Title: **Safety and Acceptability Study of a Non-Hormonal Ring**

Protocol Number: DR-OVP-001

Clinical Phase: I

Sponsor: Daré Bioscience
3655 Nobel Drive, Suite 260
San Diego, CA 92122

Original Protocol: Version 06.00 (June 13, 2019)

PROTOCOL SIGNATURE PAGE

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07/08/2019

Sabrina Martucci Johnson — Date
President and CEO

Christine Mauck — 6/14/19
Christine Mauck — Date
Medical Director

I have read and I understand this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein and will make all reasonable efforts to complete the study within the designated time. I agree to conduct this trial in accordance with the Declaration of Helsinki, the International Conference on Harmonisation (ICH), Guideline for Good Clinical Practice (GCP), and all applicable regulatory requirements.

I will provide copies of the protocol and access to all information furnished by Daré Bioscience, Inc. to study personnel under my supervision. I will discuss the material with them to ensure that they are fully informed about the study.

I understand that the study may be terminated or enrollment suspended at any time by Daré Bioscience, Inc., with or without cause, or by me, if it becomes necessary to do so in the best interests of the study subjects.

Principal Investigator Signature **Date**

Printed Name: _____

Site Name: _____

CONTACT LIST

A full list of study contacts is provided in the Study Procedures Manual.

Table 1 Study Contact List

Sponsor	Daré Bioscience 3655 Nobel Drive, Suite 260 San Diego, CA 92122
Sponsor's Responsible Medical Director	Christine Mauck, MD, MPH CKM Consulting, LLC 18410 Polynesian Lane Boyds, MD 20841
Contract Research Organization (CRO)	Health Decisions, Inc. 2510 Meridian Parkway Durham, NC 27713

1. SYNOPSIS

Title of Study:
A Feasibility, Open-Label, Postcoital, Safety, Release, Fit, and Acceptability Study of Ovaprene™

Study Centers:
Approximately 3-5 centers in the United States will conduct this study.

Studied period (years):
Estimated date first participant enrolled: March 31, 2018
Estimated date last participant completed: September 1, 2019

Phase of development: I

Objectives:

- Primary: Changes in PCT results due to device use
- Secondary: Release of active component from device and safety
- Tertiary: Acceptability and fit

Design:
This will be a feasibility, multi-center, open-label, non-significant risk device 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 participants (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 below 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.

Participants 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.)

Table 2 Study Visits and cycles (following Visit 1)

	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	13 OP2	14 OP3	15 OP4	16 OP5	17 OP1	18 OP2	19 OP3	20 OP4	21 OP5

Number of participants (planned):
Approximately 45 women will be enrolled to have approximately 25 participants complete five cycles

Diagnosis and main criteria for inclusion:
Healthy, sexually active women with regular menstrual cycles who have undergone female tubal sterilization and who meet eligibility criteria.

Investigational product and mode of administration:
Ovaprene™ inserted vaginally at the end of menses and left in place until the onset of the next menses

Duration of treatment:
Ovaprene™ will be used in 3 scheduled menstrual cycles

Reference therapy, dosage and mode of administration:

The Caya diaphragm will be used in one PCT cycle to demonstrate 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.

Criteria for evaluation:

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 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 women, 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) Change from baseline in the mean, median, standard deviation and interquartile range (IQR) during each Ovaprene™ test cycle, across all women.	Ovaprene™ PCT cycles vs. baseline PCT cycle
Secondary: 2. Release of active component from device	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
	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 cycle
	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 participants during Ovaprene™ use.	Ovaprene™ safety cycle and Ovaprene™ PCT cycles
	b) Urogenital, product-related, and/or serious AEs among female and male participants during Ovaprene™ use.	Ovaprene™ safety cycle and 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 and 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 and 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 and Ovaprene™ PCT cycles
Tertiary: 4. Acceptability	a) Responses 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 and Ovaprene™ PCT cycles
5. Fit	a) Proportion of participants who can be fitted with Ovaprene™.	Baseline PCT cycle
	b) Proportion of participants who can correctly insert, position, and remove the device using written instructions only.	Baseline PCT cycle, Ovaprene™ safety cycle and Ovaprene™ PCT cycles
	c) Proportion of participants who require assistance to correctly insert, position, and remove the device.	Baseline PCT cycle, Ovaprene™ safety cycle and 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 and Ovaprene™ PCT cycles

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms may be used in this study protocol.

Table 3 Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ACOG	American Congress of Obstetricians and Gynecologist
AE	Adverse Experience or Adverse Event
BV	Bacterial Vaginosis
CE	*Conformité Européenne*, Manning "European Conformity"
CFR	Code of Federal Regulations
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Act
CMC	Cervical Mucus Check
CV	Curriculum Vitae
DAIDS	Division of AIDS, National Institute of Allergy and Infectious Disease
eCRF	Electronic Case Report Form
EEA	European Economic Area
EU	European Union
EVMS	Eastern Virginia Medical School
FDA	Food and Drug Administration
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIPAA	Health Information Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPF	High Power Field
IDE	Investigational Device Exemption
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
IQR	Interquartile Range
MPA	Multiple Project Assurance
N-9	Nonoxynol-9
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
OPK	Ovulation Predictor Kit
PCT	Postcoital Test
PI	Principal Investigator
PMA	Premarket Approval – Food and Drug Administration
PMS	Progressively Motile Sperm
SAE	Serious Adverse Drug Experience
SAP	Study Analysis Plan
SD	Standard Deviation
STI	Sexually Transmitted Infection
TEAE	Treatment-Emergent Adverse Experience or Event
US	United States
UTI	Urinary Tract Infection

4. INTRODUCTION

Ovaprene™ is a sole use, non-hormonal contraceptive device intended for use in female contraception by women of child-bearing age. Ovaprene™ is an intra-vaginal ring with an incorporated mesh insert that is designed to reside in the vaginal fornix, essentially covering the external os of the cervix. As such, the physical dimensions were designed to enable: 1) ease of intravaginal placement and; 2) maintenance of position in the vaginal fornix. The dimensions of the ring were also selected to create a "one size fits most" barrier device for this placement. The product design goals were to achieve the same function as a diaphragm, but in a device that could be left in place over the course of one menstrual cycle. The product is removed at the start of menses and a new device is inserted at the end of menses. A Phase 1, safety and Postcoital clinical study has been performed, which demonstrated successful feasibility of the product design and concept.[1]

Ovaprene™ consists of a flexible ring combined with a mesh 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. FG causes oxidative damage to the lipid bilayer of the sperm tail and promotes lipid peroxidation, leading to spermiostasis. Ascorbic acid (AA) helps to keep the iron in its ferrous state. Polyglycolide (PG) breaks down, enabling FG and AA dissolution from the silicone ring, and along with AA, generates acidic compounds that are not expected to significantly disrupt the healthy vaginal microbiota. Work from several groups informed the type and amount of each component included in Ovaprene™ product to maintain their respective functions. Ovaprene™ is designed to ensure that the release level of FG is maintained above the minimum concentration through the maximum duration of Ovaprene™ use (~35 days). Thus, it is the novel combination of the sperm-trapping mesh and the local activity of a spermiostatic agent that work together to impart Ovaprene's high contraceptive activity. Market research suggests that the device will be attractive to women who desire a non-hormonal, user-controlled contraceptive alternative.

An Ovaprene™ postcoital test (PCT) study in 21 women has been published.[1] 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. In that setting, the PCT can demonstrate that, in the absence of the barrier, progressively motile sperm from the male partner can achieve access into the woman's midcycle cervical mucus, and, in the presence of the barrier, this access is reduced or eliminated. Three vaginal barrier devices, Lea's Shield, FemCap™, and the SILCS diaphragm (also known as Caya®), were evaluated by a postcoital study and then by a contraceptive effectiveness study prior to FDA approval. No progressively motile sperm were seen in midcycle mucus among all 10 users of Lea's Shield+Nonoxynol-9 (N-9) or in any of the 13 users of SILCS (Caya) diaphragm + N-9, and 6-month typical use pregnancy rates of 8.7% and 12.5% were observed in the subsequent contraceptive efficacy studies, respectively.[2,3,4,5] Progressively motile sperm were seen in midcycle mucus in 1 of 7 users of FemCap+N-9 and a 6-month typical use pregnancy rate of 13.5% was observed in the contraceptive efficacy study.[6,7] If PCT testing of Ovaprene™ were to show results similar to the results of these FDA-approved diaphragms, it is likely that Ovaprene™ would also show similar results in a contraceptive effectiveness study.

In the standard PCT test referenced above, the definition of a successful barrier function requires that thin cervical mucus is present during ovulation and that despite this, fewer than 5 progressively motile sperm per high power field (HPF) are seen in the cervical mucus. If the cervical mucus is thick, which may be the case if ovulation does not occur or if the test is done before or after ovulation, and there are fewer than 5 progressively motile sperm per HPF, the cycle must be repeated on the grounds that the thickness of the mucus may have prevented the appearance of sperm in it. Since Ovaprene™ is *designed* to release acid, which may increase cervical mucus viscosity, the interpretation of the PCT will require modification. The expected result, if Ovaprene™ is effective, will be fewer than 5 progressively motile sperm per high power field (HPF) in the cervical mucus, regardless of whether the mucus is thin or thick.

The completed Ovaprene™ PCT study demonstrated proof of concept in terms of reducing the number of progressively motile sperm seen in cervical mucus with the device in place.[1] The new study of Ovaprene™

described in this document has been designed to provide further evidence of changes in the PCT as a result of Ovaprene™ use. A Caya PCT cycle has been included 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.

In addition, the release of agents from Ovaprene™, safety, user acceptability, and fit will be assessed. All participants will undergo a baseline PCT cycle without the use of the device, one PCT cycle with Caya, and two modified PCT cycles with Ovaprene™. Additional data will be collected in an Ovaprene™ cycle without sex acts.

With regard to release, the study will address the following questions:

1) What are the levels of ferrous gluconate in cervicovaginal fluid (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?
2) How long after insertion does it take to achieve these levels?
3) Are these levels still present after 24-35 days of use?
4) What is the level of ferrous gluconate in CVF after sex at ovulation with the device in place and, if different from before sex, how much time is needed to return to pre-sex levels?
5) Does the presence of the device affect vaginal pH compared with the absence of the device?
6) Is there residual ferrous gluconate in Ovaprene™ devices that have been worn over a cycle of use?

Safety data are also needed. Treatment-emergent systemic and genital adverse events (AEs) will be collected from both the female participants and their male partners, via report from the female participants. Additional information on systemic effects in the female participant will be collected in the form of standard safety labs (complete blood count and serum chemistries) as well as labs that are specific to Ovaprene™. The latter will include serum ferritin, a protein that is involved in iron storage and which becomes elevated in situations of iron overload. While the likelihood of iron overload developing from the small amount of iron in Ovaprene™ (569.8 mg, [1] the maximum amount that could be released over an entire cycle of use, as compared with 325 mg daily included in many multivitamins) is minimal, systemic safety will be documented.

Additional genital safety data will come from findings via pelvic exam, including colposcopy, and changes in Nugent score and microflora. The ability of the product to maintain vaginal innate immunity will be assessed using antibacterial activity in the CVF and soluble markers of inflammation in CVF. Any potential colonization of the product by *Staphylococcus aureus* or group A Streptococcus, the organisms associated with Toxic Shock Syndrome, will be assessed on devices that have been worn over a cycle of use.

Finally, a product that is unacceptable to women or their partners will not have commercial potential. This study will collect acceptability information from both partners. It will also assess the proportion of women for whom Ovaprene™ will fit and those who can insert, position, and remove the device with only written instructions. It will also determine where, in relation to the cervix, the device comes to reside after insertion and after sex, and the relationship of that location to PCT results, safety, and acceptability. The study described here will have as its objectives the collection of all these types of data – changes in PCT results due to device use, release, safety, acceptability, and fit.

5. TRIAL PURPOSE, OBJECTIVES AND ENDPOINTS

5.1 PURPOSE

The purpose of this clinical trial is to assess the ability of Ovaprene™ to prevent sperm from penetrating midcycle cervical mucus. In addition, safety, release of ingredients, acceptability and fit will be assessed.

