details of those adverse events such as

severity, relationship to study device, and outcome. Other supportive data, such as the subject's age, will be provided. For the listing of "subjects who developed a UTI during the study", it will include the information of medical history of UTI, if any, at the study entry.

3.7.2 Hematology, Chemistry and Serum Ferritin

Hematology, chemistry and serum ferritin changes from Baseline (Visit OS1) to Visit OS5 visit will be summarized by 6-number statistics. A summary of shifts from Baseline (Visit OS1) to Visit OS5 will be presented for each lab test parameter. The normal range for each parameter will be used to create categories of Low, Normal, or High. Any result that is higher (lower) than the upper (lower) limit of normal will be categorized as High (Low), and any result within the lower and upper limits of normal will be categorized as Normal. The number and percent of subjects in each category (Low, Normal, or High) from Baseline (Visit OS1) to Visit OS5 visit will be presented for each lab test parameter.

3.7.3 Urinalysis

Urinalysis is only required if subject is symptomatic for urine tract infection (UTI). All urinalysis parameters, except for Specific Gravity, will be summarized categorically. Specific Gravity will be summarized by 6-number statistics.

3.7.4 Colposcopy

Colposcopic assessment CRF does not have visit identifier. It will be linked with Visit CRF data by making the colposcopic assessment date to be equal to the visit date in Visit CRF, and then summarized categorically for the parameters in Colposcopic Findings CRF by visit:

- Were there any colposcopic findings? (Yes, No)
- If yes,
- Product related (No-present before product use, No-latrogenic, No-other, Yes-possibly, Yes-probably, Yes-definitely)
- Serious (Yes, No)
- Outcome (Resolved without sequelae, Resolved with sequelae, Finding still present at discontinuation/ exit, Subject died as a result of this finding, Unknown, subject lost to follow-up)
- Diagnosis (Normal, Erythema, Edema, Grossly white finding, Petechiae, Ecchymosis, Peeling, Ulcer, Abrasion, Laceration, Other)

Frequencies of each categorical result at Visit OS1 and Visit OS5 will be presented. The number and percentage of subjects with a worsening since baseline (OS1) of a finding will be summarized. The medical monitor will perform a review of the data to indicate subjects who had a worsening.

3.7.5 Gynecological Examination

Gynecological examination will be performed during the screening and after the study device placement in the following areas, and the results at the last assessment before the device placement will be summarized categorically ("Normal", "Abnormal") by visit.

- Vulva (Normal, Abnormal)
- Vaginal (Normal, Abnormal)
- Cervix (Normal, Abnormal)

- Adnexae (Normal, Abnormal)
- Uterus (Normal, Abnormal)

The number of subjects with clinically significant result in gynecological examination will also be presented. Change from Baseline results will be classified and defined as follows, and then summarized categorically at each post-baseline visit.

- "Improved" = if Abnormal at Baseline and Normal at post-Baseline;
- "No Change" = if post-Baseline result is the same as the Baseline;
- "Worsened" = if Normal at Baseline and Abnormal at post-Baseline.

3.7.6 Nugent's Score and Vaginal Microflora

Nugent's score (from central lab, if available; otherwise, use local lab) and antibacterial (anti-E. coli) activity in CVF, soluble markers of inflammation in CVF and changes in these endpoints from Visit OS1 to OS2 through OS5 and from Visit OP1 to OP5,will be summarized by 6-number statistics at each visit. Antibacterial and soluble marker changes will also be summaries for these changes: BP1 to OS1, BP2 to OP3 and OP1 to OP3. Vaginal microflora and staphylococcus aureus assessment on the ring will not be analyzed by HD and the vendor analysis of the data will be included as an appendix of the final clinical study report.

3.7.7 Physical Examination

Physical examination is optional, and will be performed if the history is significant for a medical condition. The number and percent of subjects in each category of "Normal" / "Abnormal" will be presented by body system at each visit.

