Title:	AMPOWER A SINGLE-ARM, PHASE III, OPEN-LABEL, MULTICENTER, STUDY IN WOMEN AGED 18-35 YEARS OF THE CONTRACEPTIVE EFFICACY AND SAFETY OF AMPHORA® CONTRACEPTIVE VAGINAL GEL
Protocol Number:	AMP002
IND Number:	109300
Clinical Phase:	III
Sponsor:	Evofem, Inc. 12400 High Bluff Dr., Suite 600 San Diego, CA 92130 USA Phone: +1 858 550 1900 Fax: +1 844 828 2010
Clinical Research Organization:	PAREXEL International 195 West Street Waltham, MA 02541 USA Phone: +1 781 487 9900 Fax: +1 781 487 0525
Original Protocol:	Version 1, 05 May 2017
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PROTOCOL SIGNATURE PAGE

Title: **AMPOWER**
A SINGLE-ARM, **P**HASE III, **O**PEN-LABEL, MULTICENTER, STUDY IN **W**OMEN AGED 18 TO 35 YEARS OF THE CONTRACEPTIVE **E**FFICACY AND SAFETY OF AMPHORA® CONT**R**ACEPTIVE VAGINAL GEL

Protocol Number: **AMP002, Version 4**

IND Number: **109300**

Clinical Phase: **III**

Sponsor/Designee Signature:

Kelly Culwell, MD, MPH, FACOG
Chief Medical Officer
Evofen, Inc.

11/1/2017
Date

SIGNATURE PAGE FOR THE INVESTIGATOR

Title: AMPOWER
A SINGLE-ARM, PHASE III, OPEN-LABEL, MULTICENTER, STUDY IN WOMEN AGED 18-35 YEARS OF THE CONTRACEPTIVE EFFICACY AND SAFETY OF AMPHORA® CONTRACEPTIVE VAGINAL GEL

Protocol Number: AMP002

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US state and federal regulations, all other applicable local regulatory requirements, and ICH guidelines.

Organization:

Signed: _____ Date: _____
Investigator

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PROTOCOL SYNOPSIS

TITLE OF CLINICAL TRIAL:

AMPOWER

A SINGLE-AR**M**, **P**HASE III, **O**PEN-LABEL, MULTICENTER STUDY IN **W**OMEN AGED 18 TO 35 YEARS OF THE CONTRACEPTIVE **E**FFICACY AND SAFETY OF AMPHORA® CONT**R**ACEPTIVE VAGINAL GEL

STUDY PRODUCT(S):

Eligible subjects will receive:

- Amphora® non-hormonal contraceptive vaginal gel (Amphora) supplied in individually wrapped 5 g single dose, pre-filled vaginal applicators. Amphora is a dense, viscous, off white to tan gel of uniform consistency. Its active ingredients are L-lactic acid United States Pharmacopeia (USP), citric acid USP, and potassium bitartrate USP, with alginic acid and xanthan gum included as viscosity and bioadhesive controllers

CLINICAL PHASE: Phase III

CLINICAL TRIAL OBJECTIVES:

Primary:

- To evaluate the contraceptive efficacy of Amphora over seven cycles of use

Secondary:

- To evaluate the contraceptive efficacy of Amphora as measured by the Pearl Index
- To evaluate the safety of Amphora over seven cycles of use
- To assess pregnancy outcomes

Exploratory:

- To assess subject satisfaction (including sexual satisfaction) with Amphora over seven cycles of use
- To assess pregnancy intendedness for subjects treated with Amphora over seven cycles of use
- To assess dosing time deviations for study drug-associated pregnancies

OUTCOME EVALUATIONS:

Primary:

- Seven-cycle cumulative pregnancy rate as calculated using the Kaplan-Meier (KM) method

Secondary:

- Efficacy measured by the Pearl Index
- Adverse events (AEs)
- Pregnancy outcomes

Exploratory:

- Subject satisfaction
- Sexual satisfaction
- Pregnancy intendedness
- Dosing time deviations for study drug-associated pregnancies

CLINICAL TRIAL DESIGN:

This is a single-arm, open-label, Phase III study in approximately 100 sites in the United States (US) over seven cycles of use in women aged 18 to 35 years who are at risk of pregnancy.

TREATMENT DURATION:

After a screening period of up to 60 days, women will be enrolled and receive Amphora. Each woman will participate in the study until after she has completed treatment during seven on-study menstrual cycles. The cycle during which enrollment occurs is Cycle 0. If the time from enrollment to the subject's next menstrual period is ≥21 days, the subject's seven study cycles will be Cycles 0-6. If the time from enrollment to the subject's next menstrual period is <21 days, the subject's seven study cycles will be Cycles 1-7. The final visit to the clinical site will take place 14 to 30 days after the seventh study cycle, or after the end of treatment if the subject discontinues treatment prematurely.