5.2 OBJECTIVES

1. Primary: Changes in PCT results due to device use
    a) Demonstrate successful barrier performance, as defined in **Appendix 3** during Ovaprene™ use in women who were able to demonstrate good results in a baseline cycle. 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.
2. Secondary: Release of active component from device
    a) Determine the levels of ferrous gluconate in CVF before sex that are associated with fewer than 5 progressively motile sperm per high powered field (HPF) in the cervical mucus (i.e. success) after sex, during ovulation.
    b) Determine how long after insertion it takes to reach these levels
    c) Determine whether these levels are still present 27-29 days after device insertion
    d) Determine the levels of ferrous gluconate in CVF after sex at ovulation with the device in place and if different from before sex, how much time is needed to return to pre-sex levels.
    e) Demonstrate the device's effect on CVF pH.
    f) Assess residual amount of ferrous gluconate in Ovaprene™ devices that have been worn over a cycle of use.
3. Secondary: Safety
    a) Assess systemic and genital safety using traditional endpoints and Ovaprene-specific endpoints
4. Tertiary: Acceptability
    a) Assess acceptability of Ovaprene™ when left in place as directed for 3 cycles.
5. Tertiary: Fit
    a) Assess fit of Ovaprene™.
    b) Assess ability of women to insert, position, and remove the device
    c) Assess the position of Ovaprene™ before and after intercourse and the relationship of position to other endpoints

6. 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 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 women, 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) Change from baseline in the mean, median, standard deviation and interquartile range (IQR) during each Ovaprene™ test cycle, across all women.	Ovaprene™ PCT cycles vs. baseline PCT cycle
Secondary: 2. Release of active component from device	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
	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 cycle
	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 and 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 participants during Ovaprene™ use.	Ovaprene™ safety cycle and Ovaprene™ PCT cycles
	b) Urogenital, product-related, and/or serious AEs among female and male participants during Ovaprene™ use.	Ovaprene™ safety cycle and 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 and 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 and 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 and Ovaprene™ PCT cycles
Tertiary: 4. Acceptability	a) Responses 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 and Ovaprene™ PCT cycles
5. Fit	a) Proportion of participants who can be fitted with Ovaprene™.	Baseline PCT cycle
	b) Proportion of participants who can correctly insert, position, and remove the device using written instructions only.	Baseline PCT cycle, Ovaprene™ safety cycle, and Ovaprene™ PCT cycles
	c) Proportion of participants who require assistance to correctly insert, position, and remove the device.	Baseline PCT cycle, Ovaprene™ safety cycle, and 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 and Ovaprene™ PCT cycles

7. INVESTIGATIONAL PLAN

7.1 OVERALL STUDY DESIGN

This is a feasibility, multi-center, open-label, non-significant risk device 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 participants (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.

Participants 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.)

Table 3 Study Visits and cycles (following Visit 1)

	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	13 OP2	14 OP3	15 OP4	16 OP5	17 OP1	18 OP2	19 OP3	20 OP4	21 OP5

Many of the PCT and safety aspects of this study design are based on two previous studies:

- A PCT study of the SILCS diaphragm, now referred to as Caya, used with 2% N-9 or a personal lubricant, described in Schwartz, et al, 2008.[3]
- A PCT study of the SILCS diaphragm, now referred to as Caya, used with 3% N-9, ContraGel, or no gel, described in Mauck, et al, 2017 [8]

7.2 ANTICIPATED LENGTH OF STUDY

Each subject's participation will last 6-7 months. Cycles may need to be repeated; thus, participation for some women may be more than 7 months.

7.3 NUMBER OF SUBJECTS

Approximately 45 women will be enrolled with the goal to have approximately 25 participants complete the trial. Subjects who discontinue early may be replaced.

7.4 TREATMENT ASSIGNMENT

This is an open-label study in which all participants will use the same study product, thus no treatment assignment will take place.

7.5 CRITERIA FOR PARTICIPANT DISCONTINUATION

Each participant will be informed of her and her partner's right to withdraw from the study at any time and for any reason. A participant may be discontinued from study treatment at any time if the participant, the Investigator, or the Sponsor feels that it is not in the participant's best interest to continue on study.

Participants who sign the informed consent and agree to participate in the study, but do not meet eligibility criteria will be considered screen failures.

Following enrollment, participants may be discontinued from the study for the following reasons:

- Failure to follow protocol requirements that is judged severe enough by the investigator to significantly affect study outcomes or requires discontinuation of study treatment
- Having an average of >5 progressively motile sperm per HPF in the cervical mucus 2-3 hours after intercourse using a Caya diaphragm with nonoxynol-9 if the result was clearly the result of the participant not using or inserting the diaphragm properly.
- Adverse event, including diagnosis of symptomatic bacterial vaginosis (BV) or an STI (in the participant or her partner), or any intercurrent illness that would jeopardize the participant's health or the interpretation of the results of the study. (An outbreak of genital herpes or condylomata would require discontinuation.)
- Pregnancy
- Loss to follow-up
- Participant withdrawal of consent
- Sponsor decision to discontinue trial

Prior to discontinuing a participant from the study, the site should contact Daré or designee. The reason for discontinuation must be recorded on the appropriate section of the participant's CRF.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

The volunteers for this study will be recruited through various methods, including existing databases (as protected health information permits) and through advertisements in local media outlets which have been approved by the local Institutional Review Board (IRB).

Only women will be recruited since Ovaprene™ can only be used by women and the endpoints require genital sampling. Although the National Institutes of Health (NIH) has mandated that children, defined as younger than 21 years old, be included in research trials when appropriate, this study fits one of the "Justifications for Exclusion" as set forth by the NIH. Specifically, "insufficient data are available in adults to judge potential risk in children" and "children should not be the initial group to be involved in research studies." We will recruit female participants aged 18 to 50 years who can legally provide informed consent. Efforts will be made by the sites to recruit participants so that the racial, ethnic, and parity characteristics of the subject population will reflect the demographics of the study sites. No selection criteria shall be based on race or ethnicity.

Note: Volunteers must meet all the following inclusion criteria and none of the exclusion criteria prior to enrollment (which takes place at successful completion of the Baseline PCT Cycle):

8.1 INCLUSION CRITERIA

1. Women aged 18-50 years, inclusive
2. General good health, by volunteer history and per investigator judgment
3. History of regular menstrual cycles of 24-35 days (inclusive), by volunteer report
4. History of Pap tests and follow-up consistent with standard medical practice or willing to undergo a Pap test at Visit 1.
5. Protected from pregnancy by female tubal sterilization
6. Willing to abstain from or engage in intercourse with and without condoms and to abstain from other vaginal activity[a] as required in the protocol
7. In a mutually monogamous relationship for at least the last four months with a male partner who:
    a. Is at least 18 years old;
    b. Has no known risk for STIs;
    c. Is willing and able to comply with protocol requirements including sexual activity/ abstinence and condom use requirements; and
    d. Can engage in vaginal intercourse with the participant, with and without condoms, as specified in protocol
8. Vaginal and cervical anatomy that, in the opinion of the investigator, lends itself to easy colposcopy and genital tract sample collection
9. Willing to give voluntary consent, sign an informed consent form and comply with study procedures as required by the protocol

[a] "Other vaginal activity" includes insertion of vaginal medications/products other than the study product (prescription or over-the-counter), as well as insertion of sex toys, fingers, or anything else into the vagina. Tampons may be used during all days of menses in the Baseline PCT and Caya PCT cycles, but only during the first three days of menses in Ovaprene cycles.

8.2 EXCLUSION CRITERIA

1. History of hysterectomy
2. Vasectomy in male partner
3. Sterility or known history of sperm dysfunction in male partner
4. Within two calendar months from the last pregnancy outcome. Note: If recently pregnant must have had at least two spontaneous menses since pregnancy outcome.
5. Current use of any hormonal contraceptive or a copper IUD, or use of Depo-Provera within the last 120 days
6. Currently breastfeeding or having breastfed an infant in the last two months, or planning to breastfeed during the course of the study
7. Significant gynecological abnormalities (including abnormal vaginal bleeding or excessive vaginal discharge)
8. Either device does not appropriately fit volunteer, as determined by clinician
9. Inability of the volunteer to insert, position, and/or remove either device, even with assistance
10. History of sensitivity/allergy to nonoxynol-9 or to silicone or any other component of Ovaprene™ or Caya, for either the volunteer or her male partner
11. In the last four months, either the volunteer or her male partner diagnosed with or treated for any STI or pelvic inflammatory disease. Note: Women or male partners with a history of genital herpes or condylomata who have been asymptomatic for at least six months may be considered for eligibility
12. Positive test for Trichomonas vaginalis, Neisseria gonorrhea, Chlamydia trachomatis, or HIV
13. Deep epithelial genital findings such as abrasions, ulcerations, and lacerations, or vesicles suspicious for a sexually transmitted infection
14. Chronic or acute vulvar or vaginal symptoms (pain, irritation, spotting, etc.)
15. Known current drug or alcohol abuse which could impact study compliance. (This is defined as any illicit drug use or more than 15 alcoholic drinks per week)
16. Participation in any other investigational trial within the last 30 days or planned participation in any other investigational trial during the study
17. History of gynecological procedures (including genital piercing) on the external genitalia, vagina or cervix within the last 14 days
18. Abnormal finding on laboratory or physical examination or a social or medical condition in either the volunteer or her male partner which, in the opinion of the investigator, would make participation in the study unsafe or would complicate interpretation of data
19. Nugent score greater than or equal to 7
20. Systemic use in the last two weeks or anticipated use during the study of antibiotics (other than those used to treat UTI, vaginal candidiasis, or BV diagnosed at Visit 1, or to treat UTI or vaginal candidiasis after Visit 1) or topical antivirals (e.g., acyclovir or valacyclovir). Note: Participants should avoid non-steroidal anti-inflammatory drugs (NSAIDs) and Tylenol except for occasional use, as in treatment of headaches or dysmenorrhea.
21. Grade 2 or higher abnormality per the March 2017 update of the Division of AIDS (DAIDS), National Institute of Allergy and Infectious Disease (NIAID) Table for Grading of the Severity of Adverse Events or clinically significant lab abnormalities as determined by the investigator (see Section 13.5 for link to DAIDS table)
22. Inability to achieve adequate cervical mucus in two attempts at the baseline cycle
23. Inadequate sperm in endocervical aspirate during baseline testing without any device, despite adequate mucus and presence of sperm in vaginal pool

9. STUDY PROCEDURES

Prospective participants may be pre-screened; the study will be explained, the inclusion/ exclusion criteria reviewed, questions answered, and Visit 1 scheduled.

9.1 SCREENING (VISIT 1)

9.1.1 Goals:

- Determine eligibility
- Assess endpoints

Table 4 Visit 1 Endpoints

Tertiary: 5. Fit	b) Proportion of participants who can correctly insert, position, and remove the device using written instructions only
	c) Proportion of participants who require assistance to correctly insert, position, and remove the device

9.1.2 Procedures:

- The study and informed consent form will be reviewed and all volunteer questions will be answered. If the volunteer wishes to participate and meets the preliminary study criteria, she will be asked to review and sign an informed consent form. The PI or designee will sign the form and provide a copy to the participant. Once the consent form is signed, the participant will be considered in screening.

- The male partner will be required to sign an informed consent form prior to the start of the female participant's menstrual period in the Baseline PCT Cycle.

- An interview will be conducted to obtain a medical/obstetrical history and demographic information.

- Height and weight will be measured.

- A urine specimen will be obtained for a urine pregnancy test to confirm that the participant is not pregnant and to perform a dipstick urinalysis if the participant is symptomatic for a urinary tract infection (UTI).

- An HIV test will be performed for female participants, along with appropriate counseling and/or referral. The male partner will be offered HIV testing and counseling.

- Blood will be drawn for a complete blood count (CBC), serum chemistries, and serum ferritin.

- A directed physical exam will be performed if the history is significant for a medical condition.

- A pelvic exam will be performed, including:

- Signs of irritation of the external genitalia, cervix, and vagina, as observed with the naked eye, will be noted.
- A colposcopic exam will be completed.[b]
- Vaginal sample(s) will be collected for wet mount, vaginal pH, and Nugent score.
- Specimens for *Trichomonas vaginalis, Neisseria gonorrhea* and *Chlamydia trachomatis* will be collected.
- A Pap test will be performed, if necessary, consistent with standard medical practice as outlined in the Study Procedures Manual.

- UTI, vaginal candidiasis, and BV will be treated, preferably with oral medication. If the participant is otherwise eligible, she will continue in the study.

- The investigator will insert the Caya diaphragm and assess the fit (**Appendix 3**). If the investigator determines that the Caya diaphragm fits appropriately, she/he will remove it and give the diaphragm and the product instructions to the participant. The participant will then attempt to insert the Caya diaphragm without assistance. If she is able to insert it, the investigator will check the placement. If the participant is unable to correctly insert and position the diaphragm, the investigator will reinstruct and assist as needed. Once the participant correctly inserts and positions the device, she will be asked to remove it. If she not able to remove the diaphragm, the investigator will reinstruct her and assist as needed.

- If the investigator determines that the Caya does not fit appropriately, or if the participant cannot correctly insert, position, and remove it, even with assistance, the participant will not continue.

- Once the participant has met all eligibility requirements (with the exception of having acceptable results in lab work that is pending), the following will take place:

  - Participants will be instructed on the use of web-based application called Trials.ai. The Trials.ai application may be accessed from any computer, smart phone, or tablet and will serve as the diary for this trial. Via Trials.ai, participants will be prompted to record menses, intercourse, use of intravaginal products, AEs, medications, and any issues with the device throughout the study.