3.8 Acceptability Questionnaire

An acceptability questionnaire developed for this study is administered at the Ovaprene® cycles. The following questions' answers will be summarized with the number and percent of subjects in each response category at each visit, as well as shift tables (frequencies of each categorical response at one visit cross tabulate with the frequencies from another visit, from Visit OS5 to Visits OP3A and OP3B, and from Visit OP3A to Visit OP3B):

1. How would you describe the ease of Ovaprene® insertion? (Response: Very easy, Fairly easy, Neither easy nor difficult, Somewhat difficult, Very difficult)
2. During the study, were you aware of the Ovaprene® device during your normal daily activities? (Response: Always, Most of the time, Some of the time, Rarely, Never)
3. How did it feel to have the Ovaprene® device in place when you were not having sex? (Response: Usually comfortable, Neither comfortable nor uncomfortable, Sometimes comfortable and sometimes uncomfortable, Usually uncomfortable)
4. Have you had sex with the device in place? (Response: No, Yes)
5. How did it feel to have the Ovaprene® device in place when you were having sex? (Response: Usually comfortable, Neither comfortable nor uncomfortable, Sometimes comfortable and sometimes uncomfortable, Usually uncomfortable)
6. If Ovaprene® became available and you needed protection from pregnancy, would discomfort prevent you from using it? (Response: No, Yes)

7. Was your partner aware of the device when you were having sex? (Response: Always, Most of the time, Some of the time, Rarely, Never)
8. Did your partner experience discomfort from the device when you user having sex? (Response: Always, Most of the time, Some of the time, Rarely, Never)
9. If Ovaprene® became available and you needed protection from pregnancy, would your partner's discomfort prevent you from using it? (Response: No, Yes)
10. Do you think it would be possible for a woman to use this product without her partner's knowledge? (Response: No, Yes)
11. While you have already had tubal sterilization, if you needed protection against pregnancy, how likely would you be to use Ovaprene® if it became available? (Response: Very unlikely, Unlikely, Likely, Very likely)
12. Have you ever used a diaphragm when you needed protection against pregnancy? (Response: No, Yes)
13. While you have already had tubal sterilization, if you needed protection from pregnancy and you could only choose between Ovaprene® and a diaphragm, which would you choose? (Response: Ovaprene®, Diaphragm)
14. How likely would you be to recommend Ovaprene® to a friend who needed protection against pregnancy if Ovaprene® became available? (Response: Very unlikely, Unlikely, Likely, Very likely)

There are a few open-ended questions in the questionnaire, such as the following four:

- List up to three things you like about Ovaprene®,
- List up to three things you don't like about Ovaprene®
- Do you have any suggestions for changes or improvements to the Ovaprene device? (No, Yes-please describe)
- Please write down any additional comments you have not reported elsewhere on this questionnaire and that you would like to share with us.

These open-ended questions will be summarized categorically with all actual responses, after some basic processing, such as removing redundant spaces (i.e., double spaces) between words, converting texts to lower cases, but making the first letter of a sentence in upper case.

Frequencies of answers to the closed-ended acceptability questions will also be cross-tabulated with Ovaprene device position (based on digital exam) after linking the Device Position CRF data with Acceptability Questionnaire CRF data.

3.9 Device Fit Judged by Clinicians

Device fit analyses will be done for each visit and will be based on the data collected in the Device Position CRF, and includes the following endpoints:

a) Proportion of subjects who can be fitted with Ovaprene®. This is from the CRF questions "Did the Ovaprene® device fit the subject?" (Response: Yes, No). The numerator is the number of clinicians who have answered "Yes", and denominator is the total number of clinicians who have answered the question.

b) Proportion of subjects who can correctly insert the Ovaprene® device using written instructions only. This is from the question "Was the subject able to insert the Ovaprene® device using:" with response: Only written instructions, Written and verbal instructions, Written and verbal instruction and physical assistance. The numerator is the number of clinicians who have answered "Only written instructions", and denominator is the total number of clinicians who have answered the question.

c) Proportion of subjects who can correctly position the device using written and verbal instructions. This is from the question "Was the subject able to position the Ovaprene® device using:" with response: Only written instructions, Written and verbal instructions, Written and verbal instruction and physical assistance. The numerator is the number of clinicians who have answered "Written and verbal instructions", and denominator is the total number of clinicians who have answered the question.

d) Proportion of subjects who can correctly remove the device using written and verbal instruction and physical assistance. This is from the question "Was the subject able to remove the Ovaprene® device using:" with response: Only written instructions, Written and verbal instructions, Written and verbal instruction and physical assistance. The numerator is the number of clinicians who have answered "Written and verbal instruction and physical assistance", and denominator is the total number of clinicians who have answered the question.