SAMPLE SIZE:

A sample of approximately 1349 women will receive Amphora.

STUDY POPULATION:

Study Sites:

The study will be conducted at approximately 100 clinical sites in the US. Subjects will be selected for the study according to the eligibility criteria detailed below.

Inclusion Criteria:

To enroll in the clinical study, potential subjects must:

1. Be healthy women, who are sexually active, at risk of pregnancy, and desiring contraception.
2. Be within the age range of 18 to 35 years old (inclusive) at enrollment.
3. In the opinion of the Investigator, be at low risk for both human immunodeficiency virus (HIV) and sexually transmitted infections (STIs) based on review of high risk behaviors and exposures according to the Centers for Disease Control Sexually Transmitted Infections (STI) Guideline.
4. At the time of enrollment, have a single male sex partner for ≥3 months.
5. Have a negative urine pregnancy test at enrollment.
6. Have normal, cyclic menses with a usual length of 21 to 35 days over the last two cycles or at least two consecutive spontaneous menses (21 to 35 days in length) since delivery, abortion, or after discontinuing hormonal contraception or hormonal therapy prior to the date of consent. In addition:
   a. If the subject recently discontinued breastfeeding, she must have demonstrated return to regular cycling and have had at least three consecutive, spontaneous menses

post-lactation prior to the date of consent.

b. If the subject received prior administration of injectable contraceptives (e.g., depot-medroxyprogesterone acetate [DMPA], Depo-Provera), there must be at least 10 months since the last injection and the subject must have had at least two consecutive, spontaneous menses prior to the date of consent.

c. If a contraceptive implant was recently removed, the subject must have had at least two consecutive, spontaneous menses prior to the date of consent.

d. If an intrauterine device (IUD) was recently removed, the subject must have had at least one spontaneous menses following removal and prior to the date of consent.

7. Be willing to engage in at least three acts of heterosexual vaginal intercourse per cycle.
8. Be willing to use the study drug as the only method of contraception over the course of the study (with the exception of emergency contraception [EC] in the event a subject engages in vaginal intercourse but believes that the study drug was not used properly or she is at risk for pregnancy for any other reason).
9. Be capable of using the study drug properly and agree to comply with all study directions and requirements, including retaining the wrappers and returning them to the clinical site at the next study visit.
10. Be willing to keep a daily electronic diary (eDiary) to record coital information, study drug use information, use of concomitant medications including other vaginal products and other contraceptives, menses, and sign and symptom data for the subject or as reported to her by her partner.
11. Agree not to participate in any other clinical studies during the course of the study.
12. Be capable and willing to give written informed consent to participate in the study.

Exclusion Criteria:

To enroll in the clinical study, potential subjects **must not**:

1. Have had three or more urinary tract infections (UTIs) in the past year from the date of consent.
2. Have a UTI by urine culture, chlamydia, gonorrhea, or symptomatic yeast vaginitis or symptomatic bacterial vaginosis (BV) diagnosed by wet mount, or trichomoniasis, unless treated and proof of cure is documented within the screening period.
3. Have used vaginal or systemic antibiotics or antifungals within 14 days prior to enrollment, with the exception of vaginal or systemic antibiotics or antifungals completed for the treatment of a UTI, BV, or yeast vaginitis diagnosed at screening within seven days of the Enrollment Visit.
4. Have a history of any recurrent vaginal infections/disorders (either greater than or equal to four times in the past year or greater than or equal to three times in the previous six months from the date of consent).
5. Be pregnant, have a suspected pregnancy, or desire to become pregnant during the course of the study.
6. Have a history of diagnosed infertility or of conditions that may lead to infertility, without subsequent non-assisted reproductive technology intrauterine pregnancy.
7. Have any maternal contraindications to pregnancy (medical condition) or chronic use of medications for which significant evidence of fetal risk exists.