  - An ovulation predictor kit (OPK) with instructions will be dispensed. The participant will be instructed to:
    - Contact the site at the onset of her next menses;[c]
    - Begin daily urine testing on day 10 of that cycle (adjusted as needed to normal cycle length); and

[b] All colposcopic exams will be carried out using the CONRAD/WHO Manual For The Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004

[c] If Visit 1 took place before Day 10 in the woman's cycle, and the woman and her partner have been abstaining or using condoms since day 1 of that cycle, and all other eligibility criteria are met, it may be possible to complete the baseline PCT cycle within the same cycle as Visit 1.

- Contact the study coordinator when the OPK test yields a "high" result. Visit 2 (BP1 - the mucus check visit) will be scheduled for that day or the next day.

- A supply of non-spermicidal, lubricated condoms will be dispensed. The participant will be instructed as follows:
  - From the start of her next menses until day 10, she and her partner should use these condoms for each act of intercourse; and
  - There should be no intercourse or other vaginal activity[d] and the male partner should not have an ejaculation, starting on day 10 until after Visit 2 (BP1).

[d] "Other vaginal activity" includes insertion of vaginal medications/products other than the study product (prescription or over-the-counter), as well as insertion of sex toys, fingers, or anything else into the vagina. Tampons may be used during all days of menses in the Baseline PCT and Caya PCT cycles, but only during the first three days of menses in Ovaprene cycles.

9.2 BASELINE PCT CYCLE - NO DEVICE IN PLACE, ONE ACT OF INTERCOURSE FOLLOWED BY PCT

Table 5 Baseline PCT Endpoints

Primary: 1) Changes in PCT results due to device use	a) Proportion of women with an average of fewer than 5 progressively motile sperm per HPF after sex at ovulation, in the *absence* of the device.
	b) Mean, median, standard deviation and interquartile range (IQR) for the average number (across 9 HPFs) of progressively motile sperm per HPF, across all women, in the *absence* of the device.
	e) Change from baseline in the mean, median, standard deviation and interquartile range (IQR) during each Ovaprene™ test cycle, across all women.
Secondary: 2. Release of active component from device	d) Cervicovaginal pH before and after sex in the absence and presence of the device.
Tertiary: 5. Fit	a) Proportion of women who can be fitted with Ovaprene™

9.2.1 Baseline PCT Visits and Procedures:

a) Visit 2 (BP1) - Cervical Mucus Check (CMC) visit, on the day of the "high" result or the next

- Entry criteria will be reviewed to confirm the participant's eligibility.

- Diary entries will be reviewed. Particular attention will be paid to:
  - Any new or worsening medical problems or symptoms or used any medications since the last study visit.
  - Partner AEs involving the urogenital system and serious AEs.[e]
  - Whether the participant used condoms until Day 10, and then refrained from intercourse and other vaginal activity,[f] and whether her male partner refrained from ejaculation since Day 10. If instructions were not followed, she will be reinstructed. If she used a spermicide or spermicidal lubricated condom since day 10, Visit 2 (BP1) will be rescheduled in the next cycle. Otherwise, the visit may continue at the investigator's discretion.

- A directed physical exam will be performed if indicated.

- The participant will undergo a pelvic exam:
  - Signs of irritation of the external genitalia, cervix, and vagina, as observed with the naked eye, will be noted.
  - If the participant has symptoms of an infection at this visit, a urine dipstick and/or wet mount will be performed, as indicated. If a UTI or vaginal candidiasis is diagnosed, she will be treated with oral medication and Visit

[e] Product-related male AEs will be collected at visits during and after Ovaprene use.

[f] "Other vaginal activity" includes insertion of vaginal medications/products other than the study product (prescription or over-the-counter), as well as insertion of sex toys, fingers, or anything else into the vagina. Tampons may be used during all days of menses in the Baseline PCT and Caya PCT cycles, but only during the first three days of menses in Ovaprene cycles.

2 (BP1) will be rescheduled in the next cycle. Other tests may be performed as indicated; if a test is positive for BV or an STI, the participant will be treated but not continued in the study.
    - Cervical mucus will be examined for pH, midcycle characteristics, and the presence of sperm (see **Appendix 2**).
    - Vaginal sample(s) will be collected for pH, the presence of sperm, and baseline levels of microflora, antibacterial activity, and soluble markers[g].

- If sperm are found in the vagina or cervical mucus, the baseline cycle will be rescheduled for the following month and instructions on the use of condoms will be reviewed. Additional supplies will be provided as needed.

- If the cervical mucus score is <10, the participant may be asked to return in 1 or 2 days if it seems likely that the midcycle point has not yet been reached, or in the next cycle if it seems likely that the midcycle point has already passed.

- If no sperm are detected at this visit, and the cervical mucus score is ≥10, the participant will be instructed to have vaginal intercourse without a condom 2 to 3 hours prior to Visit 3 (BP2), which will be scheduled for the same or following day, within 27 hours of the mucus check visit.

- The participant will be instructed to otherwise avoid any other vaginal activities[h] until after Visit 3 (BP2).

- The participant will be instructed to ask her partner, prior to her next visit, if he has had any AEs involving the urogenital system or whether he has had any serious AEs.

b) Visit 3 (BP2) – the PCT visit, 2-3 hours after intercourse and within 27 hours of the CMC:

The participant will return to the clinic 2-3 hours after coitus ends and within approximately 27 hours of the mucus check visit.

- Diary review, AEs, medications, and indications for a directed physical exam, wet mount, and other tests will be managed as described for Visit 2 (BP1).

- The participant will undergo a pelvic exam:
    - Signs of irritation of the external genitalia, cervix, and vagina, as observed with the naked eye, will be noted.
    - Cervical mucus will be examined for pH, midcycle characteristics, and the presence of sperm (see **Appendix 2**).

[g] These will serve as baseline measurements for comparison with those obtained after device insertion during Visit OS1. The alternative would be to collect baseline measurements before device insertion at Visit OS1, but the collection technique (vaginal lavage) is likely to affect subsequent samples taken at that visit.

[h] "Other vaginal activity" includes insertion of vaginal medications/products other than the study product (prescription or over-the-counter), as well as insertion of sex toys, fingers, or anything else into the vagina. Tampons may be used during all days of menses in the Baseline PCT and Caya PCT cycles, but only during the first three days of menses in Ovaprene cycles.

- Vaginal sample(s) will be collected for pH and the presence of sperm.
- At sites other than EVMS, vaginal samples will be collected for microflora, antibacterial activity, and soluble markers.[i]

  Baseline PCT results will be interpreted and managed as listed in **Appendix 3**. A successful baseline PCT will show thin mucus containing an average of ≥5 progressively motile sperm per HPF.

- At the EVMS site only:
  - 0.5, 1, 2, 4, and 6 hours after the PCT:[j]
    - Cervical mucus will be collected for assessment of pH.
    - Vaginal sample(s) will be collected for assessment of pH.
  - 6 hours after the PCT, if possible:
    - Vaginal sample(s) will be collected for baseline levels of microflora, antibacterial activity, and soluble markers.[k]

- The participant will be instructed to refrain from intercourse and other vaginal activity until after Visit BP3, 24 hours after Visit BP2.

c) Visit 4 (BP3) - 24 hours after the PCT

- Diary review, AEs, medications, and indications for a directed physical exam, wet mount, or other tests will be managed as described for Visit 2 (BP1).

- The participant will undergo a pelvic exam:
  - Signs of irritation of the external genitalia, cervix, and vagina, as observed with the naked eye, will be noted.
  - Cervical mucus will be examined for assessment of pH.
  - Vaginal sample(s) will be examined for an assessment of pH and baseline microflora.

- The investigator will insert Ovaprene™ and assess the fit (**Appendix 3**). If the investigator determines that Ovaprene™ fits appropriately, she/he will remove it and give the device and written product instructions to the participant. The participant will then attempt to insert Ovaprene™ without assistance. If she is able to insert it, the investigator will check the placement. If the participant is unable to correctly insert and position the device, the investigator will reinstruct and assist as needed. Once the participant correctly inserts and positions the device, she will be asked to remove it. If she is not able to remove the device, the investigator will reinstruct her and assist as needed.

- If the investigator determines the Ovaprene® device does not fit appropriately, or if the participant cannot correctly insert, position, and remove the device, even with assistance, the participant will not continue.

[i] These will serve as baseline measurements for comparison with those obtained at the PCT visits (OP3) in Ovaprene PCT Cycles.

[j] Samples will be collected at as many of these timepoints as possible.

[k] These will serve as baseline measurements for comparison with those obtained at the PCT visits (OP3) in Ovaprene PCT Cycles.

Participants with successful baseline cycles will be considered enrolled.

- An ovulation predictor kit (OPK) with instructions will be dispensed. The participant will be instructed to:
  - Contact the site at the onset of her next menses;
  - Begin daily urine testing on day 10 of that cycle (adjusted as needed to normal cycle length); and
  - Contact the study coordinator when the OPK test yields a "high" result. Visit CP1 - the mucus check visit in the Caya PCT cycle - will be scheduled for that day or the next day.

- A supply of non-spermicidal, lubricated condoms will be dispensed. The participant will be instructed as follows:
  - Sex with or without condoms is permitted after Visit BP3 until the first day of the next menses.
  - From the start of her next menses until day 10, she and her partner should use study condoms for each act of intercourse; and
  - There should be no intercourse or other vaginal activity[l] and the male partner should not have an ejaculation, starting on day 10 until after Visit CP1.

[l] "Other vaginal activity" includes insertion of vaginal medications/products other than the study product (prescription or over-the-counter), as well as insertion of sex toys, fingers, or anything else into the vagina. Tampons may be used during all days of menses in the Baseline PCT and Caya PCT cycles, but only during the first three days of menses in Ovaprene cycles.

Table 6 Baseline PCT Cycle Schedule (in a hypothetical woman with a 5-day menses and a 28-day cycle)

Cycle Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Menses	M	M	M	M	M																							
OPK										✓	✓	✓	✓ high	✓ peak														
Visit 2 (BP1): CMC: • Cervical mucus for pH, midcycle characteristics, & presence of sperm • Vaginal sample for pH, presence of sperm, microflora, antibacterial activity, & soluble markers														✓														
Visit 3 (BP2): PCT: • Cervical mucus for pH, midcycle characteristics, & presence of sperm • Vaginal sample for pH & presence of sperm • **Non-EVMS sites**: Vaginal samples for microflora, antibacterial activity, & soluble markers **EVMS only:** o At 0.5, 1, 2, 4, and 6 hours after insertion, if possible: • Vaginal pH • Cervical pH o At 6 hrs, if possible: • Vaginal samples for microflora, antibacterial activity, & soluble markers															✓													
Visit 4 (BP3): 24 hrs after PCT: • Cervical mucus pH • Vaginal pH & microflora • Ovaprene® fit test • Dispense OPK & condoms																✓												
Sex restrictions	Condoms									No sex or other vaginal activity & no male ejaculation					Sex	No sex/ vag act.	No restrictions											

9.3 CAYA PCT CYCLE

9.3.1 Goals:

- Demonstrate ability to replicate expected results in a PCT cycle using an approved vaginal barrier:
  - Following an acceptable CMC visit, review of each participant's cervical mucus 2-3 hours after intercourse using a Caya diaphragm with nonoxynol-9 will show an average of <5 progressively motile sperm per HPF.

9.3.2 Caya PCT Cycle Visits and Procedures:

a) Visit CP1 - Cervical Mucus Check (CMC) visit, on the day of the "high" result or the next

- Diary review, AEs, medications, and indications for a directed physical exam, wet mount, and other tests will be managed as described for Visit 2 (BP1).

- The participant will be asked whether she used condoms until Day 10 and then refrained from intercourse and the use of intravaginal products, and whether her male partner refrained from ejaculation since Day 10. If instructions were not followed, she will be reinstructed. If she used a spermicide or spermicidal lubricated condom since day 10, Visit CP1 will be rescheduled in the next cycle. Otherwise, the visit may continue at the investigator's discretion.

- The participant will undergo a pelvic exam:
  - Signs of irritation of the external genitalia, cervix, and vagina, as observed with the naked eye, will be noted.
  - Cervical mucus will be examined for midcycle characteristics and the presence of sperm (see **Appendix 2)**.
  - Vaginal sample(s) will be collected for the presence of sperm.

- If sperm are found in the vagina or cervical mucus, the Caya PCT cycle will be rescheduled for the following month and instructions on the use of condoms will be reviewed. Additional supplies will be provided as needed.

- If the cervical mucus score is <10, the participant may be asked to return in 1 or 2 days if it seems likely that the midcycle point has not yet been reached, or in the next cycle if it seems likely that the midcycle point has already passed.

- If no sperm are detected at this visit, and the cervical mucus score is ≥10, a Caya diaphragm with spermicide and instructions will be dispensed. The participant will be instructed to have intercourse with the Caya diaphragm 2 to 3 hours prior to Visit CP2, which will be scheduled for the same or following day, within 27 hours of the mucus check visit.

- The participant will be instructed to otherwise avoid any other vaginal activities[m] until after Visit CP2.