e) Location of Ovaprene® in relation to the cervix as determined by digital examination. Categorical summaries will present the number and percent of clinicians who answered with "Over cervical os", "Not over cervical os - on anterior vaginal wall", and "Not over cervical os and not on anterior vaginal wall".

f) Location of Ovaprene® in relation to the cervix, or to the pubic bone, as determined by visual examination. Categorical summaries will present the number and percent of clinicians who answered with "Over cervical os", "Not over cervical os - on anterior vaginal wall", and "Not over cervical os and not on anterior vaginal wall". Furthermore, for "Not over cervical os - on anterior vaginal wall", more details are asked: "Was the anterior edge of the device behind the pubic bone?" (Yes, No, Unable to tell); "If it was not behind the pubic bone, did you attempt to push it behind the pubic bone?" (No, Yes), "If Yes, were you successful?" (Yes, No). All these answers will be summarized categorically.

g) Each subject will have the following data summarized to compare clinician assessment of position to dislodgements reported in the subject e-diary:

   - Proportion of clinician assessments of displacement (displaced being defined as Not over cervical os - on anterior vaginal wall or Not over cervical os and not on anterior vaginal wall using either visual or digital examination)
   - Number of complete expulsions on the diary
   - Number of partial displacements on the diary
   - Response at end of study to acceptability question: While you have already had tubal sterilization, if you needed protection against pregnancy, how likely would you be to use Ovaprene® if it became available?

- Response at end of study to acceptability question: How likely would you be to recommend Ovaprene® to a friend who needed protection against pregnancy if Ovaprene® became available?
- Had vaginal deliveries

h) Subjects with displacements, based on clinician assessment as defined in g) above, will be listed and the PMS results in the cycle after the displacement will be provided.

3.10 Follow Up Contact

Study follow up will be conducted by contacting all treated subjects approximately 7 days (range 7-10) after their last visit. The data will be summarized categorically for the questions:

- Was follow-up contact made with the subject? (Yes, No)
- Has the subject experienced any new adverse events or serious adverse events? (Yes, No)
- Has the subject started any new medications or had changes in medications? (Yes, No)
- Has the subject's partner experienced any new adverse events involving the urogenital system or associated with the use of the product or any serious adverse events? (Yes, No).

4.0 APPENDICES

4.1 Schedule of Assessments

X = Required, O = Optional/if indicated.

BP = Baseline Postcoital, CP = Caya® Postcoital, OS = Ovaprene® Safety, OP = Ovaprene® Postcoital, UNS = Unscheduled.

Pelvic exam procedures are listed in the recommended sequence of collection.

	Screening	BP1	BP2	BP3	CP 1	CP 2	OS 1	OS 2	OS 3	OS 4	OS 5	OP 1A	OP 2A	OP 3A	OP 4A	OP 5A	OP 1B	OP 2B	OP 3B	OP 4B	OP5 B	UNS
Informed Consent (also male, if required)	X																					
Assign Subject Number	X																					
Demographics	X																					
Assess eligibility	X	X																				
Enroll subject				X																		
Medical/Obstetrical History[1]	X																					X
Directed Physical Exam[2]	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	X
Height/Weight	X																					X
HIV (human immunodeficiency virus) [3]	X																					X
Urine Pregnancy Test	X																					X
Urinalysis[4]	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O	X
CBC, Chemistry, Serum Ferritin	X						X				X											X
Review Diary Entries		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs, Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Acceptability Questionnaire											X			X					X			
Note device position by digital exam								X	X	X	X		X	X	X	X		X	X	X	X	X
Pelvic exam - note irritation seen with naked eye		X	X	X	X	X		X	X	X			X	X	X	X		X	X	X	X	X
Exam of external genitalia, by naked eye & colposcopy	X						X				X		X	X	X	X		X	X	X	X	X