8. Have known or screen test positive for HIV infection.
9. Have three or more outbreaks of genital herpes simplex virus (HSV) within the last year from the date of consent or be receiving suppressive therapy.
10. Have visible genital condylomata (warts).
11. Be lactating or breastfeeding.
12. Have any clinically significant abnormal finding on physical examination including pelvic examination or baseline laboratory assessments which, in the opinion of the Investigator, precludes study participation.
13. Have clinically significant signs of vaginal or cervical irritation on pelvic examination.
14. Be planning to have any (e.g., diagnostic or therapeutic) vaginal or cervical procedures during the period of the study.
15. Have an abnormal Papanicolaou test (Pap test) based on the following criteria:
    a. Pap test in the past 12 months from the date of screening with atypical squamous cells of undetermined significance (ASC-US) unless at least one of the following criteria is met:
        i. Less than 21 years of age.
        ii. A repeat Pap test at least six months later was normal.
        iii. Reflex human papillomavirus (HPV) testing was performed and was negative for high-risk HPV.
        iv. A colposcopy (with or without biopsy) found no evidence of dysplasia requiring treatment or treatment was performed and follow up at least six months after the treatment showed no evidence of disease.
    b. Pap test in the past 12 months from the date of screening with low grade squamous intraepithelial lesion (LSIL) unless at least one of the following criteria is met:
        i. Less than 21 years of age.
        ii. A colposcopy (with or without biopsy) found no evidence of dysplasia requiring treatment or treatment was performed and follow up at least six months after the treatment showed no evidence of disease.
    c. Pap test in the past 12 months from the date of screening with atypical squamous cells in which high grade squamous intraepithelial lesion cannot be excluded (ASC-H), atypical glandular cells, high grade squamous intraepithelial lesion (HSIL), or ≥30 years old who are cytology-negative and HPV 16- or HPV 18-positive unless colposcopy and/or treatment was performed and follow up at least six months after the colposcopy and/or treatment showed no evidence of disease.
    d. Pap test in the past 12 months with malignant cells.
16. Consume (on average) more than three drinks of an alcoholic beverage per day.
17. In the opinion of the Investigator, have a history of substance abuse in the last 12 months.
18. Have taken an investigational drug or used an investigational device within the past 30 days from the date of consent.
19. In the opinion of the Investigator, have issues or concerns that may compromise the safety

of the subject, impact the subject's compliance with the protocol requirements, or confound the reliability of the data acquired.

20. Be an Evofem, PAREXEL, or clinical site employee regardless of direct involvement in research activities, or their close relative.