[m] "Other vaginal activity" includes insertion of vaginal medications/products other than the study product (prescription or over-the-counter), as well as insertion of sex toys, fingers, or anything else into the vagina. Tampons may be used during all days of menses in the Baseline PCT and Caya PCT cycles, but only during the first three days of menses in Ovaprene cycles.

- The participant will be instructed to ask her partner, prior to her next visit, if he has had any AEs involving the urogenital system or whether he has had any serious AEs.

b) Visit CP2 – the PCT visit, 2-3 hours after intercourse and within 27 hours of the CMC:

The participant will return to the clinic 2-3 hours after coitus ends and within 27 hours of the mucus check visit.

- Diary review, AEs, medications, and indications for a directed physical exam, wet mount, and other tests will be managed as described for Visit 2 (BP1).

- The participant will undergo a pelvic exam:
  - Signs of irritation of the external genitalia, cervix, and vagina, as observed with the naked eye, will be noted.
  - Cervical mucus will be examined for midcycle characteristics and the presence of sperm (see **Appendix 2**).
  - Vaginal sample(s) will be collected for the presence of sperm.
  - The Caya will be removed.
  - Caya PCT results will be managed as listed in **Appendix 3**.

- The participant will next undergo the Ovaprene™ safety cycle.

- Participants will be instructed as follows:
  - Call at the onset of her next menses to tentatively schedule Visit OS1 on the day following the end of menses. Adjustments to this visit will be made as needed.
  - Sex with or without condoms is permitted after Visit CP2 until the first day of the next menses, after which the participant should abstain from intercourse and other vaginal activity.[n]

[n] "Other vaginal activity" includes insertion of vaginal medications/products other than the study product (prescription or over-the-counter), as well as insertion of sex toys, fingers, or anything else into the vagina. Tampons may be used during all days of menses in the Baseline PCT and Caya PCT cycles, but only during the first three days of menses in Ovaprene cycles.

Table 7 Caya PCT Cycle Schedule (in a hypothetical woman with a 5-day menses and a 28-day cycle)

Cycle Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Menses	M	M	M	M	M																							
OPK										✓	✓	✓	✓ high	✓ peak														
Visit CP1: CMC: • Cervical mucus for midcycle characteristics & presence of sperm • Vaginal sample for presence of sperm														✓														
Visit CP2: PCT: • Cervical mucus for midcycle characteristics & presence of sperm • Vaginal sample for presence of sperm															✓													
Sex restrictions	Condoms										No sex or other vaginal activity and no male ejaculation				Sex	No restrictions											

9.4 OVAPRENE™ SAFETY, RELEASE, ACCEPTABILITY, AND FIT ASSESSMENT CYCLE (ABBREVIATED TO "OVAPRENE™ SAFETY CYCLE") - OVAPRENE™ IN PLACE, NO ACTS OF INTERCOURSE

Table 8 Ovaprene™ Safety Cycle Endpoints

Secondary: 2. Release of active component from device	b) Levels of ferrous gluconate and pH 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 ferrous gluconate levels associated with "success" and whether levels associated with "success" are still present 27-29 days after insertion.)
	e) Residual amount of ferrous gluconate in Ovaprene™ devices that have been worn over a cycle of use.
Secondary: 3. Safety	a) Treatment-emergent AEs among female participants during Ovaprene™ use
	b) Urogenital, product-related, and/or serious AEs among female and male participants during Ovaprene™ use
	c) Changes from baseline in complete blood count, serum chemistries, and serum ferritin
	d) Changes from baseline in findings on pelvic exam, including colposcopy
	e) Changes from baseline in: ▪ Nugent score and microflora ▪ Antibacterial activity in CVF ▪ Soluble markers of inflammation in CVF
	f) Presence of *Staphylococcus aureus* or group A *Streptococcus* on Ovaprene™ devices that have been worn over a cycle of use
Tertiary: 4. Acceptability	a) Responses 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
Tertiary: 5. Fit	b) Proportion of participants who can correctly insert, position, and remove the device using written instructions only
	c) Proportion of participants who require assistance to correctly insert, position, and remove the device
	d) Location of Ovaprene™ in relation to the cervix as determined by clinical exam; relationship of position to PCT results, safety, and acceptability.

9.4.1 Ovaprene™ Safety Cycle - Visits and procedures:

a) Visit OS1, the day following the end of menses (approximately cycle day 6):

- Diary review, AEs, medications, and indications for a directed physical exam, wet mount, and other tests will be managed as described for Visit 2 (BP1).

- Blood will be drawn for CBC, serum chemistries, and serum ferritin.

- The participant will undergo a pelvic exam:
  - Signs of irritation of the external genitalia, cervix, and vagina, as observed with the naked eye, will be noted.
  - A colposcopic exam will be completed.

- Cervical mucus will be collected for pH.
- Vaginal sample(s) will be collected for ferrous gluconate[o], pH, Nugent score, and microflora.
- At sites other than EVMS, vaginal samples will be collected for antibacterial activity and soluble markers.

- The participant will insert Ovaprene™ using written instructions, with assistance if needed. The clinician will check the placement.

- At the EVMS site only:
  - 0.5, 1, 2, 4, and 6 hours after insertion:[p]
    - Vaginal sample(s) will be collected for ferrous gluconate and pH
  - At 6 hours after insertion, if possible:
    - Vaginal sample(s) for antibacterial activity and soluble markers will be collected.

- The participant will be instructed to abstain from intercourse and other vaginal activities until after Visit OS5

b) Visit OS2, 24 hours after insertion:

- Diary review, AEs, medications, and indications for a directed physical exam, wet mount, and other tests will be managed as described for Visit 2 (BP1).

- The participant will undergo a pelvic exam:
  - Signs of irritation of the external genitalia, cervix, and vagina, as observed with the naked eye, will be noted.
  - The position of the device relative to the cervix will be noted.
  - Vaginal sample(s) will be collected for ferrous gluconate, pH, Nugent score, microflora, antibacterial activity, and soluble markers.

- An ovulation predictor kit (OPK) with instructions will be dispensed. The participant will be instructed to:
  - Begin daily urine testing on day 10 of that cycle (adjusted as needed to normal cycle length); and
  - Contact the study coordinator when the OPK test yields a "high" result, if that takes place before OS3 is scheduled. If possible, OS3 will be scheduled for that day or the next day. If that is not possible, OS3 will take place 7-9 days after insertion (approximately cycle day 13 -15).

c) Visit OS3, 7-9 days after insertion (approximately cycle day 13 -15, unless a "high" OPK result takes place):

[o] It is expected that ferrous gluconate will not be found in the vaginal sample before the device is inserted. Samples taken before insertion will serve as a negative control.

[p] Samples will be collected at as many of these timepoints as possible.

- The procedures described above for Visit OS2 will be completed, except that no OPK will be dispensed.
- In addition, cervical mucus will be collected for ferrous gluconate[q] and pH.

d) Visit OS4, 14-16 days after insertion (approximately cycle day 20-22, or sooner if menses is expected to begin):

- The procedures described above for Visit OS2 will be completed, except that no OPK will be dispensed.
- A tentative appointment will be made for Visit OS5, taking into account the participant's usual cycle length and the need to have Visit OS5 take place before the participant's next menses begins but as late as possible in the cycle. The participant will be instructed to contact the site immediately if it appears that her menses is starting before Visit OS5.

e) Visit OS5, 21-23 days after insertion (approximately cycle day 27-29, or sooner if menses is expected to begin):

- An acceptability questionnaire will be administered.
- Blood will be drawn for CBC, serum chemistries, and serum ferritin.
- The procedures described above for Visit OS2 will be completed, except that no OPK will be dispensed.
- Ovaprene™ will be removed and stored for later analysis.
- A colposcopic exam will be completed.
- Cervical mucus will be collected for ferrous gluconate and pH.
- The participant will next undergo an Ovaprene™ PCT cycle. She will be instructed to:
  - Call at the onset of her next menses to tentatively schedule Visit OP1 on the day following the end of menses. Adjustments to this visit will be made as needed.
  - Use non-spermicidal, lubricated condoms (dispense as needed at this visit) from the first day of her next menses until day 10 of that cycle, and to abstain from intercourse and other vaginal activity[r] starting on Day 10 until after Visit OP2, the CMC visit.

[q] Assaying for ferrous gluconate in the cervical mucus is considered exploratory throughout the study.

[r] "Other vaginal activity" includes insertion of vaginal medications/products other than the study product (prescription or over-the-counter), as well as insertion of sex toys, fingers, or anything else into the vagina. Tampons may be used during all days of menses in the Baseline PCT and Caya PCT cycles, but only during the first three days of menses in Ovaprene cycles.

Table 9 Ovaprene™ Safety Cycle Schedule (in a hypothetical woman with a 5-day menses and a 28-day cycle)

Cycle Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Menses	M	M	M	M	M																							
Ovaprene™ in place						✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Visit OS1: Prior to insertion: • Blood for CBC, chemistries, ferritin • Colposcopy • Cervical mucus for pH • Vaginal samples for FG, pH, Nugent score, & microflora. • **At non-EVMS sites:** vaginal samples for antibacterial activity and soluble markers • Device insertion. **EVMS only:** o At 0.5, 1, 2, 4, and 6 hours after insertion, if possible: • Vaginal samples for FG & pH o At 6 hrs, if possible: • Vaginal samples for antibacterial activity & soluble markers						✓																						
Visit OS2: 24 hrs after insertion: • Note device position • Vaginal samples for FG, pH, Nugent score, microflora, antibacterial activity, & soluble markers • Dispense OPK							✓																					
Visit OS3: 7-9 days after insertion: • Note device position • Vaginal samples for FG, pH, Nugent score, microflora, antibacterial activity, & soluble markers • Cervical mucus for FG & pH														✓														
Visit OS4: 14-16 days after insertion: • Note device position • Vaginal samples for FG, pH, Nugent score, microflora, antibacterial activity, & soluble markers																					✓							
Visit OS5: 21-23 days after insertion: • Questionnaire • Blood for CBC, chemistries, ferritin • Note device position																												✓

• Vaginal samples for FG, pH, Nugent score, microflora, antibacterial activity, & soluble markers • Device removed • Colposcopy • Cervical mucus for FG & pH																													
Sex restrictions	No sex or other vaginal activity																												

9.5 OVAPRENE™ PCT CYCLES, WITH ASSESSMENT OF SAFETY, RELEASE, ACCEPTABILITY, AND FIT – DEVICE IN PLACE, ONE ACT OF INTERCOURSE WITH PCT IN EACH CYCLE

Table 10: Ovaprene™ PCT Cycle Endpoints

Primary: 1. Changes in PCT results due to device use	c) Proportion of women and cycles with an average of fewer than 5 progressively motile sperm per HPF in cervical mucus sample, in the *presence* of the device.
	d) Mean, median, standard deviation and interquartile range (IQR) for the average number (across 9 HPFs) of progressively motile sperm per HPF, across all women and cycles, in the *presence* of the Ovaprene™ device.
	e) Change from baseline in the mean, median, standard deviation and interquartile range (IQR) during each Ovaprene™ test cycle, across all women and cycles.
Secondary: 2. Release of active component from device	a) Levels of ferrous gluconate in CVF before sex that are associated with fewer than 5 progressively motile sperm per high powered field (HPF) in cervical mucus after sex (i.e. success), during ovulation.
	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.)
	d) Cervicovaginal pH before and after sex in the absence and presence of the device.
	e) Residual amount of ferrous gluconate in Ovaprene™ devices that have been worn over a cycle of use.
3. Safety	a) Treatment-emergent AEs among female participants during Ovaprene™ use
	b) Urogenital, product-related, and/or serious AEs among female and male participants during Ovaprene™ use
	d) Changes from baseline in findings on pelvic exam, including colposcopy
	e) Changes from baseline in: ▪ Nugent score and microflora ▪ Antibacterial (anti-E. coli) activity in CVF ▪ Soluble markers of inflammation in CVF
	f) Presence of *Staphylococcus aureus* or group A *Streptococcus* on Ovaprene™ devices that have been worn over a cycle of use
Tertiary: 4. Acceptability	a) Responses 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
5. Fit	b) Proportion of participants who can correctly insert, position, and remove the device using written instructions only.
	c) Proportion of participants who require assistance to correctly insert, position, and remove the device.
	d) Location of Ovaprene™ in relation to the cervix as determined by clinical exam; relationship of position to PCT results, safety, and acceptability.

9.5.1 Ovaprene™ PCT Cycle - Visits and Procedures:

a) Visit OP1, the day following the end of menses (approximately cycle day 6):

- Diary review, AEs, medications, and indications for a directed physical exam, wet mount, and other tests will be managed as described for Visit 2 (BP1).

- The participant will be asked whether she used non-spermicidal, lubricated condoms from the onset of menses in this cycle. If instructions were not followed, she will be reinstructed. If she used a spermicide or spermicidal lubricated condom, Visit OP1 will be rescheduled in the next cycle. Otherwise, the visit may continue at the investigator's discretion.