Colposcopic Exam - insert speculum, do naked eye exam of visible vaginal epithelium	X						X				X	X				X	X				X	X
Note device position with speculum in place								X	X	X	X		X	X	X	X		X	X	X	X	X
Vaginal pool - Trich test	X																					X
Vaginal pool - Wet mount[7]	X	O	O	O	O	O	O	O	O	O	O	O		O		O		O			O	X
Vaginal pool - ferrous gluconate							X[12]	X	X	X	X	X		X		X[12]		X			X[12]	X
Vaginal pool - Vaginal sperm evaluation		X	X		X	X								X		X						X
Vaginal lateral wall – pH	X	X	X[10]	X			X[10]	X	X	X	X	X		X		X[10]		X			X[10]	X
Vaginal lateral wall - Nugent Score	X						X	X	X	X	X	X									X	X
Vaginal lateral wall - microflora		X	X	X			X	X	X	X	X	X									X	X
Vaginal lateral wall - back-up swab for antibacterial activity, soluble markers		X	X[11]				X[11]	X	X	X	X	X				X[11]					X[11] X	X
Displace Ovaprene® temporarily for specimen collection if necessary									X		X			X		X					X	X
Cervical pH		X	X[8]	X			X		X		X	X		X		X					X	X
Cervical mucus by pipette - midcycle characteristics and sperm[9]		X	X		X	X								X		X						X
Cervical mucus by pipette - ferrous gluconate									X		X	X		X		X					X	X
Replace Ovaprene® if displaced									X		X			X		X					X	X
Vaginal lavage - antibacterial activity, soluble markers		X	X[11]				X[11]	X	X	X	X	X				X[11]					X[11]	X
Remove Ovaprene® - swab for staph aureus and store											X					X					X	X
Colposcopic exam of cervix under magnification	X						X				X	X				X	X				X	X
Pap Test[5]	X																					

GC/CT if using cervical specimens[6]	X																					X
Colposcopic exam of fornices and vagina (latter while removing speculum)	X						X				X	X				X	X				X	X
Ovaprene® Fit Test				X																		
Caya® Fit Test	X																					X
Insert Ovaprene®[13]							X					X					X					X
Remove Caya®						X																X
Dispense Caya®					X																	
Explain Trials.ai	X																					
Dispense OPK Kit	X			X				X				X				X	X				X	X
Dispense condoms	X			X							O					O					O	X

[1] Medical and Obstetrical history will include contraceptive and gynecological history also.

[2] A physical exam will be performed if the history is significant for a medical condition. The directed physical exam can be performed at any visit.

[3] HIV testing will be performed on all female subjects. HIV testing is available for the male partners, if requested.

[4] Urinalysis is only required if subject is symptomatic for UTI. Treat UTI with oral meds. If Visit 1, continue subject. If after Visit 1, reschedule visit.

[5] The pelvic exam at every visit should look for signs of irritation of the external genitalia, cervix and vagina, as seen with the naked eye. A Pap Test will be performed at Visit 1, if necessary, consistent with the standard medical practice as outlined in the study manual.

[6] **STI**: treat with oral meds and do not continue subject.

[7] **Candidiasis**: treat with oral meds. If Visit 1, continue subject. If after Visit 1, reschedule visit. **BV**: treat with oral meds. If diagnosed at Visit 1, continue subject. If diagnosed after Visit 1, do not continue subject.

[8] EVMS site only: Cervical mucus pH will also be tested at 0.5, 1, 2, 4, and 6 hour time points, if possible.

[9] Cervical Mucus Evaluation includes: midcycle characteristics and presence of sperm**.**

[10] EVMS only: Vaginal pH will also be tested at, 0.5, 1, 2, 4, and 6 hour time points, if possible.

[11] Non-EVMS sites: Vaginal samples for antibacterial activity and soluble markers will be collected at the time of the PCT or OS1. At EVMS only, they will be collected only at 6 hrs, if possible.

[12] EVMS only: Vaginal ferrous gluconate samples will also be collected at 0.5, 1, 2, 4 and 6 hours, if possible

[13] The subject will insert Ovaprene® using written instructions, with assistance if needed. The clinician will check the placement.

4.2 Table of Contents for Data Displays

Tables, data listings, and figures will be numbered according to the nomenclature used to support the final CSR.

4.2.1 Planned Tables

The format of each unique table is provided in a separate document of "Table Shells". Some outputs from statistical programming may be slightly different in layout from that illustrated in "Table Shells". The table shells will not be amended to match the actual tables in such cases.