Table 1: Schedule of Assessments

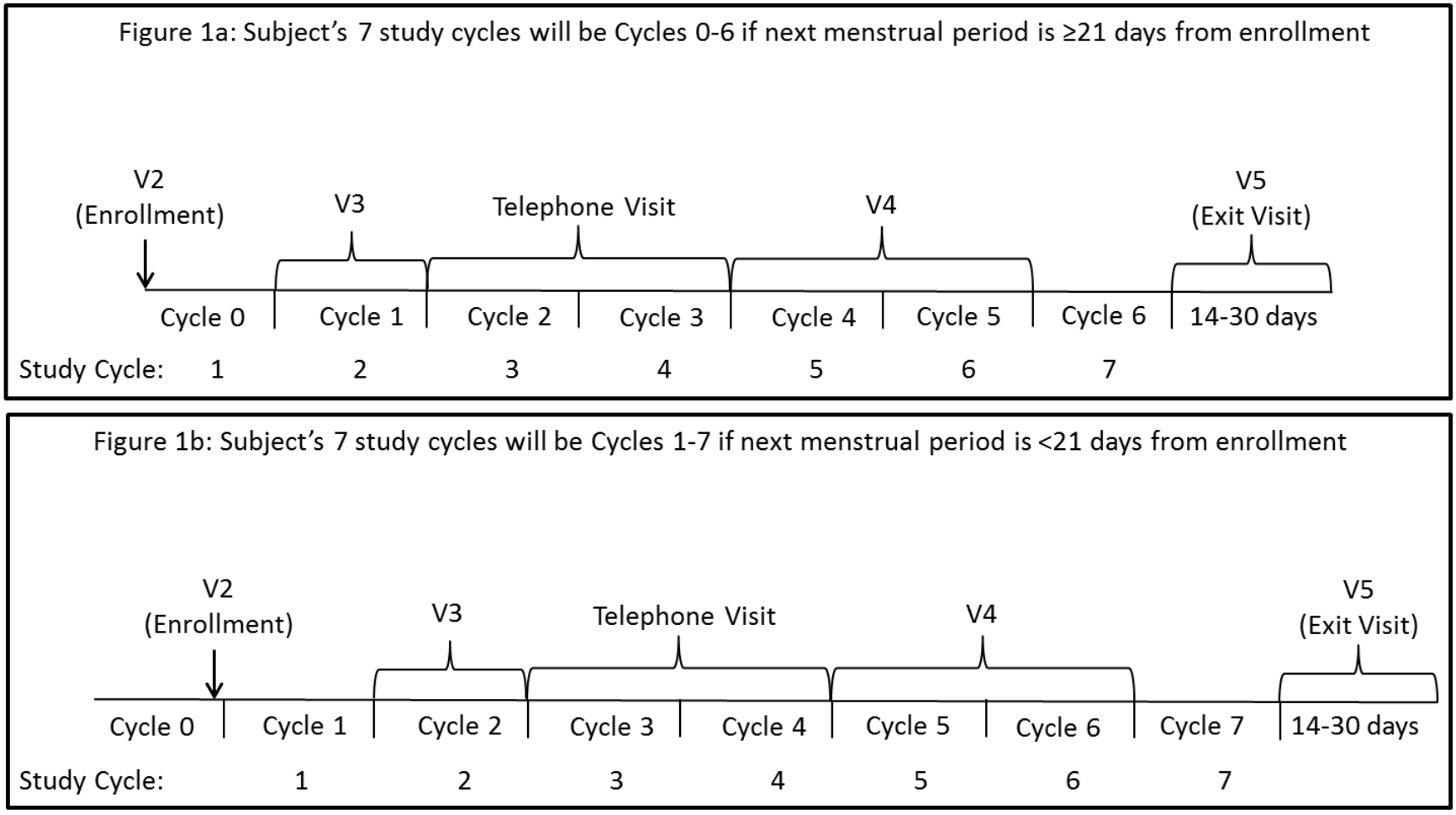
Procedures	Visit 1 Screening Day -60 to 0	Visit 2 Enrollment Cycle 0	Visit 3 (During 2nd Study Cycle)[a]	Telephone Visit Between Visits 3 and 4 (During Either 3rd or 4th Study Cycle)	Visit 4 (During Either 5th or 6th Study Cycle)	Visit 5[b] 14-30 Days After 7th Study Cycle/ Exit Visit
Written Informed Consent/HIPAA	X					
Eligibility (Inclusion/Exclusion)	X	X				
Medical/Gynecological History[c]	X	X				
Demographics	X					
Enrollment		X				
Prior History of Contraceptive Use (Past Year)	X	X				
Pre-Trial Medications	X	X				
Vital Signs[d]	X	X	X		X	X
CBC with Differential and Chemistry[e]	X					X
HIV Test[e]	X					
Physical Examination[f]	X					X
Gynecological Examination[g]	X	X	X		X	X
Pap Test	X[h]					
Chlamydia/Gonorrhea Test	X		X[i]		X[i]	X[i]
Urine Culture[j]	X					X
Dipstick Urinalysis[k]	X[l]	X	X		X	X[l]
Urine Pregnancy Test[m]	X	X	X		X	X
Serum Pregnancy Test		X				X
Distribute eDiary[n]		X				
Review eDiary[n]			X	X	X	X
Dispense/Return Study Product		X[o]	X		X	X
Subject Satisfaction with Study Product Questionnaire		X	X		X	X
Sexual Satisfaction Questionnaire		X	X		X	X
Pregnancy Intendedness Questionnaire		X	X		X	X
Adverse Events		X	X	X	X	X
Concomitant Medications		X	X	X	X	X
Between-Visit Contact[p]				X		
Schedule Next Visit/Contact[q]	X[r]	X	X	X	X	
Post-Study Treatment Contraception[s]					X	X

Footnotes from Table 1 above

Abbreviations: BV=bacterial vaginosis; CBC=complete blood count; eDiary=electronic diary; HIPAA=Health Insurance Portability and Accountability Act; HIV=human immunodeficiency virus; Pap test=Papanicolaou test; Tel=telephone contact; UTI=urinary tract infection.