- The participant will undergo a pelvic exam:
  - Signs of irritation of the external genitalia, cervix, and vagina, as observed with the naked eye, will be noted.
  - A colposcopic exam will be completed.
  - Cervical mucus will be collected for pH and ferrous gluconate.
  - Vaginal sample(s) will be collected for pH, ferrous gluconate, Nugent score, microflora, antibacterial activity, and soluble markers.

- The participant will insert Ovaprene™ using written instructions, with assistance if needed. The clinician will check the placement.

- An ovulation predictor kit (OPK) with instructions will be dispensed.

- The participant will be instructed as follows:

  - Begin daily urine testing on day 10 of that cycle (adjusted as needed to normal cycle length) and contact the study coordinator when the OPK test yields a "high" result. Visit OP2 (the mucus check visits) will then be scheduled for that day or the next day.

  - Until day 10, she and her partner should use condoms for each act of intercourse. There should be no intercourse or other vaginal activity,[s] and her male partner should not have an ejaculation, starting on day 10 until after Visit OP3.

b) Visit OP2, the CMC visit, on the day of the "high" result or the next:

- Diary review, AEs, medications, and indications for a directed physical exam, wet mount, and other tests will be managed as described for Visit 2 (BP1).

- The participant will be asked whether she used condoms until Day 10 and then refrained from intercourse and the use of intravaginal products, and whether her male partner refrained from ejaculation since Day 10. If instructions were not followed, she will be reinstructed. If she used a spermicide or spermicidal lubricated condom since day 10, Visit OP2 will be rescheduled in the next cycle. Otherwise, the visit may continue at the investigator's discretion.

- The participant will undergo a pelvic exam:
  - Signs of irritation of the external genitalia, cervix, and vagina, as observed with the naked eye, will be noted.

[s] "Other vaginal activity" includes insertion of vaginal medications/products other than the study product (prescription or over-the-counter), as well as insertion of sex toys, fingers, or anything else into the vagina. Tampons may be used during all days of menses in the Baseline PCT and Caya PCT cycles, but only during the first three days of menses in Ovaprene cycles.

- The position of the device relative to the cervix will be noted.
- Cervical mucus will be examined for pH, ferrous gluconate, midcycle characteristics, and the presence of sperm (see **Appendix 2**).
- Vaginal sample(s) will be collected for pH, ferrous gluconate, and the presence of sperm.
- It is expected that the cervical mucus could be thick and should be without sperm at the CMC. If sperm are found in the vagina or cervical mucus, this cycle will be rescheduled and instructions on condom use and abstinence will be reviewed.
- If no sperm are detected in the vagina or cervical mucus, the participant will be instructed to have intercourse without a condom but with the device in place, 2 to 3 hours prior to the next visit, which will be scheduled for the same or following day, within 27 hours of the mucus check visit.
- The participant will be instructed to otherwise avoid any other vaginal activities[t] until after Visit OP3.

c) Visit OP3, the PCT visit, 2-3 hours after intercourse and within 27 hours of the CMC:

The participant will return to the clinic 2-3 hours after coitus ends and within 27 hours of the mucus check visit.

- Diary review, AEs, medications, and indications for a directed physical exam, wet mount, and other tests will be managed as described for Visit 2 (BP1)

- An acceptability questionnaire will be administered.

- The participant will undergo a pelvic exam:
  - Signs of irritation of the external genitalia, cervix, and vagina, as observed with the naked eye, will be noted.
  - The position of the device relative to the cervix will be noted.
  - Cervical mucus will be examined for pH, ferrous gluconate, midcycle characteristics, and the presence of sperm (see **Appendix 2**).
  - Vaginal sample(s) will be collected for pH, ferrous gluconate, and the presence of sperm.
  - At sites other than EVMS, vaginal samples will be collected for antibacterial activity and soluble markers.
  - Results of the test PCT will be interpreted as shown in **Appendix 3.** A successful test PCT will show mucus containing an average of <5 progressively motile sperm per HPF.

- At the EVMS site only:
  - At 0.5, 1, 2, 4, and 6 hours after the PCT: [u]
    - Vaginal sample(s) will be collected for pH and ferrous gluconate.
  - At 6 hours after the PCT, if possible:

[t] "Other vaginal activity" includes insertion of vaginal medications/products other than the study product (prescription or over-the-counter), as well as insertion of sex toys, fingers, or anything else into the vagina. Tampons may be used during all days of menses in the Baseline PCT and Caya PCT cycles, but only during the first three days of menses in Ovaprene cycles.

[u] Samples will be collected at as many of these timepoints as possible.

- Vaginal sample(s) for antibacterial activity and soluble markers will be collected.

- The participant will be instructed to refrain from intercourse and other vaginal activity until after Visit OP4, 24 hours after Visit OP3.

d) Visit OP4, 24 hours after the PCT:

- Diary review, AEs, medications, and indications for a directed physical exam, wet mount, and other tests will be managed as described for Visit 2 (BP1).

- The participant will undergo a pelvic exam:
  - Signs of irritation of the external genitalia, cervix, and vagina, as observed with the naked eye, will be noted.
  - The position of the device relative to the cervix will be noted.
  - Vaginal sample(s) will be collected for ferrous gluconate and pH.

- Participants will be instructed as follows:

  - Intercourse is permitted after this visit for the rest of this cycle with the following restrictions:
    - Condoms lubricated with something other than nonxynol-9 must be used (dispense as needed).
    - No sex or other vaginal activity[m] is permitted in the 72 hours prior to the final visit in the cycle.

  - A tentative appointment will be made for the next visit, taking into account the participant's usual cycle length and the need to have that visit take place before the participant's next menses begins but as late as possible in the cycle. The participant will be instructed to contact the site immediately if it appears that her menses is starting before the tentatively scheduled appointment.

e) Visit OP5, approximately cycle day 28 or sooner if menses is expected to begin:

- Diary review, AEs, medications, and indications for a directed physical exam, wet mount, and other tests will be managed as described for Visit 2 (BP1).

- The participant will undergo a pelvic exam:
  - Signs of irritation of the external genitalia, cervix, and vagina, as observed with the naked eye, will be noted.
  - The position of the device relative to the cervix will be noted.
  - Vaginal sample(s) will be collected for ferrous gluconate, pH, Nugent score, microflora, antibacterial activity, and soluble markers.
  - Ovaprene™ will be removed and stored for later analysis.
  - A colposcopic exam will be completed.
  - Cervical mucus will be collected for ferrous gluconate and pH.

- If this was the participant's **first** Ovaprene™ PCT cycle, she will undergo a second Ovaprene™ PCT cycle. She will be instructed to:

- Call at the onset of her next menses to tentatively schedule Visit OP1 on the day following the end of menses. Adjustments to this visit will be made as needed.

- Use non-spermicidal, lubricated condoms (dispense as needed) from the first day of her next menses until day 10 of that cycle, and to abstain from intercourse and other vaginal activity[v] starting on Day 10 until after Visit OP2, the CMC visit.

- If this was her **second** Ovaprene™ PCT cycle, she will be contacted 7-10 days after this visit to assess AEs, and will be exited after this contact, unless she has symptoms requiring follow-up.

[v] "Other vaginal activity" includes insertion of vaginal medications/products other than the study product (prescription or over-the-counter), as well as insertion of sex toys, fingers, or anything else into the vagina. Tampons or menstrual cups may be used during all days of menses in the Baseline PCT and Caya PCT cycles, but only during the first three days of menses in Ovaprene cycles.

Table 11: Ovaprene™ PCT Cycle Schedule (in a hypothetical woman with a 5-day menses and a 28-day cycle)

Cycle Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Menses	M	M	M	M	M																							
Ovaprene™						✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
OPK										✓	✓	✓	✓ high	✓ peak														
Visit OP1: • Colposcopy • Cervical mucus for pH & FG • Vaginal samples for pH, FG, Nugent score, microflora, antibacterial activity & soluble markers • Device insertion • OPK dispensed						✓																						
Visit OP2: CMC: • Note device position • Cervical mucus for FG, pH, midcycle characteristics, and the presence of sperm • Vaginal sample for pH, FG, & presence of sperm														✓														
Visit OP3: PCT: • Questionnaire. • Note device position. • Cervical mucus for FG, pH, midcycle characteristics, and the presence of sperm • Vaginal samples for FG, pH, & presence of sperm • **At non-EVMS sites:** vaginal samples for antibacterial activity and soluble markers **EVMS only:** o At 0.5, 1, 2, 4, & 6 hrs, if possible: • Vaginal samples for FG & pH o At 6 hrs, if possible: • Vaginal sample(s) for antibacterial activity and soluble markers															✓													
Visit OP4: 24 hrs after PCT: • Note device position. • Vaginal samples for FG & pH																✓												
Visit OP5: • Note device position. • Vaginal samples for FG, pH, Nugent score, microflora, antibacterial activity, & soluble markers • Device removed																												✓

• Colposcopy • Cervical mucus for FG & pH • If 1st Ovaprene PCT, dispense OPK & condoms as needed • If 2nd Ovaprene PCT, contact in 7-10 days and exit if no AEs requiring follow-up																														
Sex restrictions	Condoms									No sex or other vaginal activity & no male ejaculation				Sex	No sex/ vag act	Condoms lubricated with something other than nonxynol-9 must be used. No sex or other vaginal activity is permitted in the 72 hours prior to the final visit in the cycle.														

9.6 FOLLOW-UP SAFETY CONTACT

The site will contact the participant approximately 7 days (range 7-10) after her last visit. She will be asked about any AEs experienced and medications taken since her last visit. In addition, she will be asked if her partner has had any AEs involving the urogenital system or associated with the use of the product, and whether he has had any serious adverse events. The participant will then be exited from the study, unless she has symptoms requiring follow-up.

9.7 UNSCHEDULED VISITS

Unscheduled visits may be performed at the participant's request or as deemed necessary by the investigator at any time during the study.

When an unscheduled visit occurs in response to an AE experienced by a study participant, study staff will assess the reported event clinically and provide or refer the participant to appropriate medical care, as necessary. Unscheduled visits that require examination or interview due to symptoms will be recorded in eCRFs.

All AEs will be evaluated and follow-up of any observed abnormalities will proceed according to **Section 13**.

9.8 DISCONTINUATION PROCEDURES

If a participant discontinues early from the study, she will be asked if she has had any new or worsening medical problems or symptoms or used any medication since the last study visit. In addition, she will be asked if her partner has had any AEs involving the urogenital system or associated with the use of the product (as applicable), and whether he has had any serious adverse events.

If it has been less than 7 days since the participant's last use of study product(s), then she will be contacted for additional follow-up safety information 7 days (range 7-10) days after her last product use, after which she will be exited from the study unless she has symptoms requiring follow-up (**Section 1.1**). If, at the time of early discontinuation, it has been more than 7 days since the participant's last study product use, she will be exited from the study at the time of discontinuation.

9.9 DATA COLLECTED FROM MALE PARTNERS

Data will be collected from male partners specific to AEs involving the urogenital system, adverse events associated with the use of the product, and all serious adverse events. Prior to each visit, the female participant should ask her partner if he has any AEs meeting these criteria; any AE information provided to the female participant should be communicated to the study coordinator at the participant's next clinic visit or phone call, whichever comes first. The study staff will contact the male partner for clarification of events, as needed. All AEs reported by the male and meeting the above criteria will be recorded on an AE eCRF and will be reported according to the procedures described in **Section 13**.

Male partners also will be instructed to contact the site if they experience severe urogenital symptoms or an SAE. The site will arrange for an evaluation at the center or a possible referral if necessary or desired by the male partner. Male partners will not be required to attend any other clinic visits.

10. TREATMENT OF PARTICIPANTS

10.1 STUDY PRODUCTS

Table 12 Ovaprene™

	Product
Product Name:	Ovaprene™
Dosage Form:	Not applicable
Unit Dose	1 device
Route of Administration	Vaginal barrier method; placed intravaginally at the end of menses and left in place until the beginning of the next menses
Physical Description	Single-size contraceptive device.
Manufacturer	Manufactured by Poly-Med

10.2 CONCOMITANT MEDICATIONS

Prohibited medications include use of intravaginal products at times specified in the protocol, as well as all hormonal contraceptives and treatment for BV and STIs. All concomitant medications will be recorded on CRFs.

10.3 TREATMENT COMPLIANCE

Treatment compliance will be evaluated by self-report. Menses, intercourse, use of intravaginal products, AEs, medications, and problems with the device will be recorded in the eDiary by the participant.

10.4 BLINDING

This is an open label study, thus no product blinding is intended. Ovaprene™ will not be repackaged. Although the individual examining cervical mucus for midcycle characteristics and the presence of sperm and examining vaginal specimens for the presence of sperm is not typically blinded in studies of this type due to the logistical difficulties inherent in doing so, the individual performing these tasks at the EVMS site will be blinded as to the type of visit and use of a barrier, if any.

10.5 RANDOMIZATION

This is an open label study, in which all participants will use the same study product, thus no randomization will take place.