Table Number	Table Title	Population
14.1.1	Summary of Subject Disposition and Reasons for Discontinuation	All Screened
14.1.2	Number and Percent of Subjects at Each Study Visit	All Enrolled
14.1.2-E	Number and Percent of Subjects at Each Visit and Time Point in East Virginia Medical School	All Enrolled
14.1.3-En	Summary of Subject Disposition by Study Site for All Enrolled Population	All Enrolled
14.1.3-Ca	Summary of Subject Disposition by Study Site for Caya Population	Caya
14.1.3	Summary of Subject Disposition by Study Site	Ovaprene
14.1.4-Ca	Summary of Protocol Deviations by Cycle for Caya Population	Caya
14.1.4	Summary of Protocol Deviations by Cycle	Ovaprene
14.1.5-En	Summary of Demographics for All Enrolled Population	All Enrolled
14.1.5-Ca	Summary of Demographics for Caya Population	Caya
14.1.5	Summary of Demographics	Ovaprene
14.1.6-En	Summary of Medical History for All Enrolled Population	All Enrolled
14.1.6-Ca	Summary of Medical History for Caya Population	Caya
14.1.6	Summary of Medical History	Ovaprene
14.1.7-En	Summary of Gynecological History for All Enrolled Population	All Enrolled
14.1.7-Ca	Summary of Gynecological History for Caya Population	Caya
14.1.7	Summary of Gynecological History	Ovaprene
14.1.8-En	Summary of Contraceptive History for All Enrolled Population	All Enrolled
14.1.8-Ca	Summary of Contraceptive History for Caya Population	Caya
14.1.8	Summary of Contraceptive History	Ovaprene
14.1.9-En	Summary of Pregnancy History for All Enrolled Population	All Enrolled
14.1.9-Ca	Summary of Pregnancy History for Caya Population	Caya
14.1.9	Summary of Pregnancy History	Ovaprene
14.1.10-Ca	Number and Percent of Subjects with Prior Medication Use by Drug Class and Generic Name for Caya Population	Caya
14.1.10	Number and Percent of Subjects with Prior Medication Use by Drug Class and Generic Name	Ovaprene

Table Number	Table Title	Population
14.1.11-Ca	Number and Percent of Subjects with Concomitant Medication Use by Drug Class and Generic Name for Caya Population for Caya Population	Caya
14.1.11	Number and Percent of Subjects with Concomitant Medication Use by Drug Class and Generic Name	Ovaprene
14.2.1.1	Number and Percent of Subjects with an Average of Fewer Than 5 Progressively Motile Sperm per HPF in Cervical Mucus	Ovaprene with at Least One PCT Cycle
14.2.1.1-Ca	Number and Percent of Subjects who Used Caya and Had an Average of Fewer Than 5 Progressively Motile Sperm per HPF in Cervical Mucus for Caya Population	Caya
14.2.1.1-R	Number and Percent of Subjects with an Average of Fewer Than 5 Progressively Motile Sperm per HPF in Cervical Mucus by Prior Vaginal Ring Use and Not Before Enrollment	Ovaprene with at Least One PCT Cycle
14.2.1.1-BMI	Number and Percent of Subjects with an Average of Fewer Than 5 Progressively Motile Sperm per HPF in Cervical Mucus by Subjects BMI at Least 30 vs Less Than 30	Ovaprene with at Least One PCT Cycle
14.2.1.1-E-NE	Number and Percent of Subjects with an Average of Fewer Than 5 Progressively Motile Sperm per HPF in Cervical Mucus by EVMS and Non-EVMS Sites	Ovaprene with at Least One PCT Cycle
14.2.1.1-Dev	Number and Percent of Subjects with an Average of Fewer Than 5 Progressively Motile Sperm per HPF in Cervical Mucus by Device Position at the Time PCT	Ovaprene with at Least One PCT Cycle
14.2.1.1-Dis	Number and Percent of Subjects with an Average of Fewer Than 5 Progressively Motile Sperm per HPF in Cervical Mucus by Subjects Had Ring Dislodgement or Not	Ovaprene with at Least One PCT Cycle
14.2.1.2	Average Number (across 9 HPFs) of Progressively Motile Sperm per HPF in Cervical Mucus and Change from Baseline Cycle to Ovaprene PCT Cycles	Ovaprene with at Least One PCT Cycle
14.2.1.3	Number and Percent of Ovaprene Cycles with Fewer Than 5 PMS per HPF in Cervical Mucus	Ovaprene with at Least One PCT Cycle
14.2.1.4	Number and Percent of Subjects with Fewer Than 5 PMS per HPF in Cervical Mucus	Ovaprene with at Least One PCT Cycle
14.2.2.1-E	Summary of the Levels of Ferrous Gluconate in CVF at Study Site EVMS	Ovaprene with at Least One PCT Cycle
14.2.2.1-E-5PMS	Summary of the Levels of Ferrous Gluconate in CVF at Study Site EVMS for Subjects with Fewer Than 5 PMS per HPF in the Cervical Mucus after Sex	Ovaprene with at Least One PCT Cycle
14.2.2.1-NE	Summary of the Levels of Ferrous Gluconate in CVF at Non-EVMS Sites	Ovaprene with at Least One PCT Cycle

Table Number	Table Title	Population
14.2.2.1-NE-5PMS	Summary of the Levels of Ferrous Gluconate in CVF at Non-EVMS Sites for Subjects with Fewer Than 5 PMS per HPF in the Cervical Mucus after Sex	Ovaprene with at Least One PCT Cycle
14.2.2.2-E	Summary of the Levels of Ferrous Gluconate in Cervix at Study Site EVMS	Ovaprene with at Least One PCT Cycle
14.2.2.2-E-5PMS	Summary of the Levels of Ferrous Gluconate in Cervix at Study Site EVMS for Subjects with Fewer Than 5 PMS per HPF in the Cervical Mucus after Sex	Ovaprene with at Least One PCT Cycle
14.2.2.2-NE	Summary of the Levels of Ferrous Gluconate in Cervix at Non-EVMS Sites	Ovaprene with at Least One PCT Cycle
14.2.2.2-NE-5PMS	Summary of the Levels of Ferrous Gluconate in Cervix at Non-EVMS Sites for Subjects with Fewer Than 5 PMS per HPF in the Cervical Mucus after Sex	Ovaprene with at Least One PCT Cycle
14.2.2.3-E	Summary of Cervical Mucus pH Values at Study Site EVMS	Ovaprene with at Least One PCT Cycle
14.2.2.3-NE	Summary of Cervical Mucus pH Values at Non-EVMS Sites	Ovaprene with at Least One PCT Cycle
14.2.2.4-E	Summary of Vaginal Lateral Wall pH Values at Study Site EVMS	Ovaprene with at Least One PCT Cycle
14.2.2.4-NE	Summary of Vaginal Lateral Wall pH Values at Non-EVMS Sites	Ovaprene with at Least One PCT Cycle
14.2.2.5	Summary of Residual Amount of Ferrous Gluconate in Device	Ovaprene with at Least One PCT Cycle
14.2.2.5-Dur	Summary of Residual Amount of Ferrous Gluconate in Device by Duration of Time the Device was Worn	Ovaprene with at Least One PCT Cycle
14.2.2.6	Summary of Cervical Mucus Scores by Visit	Ovaprene with at Least One PCT Cycle
14.2.2.6-Ca	Summary of Cervical Mucus Scores by Visit for Caya Population	Caya
14.2.2.7	Number and Percentage of Subjects with Cervical Mucus Score at Least 10 by Cycle	Ovaprene with at Least One PCT Cycle
14.2.2.7-Ca	Number and Percentage of Subjects with Cervical Mucus Score at Least 10 by Cycle for Caya Population	Caya
14.2.3.1	Summary of Open-ended Acceptability Questions	Ovaprene
14.2.3.2	Summary of Closed-ended Acceptability Questions	Ovaprene