11. STUDY MATERIALS AND MANAGEMENT

11.1 DESCRIPTION OF STUDY PRODUCT

Ovaprene™ is a new, prescription monthly method of birth control that combines a porous, soft mesh cervical barrier encircled by a silicone intravaginal ring that slowly releases non-hormonal ingredients that antagonize sperm motility and viability. The device is inserted at the end of menses, left in place over the course of one menstrual cycle, and removed at the start of menses. Ovaprene™ is designed as a single size device with a diameter of 55 mm, similar to FDA approved, hormone-containing 54 mm diameter NuvaRing® device, eliminating the need for a specifically sized fitting or insertion by a health care professional. Thus, Ovaprene™ is a single device designed to provide the features that contracepting women want: efficacy, ease of use, ease of adherence, low or no side effects and easy reversal.

Ovaprene™ was studied in a human clinical trial as a non-significant risk device published in 2009.[1] Prior to this study, Ovaprene™ underwent a series of *in vitro* and animal tests to determine usability and design parameters, and to assess its initial safety and contraceptive efficacy. These background data are considered proprietary, but major conclusions are summarized in this section, with additional detail published in Del Priore *et al.* [1]

To determine the putative barrier properties of Ovaprene™, the effectiveness of the mesh component in blocking human sperm was tested in an *in vitro* environment having features similar to those of the human cervix. After 20 hours of continuous exposure to sperm, there was no evidence of sperm passage through the Ovaprene™ mesh. Burst testing, under forces two orders of magnitude higher than expected during normal use, confirmed that no delamination or slippage of the mesh component from the ring matrix is expected during placement, and up to 35 days of use.

Uniform mixing of the spermiostatic components throughout the silicone matrix is controlled during the ring manufacturing process. In an *in vitro* model simulating *in vivo* conditions, ferrous gluconate (FG) is released from the ring immersed in synthetic vaginal fluid in three different stages. These consist of an initial burst (day 1), erosion (days 2-7) and diffusion (days 5-35). Release studies evaluated the cumulative concentration of each component and demonstrated that the average concentration of FG throughout the testing period exceeded the minimal levels required for spermiostatic activity based on literature values.

Ovaprene™ already meets the necessary toxicology requirements for human studies and regulatory approval. Ovaprene™ has been found non-mutagenic and non-clastogenic via Gene Mutation testing, Chromosomal Aberration testing, and Rodent Bone Marrow Micronucleus Assay testing, and has met the International Standards Organization (ISO 10993-10 guidelines) requirements of the Kligman Maximization Test, Rabbit Pyrogen Test, and Intracutaneous Injection Test. A four-week Muscular Implantation test in rabbits demonstrated no difference compared to controls, and a Primary Vaginal Repeat Exposure test in rabbits demonstrated that the extracts of Ovaprene™ are non-irritating.

The Ovaprene™ ring was miniaturized to evaluate contraceptive activity in rabbits. The adapted device was 100% effective in preventing pregnancy in this model.

An open label, single-arm, observational study was conducted with Ovaprene™ in sexually active women.[1] Twenty women were enrolled. Baseline Pap tests, vaginal cultures and colposcopy were performed with follow-up post-coital testing and acceptability questionnaires. Participant questionnaires revealed no pain, bleeding, or discharge and no colposcopic abnormalities were observed. Semi-quantitative cultures yielded no significant changes in vaginal flora. Post-coital testing assessed preliminary contraceptive activity by assessing motile sperm in ten high powered fields. There were no normal, forward-moving sperm seen in the

vaginal pool or cervical canal in any of the participants, consistent with high spermiostatic activity. A low pH was maintained throughout the duration of the study [of 28 measurements, 22 (79%) recorded a pH of 5.5 or less throughout the 28-day study] presumably through the release of ascorbic acid (AA) and polyglycolide (PG) from the Ovaprene™ ring.

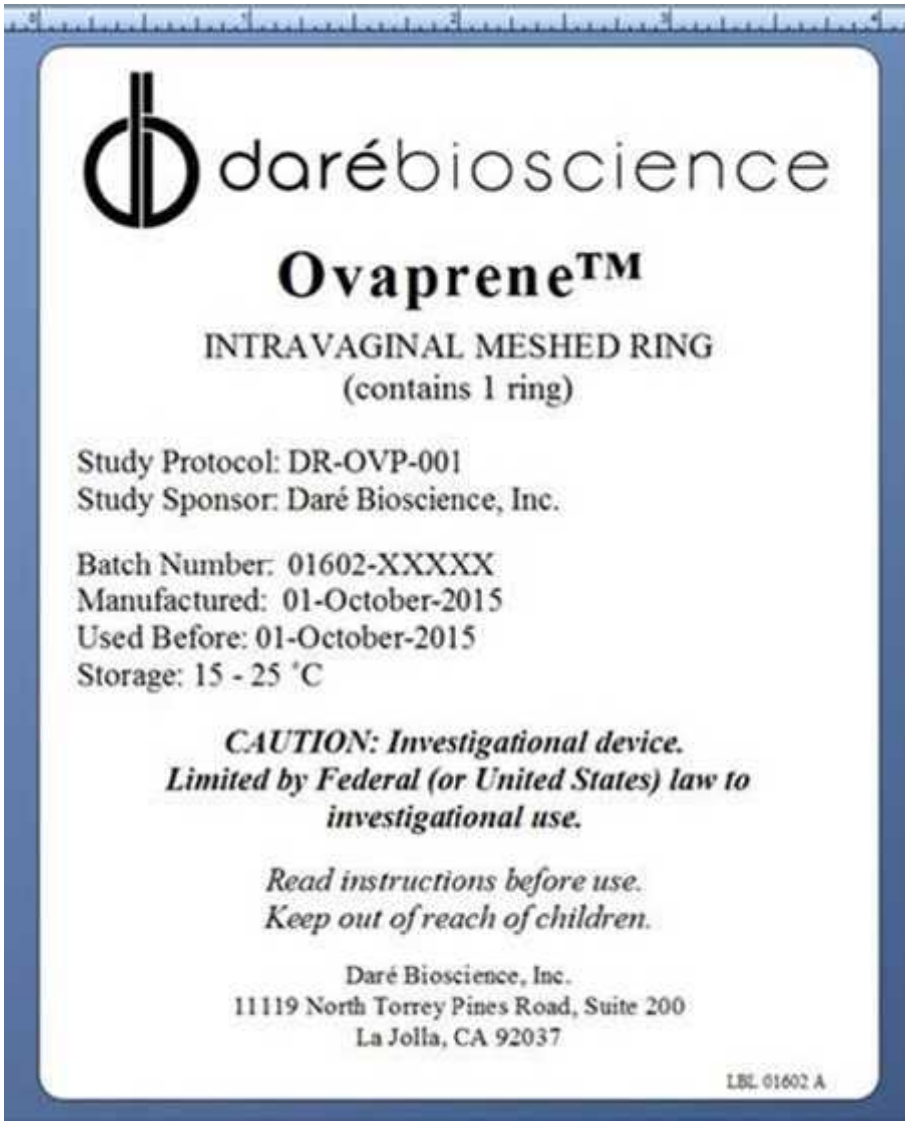
Ovaprene™ was developed by Adva-Tec, Inc., a majority owned subsidiary of Poly-Med, Inc. Poly-Med holds twelve issued patents in the U.S. and three issued European patents pertinent to the invention and protection of Ovaprene™ technology. Since the completion of the pilot study summarized above, Poly-Med/Adva-Tec has sought a suitable commercialization partner and recently entered into an agreement with Daré Bioscience, a company committed to both advancing the clinical development of novel contraceptive products and creating comprehensive global strategies for the commercialization of these products. The principals of Daré Bioscience have an excellent track record of commercializing women's health products. With a commercialization strategy identified, Poly-Med is now positioned to continue the development of this innovative technology. These three world class companies have joined forces to complete the clinical development of Ovaprene™ and bring this important product to the marketplace.

The FDA has determined that the Center for Devices and Radiological Health (CDRH) will be the lead reviewing agency for Ovaprene™, and that it will be reviewed in the context of other barrier contraceptive devices using active agents, for which clearly defined clinical and regulatory pathways toward FDA clearance exist. This pathway includes the following three steps: (1) conducting standard biocompatibility, safety exposure, and toxicology studies; (2) obtaining safety and preliminary efficacy data in 20-30 human subjects [the objective of this study]; and (3) conducting a larger scale, single arm safety and efficacy study in at least 200 subjects, comparing its efficacy results to historical controls.

11.2 STUDY PRODUCT PACKAGING AND LABELING

The Ovaprene™ pouch will have a label on each side. Figure 1 below is an example of the single-panel label that will be affixed to one side of the Ovaprene™ pouch by the manufacturer. Sites will be provided with an additional single-panel lab to affix to the other side of the Ovaprene™ pouch; these site labels will include fields for Subject ID, Date Ovaprene™ is dispensed, and Date Ovaprene™ is removed from participant. Additional information will be included in the product instructions.

Figure 1: Ovaprene™ Manufacturing Label



11.3 DESCRIPTION AND PACKAGING OF CAYA DIAPHRAGM AND NONOXYNOL-9

The Caya® diaphragm is made of silicone rubber with a continuous, variable cross-section nylon polymer spring, encapsulated in the silicone rim. Its overall length is 75 mm and its overall width is 67 mm. The rim surrounds a contoured membrane with two cup-like structures and a flat area. The larger of the cups fits over the cervix and the smaller is intended to aid finger or thumb hooking of the rim for removal. The flat area provides contact with the vaginal wall.

The Caya diaphragm is manufactured by Wefo-Tec for Kessel Marketing & Vertriebs GmbH of Germany. Kessel Marketing is headquartered in Frankfurt, Germany, and is an ISO 13485 certificated company and producer of medical devices since 2005. Caya received FDA marketing clearance for the indication of pregnancy prevention in September 2014 and is distributed in the U.S. by HPSRx Enterprises, Inc., Salem, VA. Caya will be provided to study participants in its original commercial packaging showing the product's name, manufacturer, lot number, and expiration date.

Gynol II® Vaginal Contraceptive Gel (Extra Strength, 3% N-9) is distributed by Revive Personal Products Company, Madison, NJ. It is a licensed, commercially available spermicide containing 3% nonoxynol-9 as the active ingredient. Inactive ingredients include lactic acid, methylparaben, providone, propylene glycol, purified water, sodium carboxymethylcellulose, sorbic acid and sorbitol solution. It is a clear, unscented, water-soluble, greaseless gel that should be stored at room temperature. Gynol II will be provided in its original commercial packaging showing the product's name, manufacturer, lot number, and expiration date.

11.4 STUDY PRODUCT STORAGE

All study products should be stored at room temperature as specified in the Study Procedures Manual.

11.5 STUDY PRODUCT PREPARATION

The study products are ready to use and require no preparation.

11.6 ADMINISTRATION

The participant will be instructed to insert Ovaprene™ at the end of menses, using a finger to push it into the vagina as far as it will comfortably go. She will check to make sure the device covers the cervix. Product use instructions will be provided.

The participant will be instructed to insert Caya with N-9 just before intercourse, following the package instructions, which will be provided. She will check to make sure the device covers the cervix.

11.7 STUDY PRODUCT ACCOUNTABILITY

Dispensing of the Ovaprene™ device will be recorded on the device accountability log. The final return of the device, either by the participant or at the time of removal in the clinic, will be recorded on the accountability log. Additional instructions will be provided in the Study Procedures Manual.

A Caya diaphragm and a tube of Gynol II will be provided to the participant for the Caya PCT Cycle. Because these are marketed products, the participant will not be required to return them.

11.8 STUDY PRODUCT HANDLING AND DISPOSAL

All used and unused study product remaining at the end of the study will be recorded by the site and reconciled by the site monitor. After reconciliation, the Sponsor will provide instructions regarding disposal or return of product.

12. ASSESSMENT OF SAFETY

12.1 SAFETY PARAMETERS

12.1.1 Adverse Events

As part of AE data collection, participant AEs will be assessed at each study visit; participant report of genitourinary and other symptoms will be documented and report of symptoms may result in follow-up laboratory assessments.

Female participants will be asked to provide information on any AEs their male partners experience that are at least possibly related to product use, genitourinary in nature, or serious. Partner AEs meeting these criteria must be recorded on eCRFs.

12.1.2 Physical Examination

A directed physical exam will be performed at each study visit if indicated, with changes on physical exam documented.

12.1.3 Pelvic Exam

A pelvic exam will be performed at each study visit. Signs of irritation of the external genitalia, cervix, and vagina, as observed with the naked eye will be noted.

12.1.4 Pregnancy Screen

A pregnancy test is required at Visit 1 on all participants. Note, however, that participants must be protected from pregnancy by prior female tubal sterilization in order to be eligible for study participation.

13. ADVERSE AND SERIOUS ADVERSE EVENTS

13.1 DEFINITION OF ADVERSE EVENTS (AE)

An AE is any undesirable sign, symptom, or medical condition occurring after signing the ICF. Information about all AEs, whether volunteered by the subject, discovered by questioning, or detected through physical examination, laboratory testing, or other means, will be collected and recorded on the AE eCRF page and followed as appropriate.