Table Number	Table Title	Population
13.2.3.3	Summary of Acceptability Questions by Ovaprene Device Position Based on Digital Exam	Ovaprene
14.2.4.1A	Shifts of Acceptability from Visit OS5 to Visit OP3A – Part A	Ovaprene
14.2.4.1B	Shifts of Acceptability from Visit OS5 to Visit OP3A – Part B	Ovaprene
14.2.4.1C	Shifts of Acceptability from Visit OS5 to Visit OP3A – Part C	Ovaprene
14.2.4.1D	Shifts of Acceptability from Visit OS5 to Visit OP3A – Part D	Ovaprene
14.2.4.1E	Shifts of Acceptability from Visit OS5 to Visit OP3A – Part E	Ovaprene
14.2.4.2A	Shifts of Acceptability from Visit OS5 to Visit OP3B – Part A	Ovaprene
14.2.4.2B	Shifts of Acceptability from Visit OS5 to Visit OP3B – Part B	Ovaprene
14.2.4.2C	Shifts of Acceptability from Visit OS5 to Visit OP3B – Part C	Ovaprene
14.2.4.2D	Shifts of Acceptability from Visit OS5 to Visit OP3B – Part D	Ovaprene
14.2.4.2E	Shifts of Acceptability from Visit OS5 to Visit OP3B – Part E	Ovaprene
14.2.4.3A	Shifts of Acceptability from Visit OP3A to Visit OP3B – Part A	Ovaprene
14.2.4.3B	Shifts of Acceptability from Visit OP3A to Visit OP3B – Part B	Ovaprene
14.2.4.3C	Shifts of Acceptability from Visit OP3A to Visit OP3B – Part C	Ovaprene
14.2.4.3D	Shifts of Acceptability from Visit OP3A to Visit OP3B – Part D	Ovaprene
14.2.4.3E	Shifts of Acceptability from Visit OP3A to Visit OP3B – Part E	Ovaprene
14.2.5	Summary of Device Fit	Ovaprene
14.3.1.1-Ca	Overall Number and Percent of Subjects with Adverse Events for Caya Population	Caya
14.3.1.1	Overall Number and Percent of Subjects with Adverse Events	Ovaprene
14.3.1.2-Ca	Overall Number of Adverse Events by Severity and Relatedness to the Study Product for Caya Population	Caya
14.3.1.2	Overall Number of Adverse Events by Severity and Relatedness to the Study Product	Ovaprene
14.3.1.3-Ca	Number and Percent of Subjects with Adverse Events by System Organ Class and Preferred Term for Caya Population	Caya
14.3.1.3	Number and Percent of Subjects with Adverse Events by System Organ Class and Preferred Term	Ovaprene
14.3.1.3R	Number and Percent of Subjects with Study Product-Related Adverse Events by System Organ Class and Preferred Term	Ovaprene
14.3.1.4-Ca	Number and Percent of Subjects with Adverse Events by Preferred Term in Descending Order of Frequencies for Caya Population	Caya
14.3.1.4	Number and Percent of Subjects with Adverse Events by Preferred Term in Descending Order of Frequencies	Ovaprene
14.3.1.5-Ca	Number and Percent of Subjects with Adverse Events by System Organ Class and Preferred Term and by Severity for Caya Population	Caya
14.3.1.5	Number and Percent of Subjects with Adverse Events by System Organ Class and Preferred Term and by Severity	Ovaprene

Table Number	Table Title	Population
14.3.1.6-Ca	Number and Percent of Subjects with Adverse Events by System Organ Class and Preferred Term and by Relatedness to the Study Product for Caya Population	Caya
14.3.1.6	Number and Percent of Subjects with Adverse Events by System Organ Class and Preferred Term and by Relatedness to the Study Product	Ovaprene
14.3.1.7	Number and Percent of Subjects with Adverse Events by System Organ Class and Preferred Term for each Ovaprene Cycle by Subgroups of Device Position	Ovaprene
14.3.2.1	List of Serious Adverse Events	Ovaprene
14.3.2.1-Ca	List of Serious Adverse Events for Caya Population	Caya
14.3.2.2	List of Adverse Events that Led to Premature Study Discontinuation	Ovaprene
14.3.2.2-Ca	List of Adverse Events that Led to Premature Study Discontinuation for Caya Population	Caya
14.3.2.3	List of Urogenital System Adverse Events in Subjects and Male Partners	Ovaprene
14.3.2.3-Ca	List of Urogenital System Adverse Events in Subjects and Male Partners for Caya Population	Caya
14.3.2.4	List of Subjects who Developed a UTI During the Study	Ovaprene
14.3.2.4-Ca	List of Subjects who Developed a UTI During the Study for Caya Population	Caya
14.3.5.1	Hematology Test Results and Changes from Baseline to Each Visit	Ovaprene
14.3.5.2	Hematology Test Results and Shifts from Baseline to Each Visit	Ovaprene
14.3.5.3	Chemistry and Serum Ferritin Test Results and Changes from Baseline to Each Visit	Ovaprene
14.3.5.4	Chemistry and Serum Ferritin Test Results and Shifts from Baseline to Each Visit	Ovaprene
14.3.5.5	Summary of Urinalysis	Ovaprene
14.3.5.6	Summary of Colposcopic Findings	Ovaprene
14.3.5.7-Ca	Summary of Gynecological Examination for Caya Population	Caya
14.3.5.7	Summary of Gynecological Examination	Ovaprene
14.3.5.8	Summary of Nugent's Scores	Ovaprene
14.3.5.9	Summary of Soluble Markers and Antibacterial Tests	Ovaprene
14.3.5.10-Ca	Summary of Physical Examination for Caya Population	Caya
14.3.5.10	Summary of Physical Examination	Ovaprene
14.3.5.11	Summary of Follow Up Contact	Ovaprene