Medical conditions present prior to study entry will be documented in the Medical History eCRF. However, medical conditions occurring after signing the ICF are to be recorded as AEs. Treatment-emergent AEs are defined as AEs with onset after the first dose of study drug or existing AEs that worsened after the first dose of study drug.

The Investigator is obliged to interview subjects at each clinic visit and clarify/discuss any abnormality that may indicate a potential AE.

Subjects should be encouraged to contact or visit the study site to report AEs that occur between scheduled visits.

AEs will be recorded from the time of signing the ICF until the end of the safety follow-up. If any AE is ongoing at the time of subject withdrawal, the subject will be asked to return for clinic visits or to respond to follow-up by telephone (if the AE is considered not related or unlikely related to study drug) until resolution or stabilization of this AE.

Any AE that occurs during the study must be monitored and followed up until one or more of the following criteria have been met:

- It has resolved to ≤ Grade 1 or baseline level
- Pathological laboratory findings have returned to normal
- Steady state has been achieved
- It has been shown to be unrelated to the study drug

It is the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

As far as possible, each AE will also be described by:

- Duration (start and end dates)
- Severity grade
- Relationship to the study drug
- Action(s) taken and, as relevant, the outcome

13.2 SERIOUS ADVERSE EVENT (SAE)

An AE is considered "serious" if, in the view of either the investigator or the sponsor, it:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

All participant and male partner SAEs, whether or not they are related to the study, must be recorded on eCRFs.

13.3 UNEXPECTED ADVERSE EVENT

In previous studies of vaginal contraceptive devices, genital pruritus, genital irritation, genital pain, abnormal vaginal bleeding, symptomatic vaginal infections and UTIs, and Pap test changes were reported, thus making these expected AEs. An AE or suspected adverse reaction is considered "unexpected" if it is not listed above or in the product labeling for the Ovaprene™ or is not listed at the specificity or severity that has been observed. For example (not necessarily applicable to this study), under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the labeling as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

13.4 RELATIONSHIP TO STUDY PRODUCT

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product(s) for each AE. The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. For each AE, the assessment of relatedness should be made using the following scale:

- Unrelated: Onset of the AE had no reasonable temporal relationship to administration of the study product or a causal relationship to administration of the study product is biologically implausible or the event is attributed to an alternative etiology.

- Possibly Related: Onset of the AE has a reasonable temporal relationship to study product administration and a causal relationship is not biologically implausible.
- Probably Related: Onset of the AE has a strong temporal relationship to administration of the study product that cannot be explained by the participant's clinical state and a causal relationship is not biologically implausible.
- Definitely Related: Onset of the AE shows a distinct temporal relationship to administration of the study product that cannot be explained by the participant's clinical state or other factors or the AE occurs on rechallenge or the AE is a known reaction to the product or chemical group or can be predicted by the product's pharmacology.

If the relationship between the AE/SAE and the investigational product is determined to be "possible," "probable," or "definite" the event will be considered related to the investigational product for the purposes of expedited regulatory reporting.

13.5 RECORDING AND GRADING ADVERSE EVENTS FOR SEVERITY

Adverse events spontaneously reported by the participant and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. The AE term should be reported in standard medical terminology when possible. All female adverse events and male adverse events that are assessed as at least possibly related to product use should be recorded on the AE eCRF. For each AE, the investigator will evaluate and report the date of onset, date of resolution, severity, causality, action taken, serious outcome (if applicable), and whether or not it caused the participant to discontinue the study. Each AE will be graded for severity using the March 2017 update of the Division of AIDS, National Institute of Allergy and Infectious Diseases (DAIDS) Table for Grading the Severity of Adverse Events, and the addenda for female and male genital AEs, which can be found at the following websites:

Table 13 Guidance for Adverse Events

Adult and Pediatric AEs	https://rsc.tech-res.com/docs/default-source/safety/daids-ae-grading-table-mar2017.pdf
Female Genital AEs	http://rsc.tech-res.com/docs/default-source/safety/addendum_1_female_genital_grading_table_v1_nov_2007.pdf?sfvrsn=8
Male Genital AEs	http://rsc.tech-res.com/docs/default-source/safety/addendum_2_male_genital_grading_table_v1_nov_2007.pdf?sfvrsn=8

For clinical AEs NOT identified in the DAIDS AE Grading Tables, the following scale (as listed in the DAIDS Table for Grading the Severity of Adult and Pediatric AEs) should be used to grade severity:

- Mild: Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated
- Moderate: Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated
- Severe: Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated
- Potentially Life-Threatening: Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under **Section 13**. An AE of severe intensity may not be considered serious.

Participants are required to be protected from pregnancy by female tubal sterilization. Should a pregnancy occur, however, it must be reported as soon as possible to the Sponsor or designee and recorded on the pregnancy CRF. The participant will be discontinued from the study and appropriate exit procedures will be followed (**Section 9.8**). Note that pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.
If the participant has been exposed to study product, the course of the pregnancy should be followed until it has an outcome (spontaneous miscarriage, elective termination, normal birth or congenital abnormality). If the participant seeks care outside the site, every effort should be made to obtain her consent for the site to receive a copy of her medical records related to the pregnancy, its outcome and the health of the neonate, if applicable.

Reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be reported as AEs.

13.6 REPORTING SERIOUS ADVERSE EVENTS

All SAEs experienced by either a female participant or her partner, whether or not considered a suspected reaction, will be recorded from the time of signing the Informed Consent Form until 7 days following the end of treatment exposure.

Any SAE must be reported to the Sponsor or designee within 24 hours of discovery. If there is any question whether the event meets the criteria for “serious” it should be reported anyway. In addition, a completed Serious Adverse Event (SAE) Form must be faxed or emailed to the Sponsor or designee as soon as possible. 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

Additional follow-up information, if required or available, should all be faxed or emailed as instructed to the Sponsor or designee within one business day of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the study file.

The Sponsor or designee will notify all participating investigators of potentially serious risks, from clinical trials or any other source, as soon as possible.

The Sponsor or designee will promptly investigate and follow up on all safety information it receives, with the cooperation of the investigator.

The investigator is responsible for complying with IRB requirements for AE reporting and the Sponsor or designee with copies of such correspondence.

14. STATISTICS

14.1 SAMPLE SIZE JUSTIFICATION

Approximately 45 participants 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 that could feasibly be enrolled and complete this rigorous protocol in a reasonable time frame.

14.2 ANALYSIS PLAN

All analyses will be conducted on an "as treated" basis; that is, product conditions are defined on the basis of treatment experienced and allocation errors are taken into account.

14.2.1 Interim Analysis

An interim analysis will take place after at least 10 women have completed one Ovaprene® PCT cycle. The interim analysis is being performed to evaluate all primary endpoints as defined in Section 6 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.

14.2.2 Sperm Penetration of Midcycle Cervical Mucus: Evaluation of Primary Objective

The primary method of evaluating changes in the PCT due to device use (primary objective) for each product condition will be the proportion of women and cycles (and 95% confidence interval [CI]) with an average (across 9 HPFs) of fewer than 5 PMS per HPF.

The mean, median, SD, and IQR of each woman's and cycle's average number (across 9 HPFs) of progressively motile sperm per HPF will be calculated separately for baseline and each test PCT. Qualitative assessments of change from baseline, if any, will be based on the median and IQR, because of expected non-normality of test cycle data. These descriptive statistics will be calculated by site and pooled across sites.

There will be no statistical comparison between Caya PCT cycle results and Ovaprene™ PCT cycle results. Caya PCT cycle results will be reviewed in the context of published Caya PCT studies; it is expected that Caya PCT results in this study will be similar to published Caya PCT results, which will give confidence to the Ovaprene™ PCT results in this study.

14.2.3 Secondary Objective: Release of active component from device

The mean, median, SD, and IQR of ferrous gluconate values associated with fewer than 5 progressively motile sperm per HPF will be calculated across all women. The mean, median, SD, and IQR of ferrous gluconate values at each time point at which it is collected will also be calculated across all women. The mean, median, SD, and IQR of ferrous gluconate values in used devices will be calculated. The mean, median, SD, and IQR of cervical mucus and vaginal pH before and after sex in the absence of and the presence of the device will be calculated across all women.

14.2.4 Secondary Objective: Safety

Tables and listings will be created for all treatment-emergent AEs (TEAEs), defined as those occurring on or after first product use. However, the primary evaluation of safety will be the subpopulation of safety AEs that are urogenital, product-related, and/or serious. Data will be presented according to relatedness of the finding to study product, whether AEs had onset before or after intercourse, by gender and by site, and pooled across sites separated by gender, and the severity/seriousness of the AE. There are no planned statistical tests for this objective.

For other safety endpoints, baseline and comparison time points will be qualitatively compared as shown below:

Table 14: Endpoint Evaluations

	Goal	Baseline	Compared with
Changes in CBC,* chemistries,* and ferritin, colposcopy*	Assess effect of device on these endpoints after one cycle of use in the absence of sex, compared with before insertion	OS1	OS5
Nugent score,* vaginal microflora, vaginal antibacterial activity, and soluble markers	Assess effect of device on these endpoints over one cycle, in the absence of sex, compared with before insertion	OS1	OS2, OS3, OS4, OS5
	Assess effect of device on these endpoints after the device has been in place for one cycle, with multiple acts of sex up until 72 hours before the last visit, compared with before insertion	OP1	OP5
Vaginal antibacterial activity and soluble markers of inflammation	Assess effect of device insertion on these markers, in the absence of sex	BP1	OS1 after device insertion Baseline sample cannot be collected before device insertion at this visit because collection technique (vaginal lavage) is likely to affect subsequent samples taken at this visit.
	Assess effect of device on these markers after sex, compared with after sex with no device in place	BP2	OP3
	Assess effect of device on these markers after sex, compared with before sex	OP1	OP3

* Also done at Visit 1 to establish eligibility

14.2.5 Tertiary: Acceptability

Tables and listings will be created for all responses on the acceptability questionnaire/eDiary. Results will be evaluated qualitatively. There are no planned statistical tests for this objective.

14.2.6 Tertiary: Fit

The proportion of screened women who could correctly insert, position, and remove the device without assistance will be calculated for each visit at which it was assessed. The proportion who required assistance will also be calculated. The proportion of women in whom the device was found to be located over the cervix will be calculated for each visit at which it was assessed. The proportion of successful PCT visits at which the device was found to be located over the cervix will also be calculated. The proportion of visits in which adverse safety outcomes were recorded at which the device was found to be located over the cervix will be calculated. The proportion of participants who recorded adverse acceptability outcomes in whom the device was found not to be located over the cervix will be calculated.

15. MANAGEMENT OF INTERCURRENT EVENTS

15.1 LOST TO FOLLOW-UP

If a participant fails to appear for a scheduled visit, at least three attempts to contact her should be made over the subsequent 30 days and these attempts should be documented in the participant's study file. The final attempt must be a certified letter to the participant with return-receipt requested. A copy of this letter should be in her file. After these three attempts, no further efforts need be made to find her, but her file should remain open until study close-out.

If the participant does not contact the clinic before the study is closed, the End of Trial eCRF will be completed at the time of study close-out. The form should indicate that the participant was lost to follow-up. The lost to follow-up designation cannot be made for any participant until the closing date of the study.

15.2 PROTOCOL ADHERENCE

Participants will be considered compliant with the study regimen if they have used the study product as directed during the Ovaprene™ Safety Cycle and both Ovaprene™ PCT Cycles and have returned at the correct time for visits in those cycles.

15.3 PROTOCOL VIOLATIONS

If a procedure that would meet criteria for a protocol violation is required to protect the life or physical well-being of a participant in an emergency, it may be completed without prior approval from the sponsor or the IRB. The investigator must, however, report the violation to the sponsor and the IRB as soon as possible, no later than within 5 working days after the emergency occurred.

Other violations from the protocol may not be completed without prior approval from the IRB if the change involves the rights, safety, or welfare of participants and without prior approval of the sponsor if the change involves the validity of the data, the study's scientific soundness or the rights, safety, or welfare of participants.

If an inadvertent protocol violation has occurred, the sponsor should be notified immediately to determine what steps should be taken.

All protocol violations should be listed in the Protocol Violation Log provided by the sponsor.

15.4 MODIFICATIONS OF PROTOCOL

No modification of this protocol may be made without the approval of the sponsor.

16. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

16.1 STUDY MONITORING

The study will be monitored to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

Before the study start, at a site initiation visit, a Sponsor representative will review the protocol and the eCRF with the Investigator(s) and their staff.

During the study, on-site monitoring visits will be made at appropriate times. Clinical monitors will visit the site regularly to check the completeness of subject records, the accuracy of entries on the eCRF, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the clinical monitor during these visits.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables will be checked. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

16.2 RECORD RETENTION

Per CFR Section 21 Part 312.62, the signed original informed consent documents for each participant/partner and originals of all study documentation (e.g., study product inventory forms, participant clinic records, and original laboratory reports) will be retained by the PI for minimum of two years after FDA approval or withdrawal of a PMA. If no PMA is submitted within five years of the last follow-up visit, the center may request permission in writing from the sponsor to destroy the records. No records may be destroyed without written permission from the sponsor.