4.2.2 Planned Data Listings

No data listing shells are provided. A data listing may be split into 2 or more sub-listings (as Part A, Part B, etc.) when there are too many columns (variables), thus it's difficult to fit them in the same page. All data collected in this study, including those from unscheduled visits, will be presented in data listings.

Listing Number	Listing Title	Population
16.2.1.1	Subject Disposition	All Screened
16.2.1.2	Subject Visits	All Screened
16.2.1.3	Eligibility	All Screened
16.2.1.4	Reconsent	All Screened
16.2.2	Protocol Deviations	All Screened
16.2.4.1	Demographics	All Screened
16.2.4.2A	Gynecological History – Part A	All Screened
16.2.4.2B	Gynecological History – Part B	All Screened
16.2.4.3	Medical History	All Screened
16.2.4.4	Contraceptive History	All Screened
16.2.4.5	Pregnancy History	All Screened
16.2.4.6	Prior and Concomitant Medications	All Screened
16.2.5.1	Study Procedure	All Screened
16.2.5.2	Device Position	All Screened
16.2.6.1	Vaginal Sample	All Screened
16.2.6.2A	Cervical Mucus – Part A	All Screened
16.2.6.2B	Cervical Mucus – Part B	All Screened
16.2.6.3	Cervical Mucus Timepoints	All Screened
16.2.6.4	Usability Questionnaire	All Screened
16.2.7.1A	Adverse Events – Part A	All Screened
16.2.7.1B	Adverse Events – Part B	All Screened
16.2.8.1	Hematology	All Screened
16.2.8.2	Chemistry	All Screened
16.2.8.3	Urinalysis	All Screened
16.2.8.4	E.coli Assay by Einstein-Yu Lab	All Screened
16.2.8.5	Iron Gluconate Hydrate per Ring by Catalent Pharma Solutions Lab	All Screened
16.2.8.6	Iron Assay by Avomeen Analytical Services	All Screened
16.2.8.7	Interleukin 8 Assay by Conrad Lab in Eastern Virginia Medical School	All Screened
16.2.9.1	Gynecological Examination	All Screened
16.2.9.2	Physical Examination	All Screened
16.2.9.3	Colposcopic Findings	All Screened

Listing Number	Listing Title	Population
16.2.9.4	Pregnancy Test	All Screened
16.2.9.5	Follow-up Contact	All Screened
16.2.9.6A	Subject Diary - OPK Results	All Screened
16.2.9.6B	Subject Diary - Baseline Version 1 PCT Diary Entries	All Screened
16.2.9.6C	Subject Diary - Baseline PCT Version 3 Diary Entries for Study Site EVMS	All Screened
16.2.9.6D	Subject Diary - Baseline PCT Version 3 Diary Entries for Non-EVMS Study Sites	All Screened
16.2.9.6E	Subject Diary - Caya PCT Version 3 Diary Entries for Study Site EVMS	All Screened
16.2.9.6F	Subject Diary - Caya PCT Version 3 Diary Entries for Non-EVMS Study Sites	All Screened
16.2.9.6G	Subject Diary - Ovaprene® Version 3 Diary Entries for Study Site EVMS	All Screened
16.2.9.6H	Subject Diary - Ovaprene® Version 3 Diary Entries for Non-EVMS Study Sites	All Screened

4.2.3 Planned Graphs

No graph shells are provided.

Graph Number	Graph Title	Population
14.2.2	Plot of Vaginal Lateral Wall pH values along the collection time at EVMS site	All Treated

4.3 References

[1] Del Priore G1, Malanowska-Stega J, Shalaby SW, Richman S. A pilot safety and tolerability study of a non-hormonal vaginal contraceptive ring. J. Reprod. Med. 2009 Nov-Dec;54 (11-12):685-90.

[2] http://support.sas.com/documentation/cdl/en/procstat/66703/HTML/default/viewer.htm#procstat_freq_details37.htm