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information. The Investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with Directive 95/46/EC: Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data and in a form satisfactory to the Sponsor.

16.3 QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor or its designee will perform the quality assurance and quality control activities of this study. However, responsibility for the accuracy, completeness, and reliability of the study data presented to the Sponsor lies with the Investigator generating the data.

16.4 AUDITS AND INSPECTIONS

Authorized representatives of the Sponsor, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all

study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements.

16.5 INSTITUTIONAL REVIEW BOARD (IRB)

The Principal Investigator must obtain IRB approval for the investigation prior to screening subjects. Initial IRB approval, and all materials approved by the IRB for this study including the participant consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

16.5.1 IRB/Ethics Review

The final study protocol, including the final version of the Informed Consent Forms, must be approved or given a favorable opinion in writing by an IRB or IEC (Institutional Ethics Committee) as appropriate. The investigator must submit written approval to the sponsor before he or she can screen any participant into the study. The study must be conducted in accordance with all conditions of approval by the IRB. *Note: The FDA has determined that this study is not a significant risk study since the enrolled population is not at risk for pregnancy or STI and all components of Ovaprene™ are Generally Regarded as Safe (GRAS). Therefore, this study is not required to be completed under an IDE.*

The PI is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit participant s for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The PI is also responsible for providing the IRB with reports of any reportable serious adverse reactions from any other study conducted with the investigational product. The sponsor will provide this information to the PI.

Progress reports and notifications of serious adverse reactions will be provided to the IRB or IEC according to local regulations and guidelines.

16.6 ETHICAL CONDUCT OF THE STUDY

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP, and applicable regulatory requirements. In addition, the PI will follow U.S. Department of Health and Human Services regulations regarding the Health Information Portability and Accountability Act (HIPAA 45, CFR 164). The PI will ensure that appropriate health care or referral is provided for the participants throughout the study.

17. WRITTEN INFORMED CONSENT

17.1 PROCEDURE FOR OBTAINING INFORMED CONSENT

No volunteer may be admitted into this study until the PI (or designee) has obtained her legally effective informed consent. The Investigator shall seek such consent only under circumstances that provide the prospective participant with sufficient opportunity to consider whether or not to participate in the study. Informed consent must be obtained without coercion, undue influence, or misrepresentation of the potential benefits or risks that might be associated with participation in the study. Per site IRB requirements, the male partner may be asked to sign an information sheet or informed consent form.

Informed consent encompasses all oral and written information given to the volunteer about the study and the study materials. This includes the consent form signed by the participant and her partner, the instructions for use of study materials that are provided to the participant, recruitment advertising, and any other information provided to the participant and/or her partner. All such information that is given will be in a language that is understandable to the participant and/or her partner. The information will not include any language in which they are made to waive any of her rights or which releases or appears to release the PI, the PI's institution, or the sponsor from liability for negligence.

Informed consent will be documented by the use of a written consent form that is signed by the participant/partner and the PI (or designee). A copy of the signed consent form will be given to each participant/partner. The original signed consent form for each participant will be kept at the site. The consent form must include each of the basic and additional elements of informed consent described in 21 CFR Part 50.25 and must describe each of the risks or discomforts to the participant that have been identified by the sponsor as reasonably foreseeable. The sponsor will provide sample consent forms that meet these requirements. If the PI revises the sample consent forms or develops new ones, the new or revised consent forms should be submitted to the sponsor for review before it is submitted to the local IRB.

17.2 SUBJECT CONFIDENTIALITY

The confidentiality of all participants consented into this clinical study will be protected to the fullest extent possible. Participant clinic records may be audited by the sponsor staff or other individuals authorized in writing by the sponsor to audit the study. However, study subjects will not be identified by name on any eCRF, or on any other documentation sent to the sponsor or other organizations involved in this study, and will not be reported by name in any report or publication resulting from data collected in this study.

18. DATA HANDLING AND RECORDKEEPING

18.1 METHOD OF DATA CAPTURE

Clinical data will initially be recorded on source documents at the clinical site. The source documents, including signed informed consent forms, laboratory reports, and participant records, should be maintained at the site, and should be available for review during monitoring visits.

Information from the source documents will be entered into eCRFs. A data management plan will be written before data are collected for this study.

19. INVESTIGATOR RESPONSIBILITIES

19.1 SIGNING OF INVESTIGATOR'S AGREEMENT AND AMENDMENTS

Prior to study start the PI is responsible for signing and dating the Investigator's Agreement for this study protocol. The signed and dated original must be submitted to the sponsor, and a copy must be maintained by the PI at the site with the study files.

All protocol amendments must be signed and dated by the PI. The signed and dated original must be submitted to the sponsor, and a copy must be maintained by the PI at the site. Amendments must be approved by the sponsor and the IRB before implementation.

19.2 FORMS AND RECORDS

Prior to study initiation, the following forms and records will be provided to the sponsor, and a copy maintained in site files:

- Statement of the Investigator
- Curriculum vitae (CV) for staff listed on Statement of the Investigator:
    - The PI will provide the sponsor with a CV for him/herself showing the education, training, and experience that qualifies him/her as an expert in the area of clinical investigation specific to the product under investigation and his/her affiliation with the site at which the study is being conducted.
    - CVs will also be provided for study staff listed on the Statement of the Investigator showing the education, training, and experience that qualifies them for their role in the study, and their affiliation with the study site.
- Financial Disclosure Statement (completed by each staff member listed on the Statement of the Investigator). Note that this form will also need to be provided for each staff person at the end of the study and one year following completion of the study, as possible.
- IRB information consisting of:
    - Name, address, and chairperson of the IRB
    - Multiple Project Assurance (MPA) or Federal-Wide Assurance (FWA) number
    - List of IRB members (names may be withheld in accordance with IRB policy) with title, occupation and affiliation for each member
    - Copy of IRB approval letter for protocol, consent form, advertisement, and other written materials provided to participants
    - Copy of IRB-approved consent form, advertisements, and other written materials provided to participants, as applicable
- Laboratory information including:
    - Name of laboratories to be used to process study specimens
    - CV of laboratory director(s)
    - Current license(s) and/or laboratory certification (such as the Clinical Laboratory Improvement Act [CLIA] certification), with expiration date
    - Copy of normal values for tests done by each laboratory for this study

19.3 DURING THE STUDY: FORMS AND RECORDS

The following forms and records will be maintained at the study site:

- Subject Status Log(s)
- Subject Identification Code List
- Signature and Delegation of Responsibility Log
- Site Visit Log
- Study Supplies Inventory Logs and packing slips
- Protocol Violation Log
- Source documents
- Signed and dated informed consent forms
- CRFs
- IRB documents:
    - Submission and approval letters for protocol and any protocol amendments
    - Submission and approval letters for original and any revised consent forms and any other written material provided to participants
    - Annual submission and approval letters

- Other IRB correspondence
- Updates on CVs and laboratory information
- General correspondence

Copies of all correspondence between the site and its IRB should be sent to the sponsor.

The PI is responsible for obtaining any updates to these documents, including certification renewals, and sending them to the sponsor in a timely fashion.

20. PUBLICATION POLICY

All information concerning the study supplied by the sponsor to the PI and not previously published is considered confidential.

No data collected in this study will be presented or published without prior approval from the sponsor.

APPENDIX 1. SCHEDULE OF ASSESSMENTS

X = required O = if indicated

The pelvic exam procedures are listed in the recommended sequence of collection.

	Screening	BP1	BP2	BP3	CP1	CP2	OS1	OS2	OS3	OS4	OS5	OP1	OP2	OP3	OP4	OP5	UNS
Informed Consent (also male, if required)	X																
Assign Subject Number	X																
Demographics	X																
Assess eligibility	X	X															
Enroll participant				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	X
Height/Weight	X																X
HIV[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	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
AEs, Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Acceptability Questionnaire											X			X			
Note device position by digital exam								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
Exam of external genitalia, by naked eye & colposcopy	X						X				X	X				X	X
Colposcopic Exam - insert speculum, do naked eye exam of visible vaginal epithelium	X						X				X	X				X	X
Note device position with speculum in place								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	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	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	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	X
Remove Ovaprene - swab for staph aureus and store											X					X	X
Colpo exam of cervix under magnification	X						X				X	X				X	X
Pap Test[5]	X																
GC/CT if using cervical specimens[6]	X																X
Colpo exam of fornices and of vagina (latter while removing speculum)	X						X				X	X				X	X
Ovaprene Fit Test				X													
Caya Fit Test	X																X
Insert Ovaprene[13]							X					X					X
Remove Caya						X											X
Dispense Caya					X												
Explain Trials.ai	X																
Dispense OPK Kit	X			X				X				X				X	X
Dispense condoms	X			X							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 participants. HIV testing is available for the male partners, if requested.

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

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

[8] EVMS 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, see **Appendix 2.**

[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 participant will insert Ovaprene™ using written instructions, with assistance if needed. The clinician will check the placement.

APPENDIX 2. ACTIONS AT THE PCT VISIT IN BASELINE AND TEST CYCLES (ADAPTED FROM SCHWARTZ ET AL, 2008[3])

Vaginal pool - any sperm present (including fragments) *	Mucus – adequate (thin)	Endocervix			Action at Baseline Cycle	Action at Test Cycle
		No sperm	Some sperm but an average of <5 progressively motile/HPF**	An average of ≥5 progressively motile/HPF		
Yes	Yes	✓			Similar results in test cycle would make it appear that the product was successful. Do not continue participant.	**Barrier successful** Continue to next cycle.
Yes	Yes		✓			
No	Yes		✓			
Insufficient material	Yes		✓			
Yes	Yes			✓	Good PCT. Continue to next cycle	**Barrier failed.** If **Caya** cycle, do not continue participant if the result was clearly due to participant misuse of the product. Otherwise, continue to next cycle. If **Ovaprene**™ cycle, continue to next cycle.
Yes	No			✓		
No	Yes			✓		
No	No			✓		
Insufficient material	Yes			✓		
Insufficient material	No			✓		
Yes	No	✓			Poor mucus may be responsible for scarcity or lack of sperm in cervix. Repeat cycle.	If **Caya** cycle, repeat cycle. If **Ovaprene**™ cycle, continue to next cycle. Considered successful for Ovaprene™ due to its potential mucus-thickening properties.
Yes	No		✓			
No	No		✓			
Insufficient material	No		✓			
No	Yes	✓			Ejaculation may not have taken place. Repeat cycle.	Ejaculation may not have taken place. Repeat cycle.
No	No	✓				
Insufficient material	Yes	✓				
insufficient material	No	✓				

* Absence of sperm in vagina means either that ejaculation did not take place or the vaginal environment is unusually hostile to sperm, possibly due to presence of spermicide in Caya cycle.

** Confirms that ejaculation took place, but presumed to be insufficient for conception

APPENDIX 3. CORRECT FIT OF OVAPRENE™ AND CAYA

The criteria below must be met in two situations:

- For the clinician to conclude that the device fits a participant, assessed at Visit 1 for Caya and BP3 for Ovaprene™
- For the clinician to conclude that the participant has correctly positioned the device, assessed at Visit 1, BP3, and in cycles in which the Ovaprene™ or Caya device is used

Fit criteria:

1. Location: the device should cover the cervical os and not protrude outside the introitus
2. Security: the device should not be easily dislodged by the clinician's finger
3. Comfort: the participant should not report discomfort or pain

APPENDIX 4. REFERENCES

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

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[4] Mauck CK, Glover LH, Miller E, et al. *Lea's Shield: a study of the safety and efficacy of a new vaginal barrier contraceptive used with and without spermicide*. Contraception 1996; 53(6):329-35.

[5] Schwartz JL, Weiner DH, Lai JJ, Frezieres RG, Creinin MD, Archer DF, Bradley L, Barnhart KT, Poindexter A, Kilbourne-Brook M, Callahan MM, Mauck CK. *Contraceptive efficacy, safety, fit, and acceptability of a single-size diaphragm developed with end-user input.* Obstet Gynecol. 2015 Apr;125(4):895-903.

[6] Mauck CK, Baker JM, Barr SP, Johanson W, Archer DF. *A phase I study of Femcap used with and without spermicide. Postcoital testing.* Contraception 1997; 56(2):111-5.

[7] Mauck C, Callahan M, Weiner DH, Dominik R. *A comparative study of the safety and efficacy of FemCap, a new vaginal barrier contraceptive, and the Ortho All-Flex diaphragm*. The FemCap Investigators' Group. Contraception 1999;60(2):71-80.

[8] Mauck CK, Brache V, Kimble T, Thurman A, Cochon L, Littlefield S, Linton K, Doncel GF, Schwartz JL. *A phase I randomized postcoital testing and safety study of the Caya diaphragm used with 3% Nonoxynol-9 gel, ContraGel or no gel*. Contraception. 2017 Aug;96(2):124-130.