a. The time period between Visit 2 and Visit 3 will vary based subject's first on-study cycle as defined in Figure 1.
b. Treatment will end after seven study cycles. The cycle at enrollment will be included as one of the seven study cycles only if the time from enrollment to the start of the next menstrual period was ≥21 days.
c. Includes documentation of the start date of last menstrual period.
d. Height, weight, and blood pressure will be measured at Screening. Only weight and blood pressure will be measured at subsequent visits.
e. Central laboratory will analyze CBC with differential, chemistry panels, and perform HIV test and chlamydia and gonorrhea assessments at Screening. Urine microscopy and culture and Pap tests will be performed locally.
f. Physical examination to include assessment of heart, lungs, and abdomen, and a breast examination at the discretion of the Investigator.
g. Gynecological examination is to include a speculum and bimanual examination. Investigators will note the presence or absence of vulvar, vaginal, or cervical findings, including epithelial disruption, or areas of obvious erythema; these will be assessed as either not present, mild, moderate, or severe; the presence or absence of bleeding, petechiae, or sloughing will also be recorded (Section 5.4.3). Clinically significant changes from Baseline as judged by the Investigator are to be reported as AEs. If a woman experiences any significant gynecological symptoms, she should return to the clinical site as soon as possible for a gynecological examination. Wet mount and vaginal pH for monilia, BV, and trichomonas will be performed only for symptomatic women.
h. Results from a Pap test performed at the screening clinical site ≤12 months prior to the Screening Visit may be used provided the report is available.
i. Chlamydia and gonorrhea assessments to be performed at Visits 3, 4, and 5 only if the subject indicates that she has changed sexual partners or is symptomatic. If the subject reports that her partner has been diagnosed or is being treated, she should be assessed/treated as per clinical site standard.
j. In addition to the urine culture at Screening and Visit 5, subjects will be instructed to contact the clinical site to schedule a dipstick urinalysis and possibly a urine culture any time they suspect they may have a UTI.
k. If dipstick urinalysis is 1+ for analytes of blood, leukocyte esterase, protein or nitrites, the urine should be sent for urine culture and microscopic urinalysis.
l. Only to be performed if the subject presents to the clinical site with urinary symptoms. Dipstick urinalysis should be performed at any visit where a subject presents to the center with urinary symptoms.
m. A urine pregnancy test should be administered any time a subject misses her period or suspects pregnancy. If a subject reports a positive home pregnancy test, a serum β-hCG should be performed.
n. Subjects will record in their eDiary dates/times of gel use, dates/times of sexual activity, vaginal bleeding, and use of back-up contraception (including reasons for back-up contraception, if applicable). Additionally, subjects will record gel-related genitourinary side effects (vaginal itching, burning, or pain) and assess them as mild, moderate, or severe; these side effects and non-menstrual cycle vaginal spotting/bleeding will be analyzed as AEs. At each visit, Amphora and eDiary compliance data will be reviewed and subjects assessed for re-education. Between visits, sites and subjects will receive alerts if a subject has missed eDiary entries. Sites will record documentation of contact with the subject around eDiary compliance.
o. Provide instructions on how to use the study drug at Enrollment Visit.
p. Between-visit telephone contact is to include assessment of AEs, concomitant medications, sexual activity, use of backup contraception, compliance with use of the study drug and eDiary, need for an unscheduled visit, and confirmation of contact information.
q. Includes confirmation of subject contact information. At the Enrollment Visit and each subsequent study visit/contact, the subject should be reminded to not have intercourse, use the study drug, or place anything in the vagina within 24 hours of the next scheduled visit to the clinical site.
r. Perform Enrollment Visit upon verification that all eligibility criteria have been met.
s. At Visit 4, the clinical site staff is to discuss post-treatment contraception with the subject, which would be started at completion of Cycle 7.
t. The final visit to the clinical site will take place 14-30 days after the seventh study cycle or after the end of treatment if the subject discontinues treatment prematurely.

Figure 1: Study Visit Timing Based on Menstrual Cycle at Enrollment



V=clinical site visit
Visit 5/Exit visit is to take place 14-30 days after the seventh study cycle or from last use of study product for early termination (unless being followed for pregnancy)
Telephone Visit is to take place between V3 and V4
Notes: Duration of Cycle 0 is number of days from enrollment to start of first on-study menstrual period.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADL	Activities of Daily Living
AE	Adverse event
AMPOWER	A Single-Arm, Phase III, Open-Label, Multicenter, Study in Women Aged 18 to 35 Years of the Contraceptive Efficacy and Safety of Amphora® Contraceptive Vaginal Gel
ASC-H	Atypical squamous cells, cannot exclude high grade squamous intraepithelial lesion
ASC-US	Atypical squamous cells of undetermined significance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
β-hCG	Beta-human chorionic gonadotropin
BUN	Blood urea nitrogen
BV	Bacterial vaginosis
CBC diff	Complete blood count differential
CFR	Code of Federal Regulations
CFU	Colony-forming units
CI	Confidence interval
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DMPA	Depot medroxyprogesterone acetate
DRL	Drug Reference List
EC	Emergency contraception
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EE	Efficacy-evaluable
FDA	Food and Drug Administration
FSFI	Female sexual function index
GCP	Good Clinical Practice
hCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation	Definition
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HSIL	High grade squamous intraepithelial lesion
HSV	Herpes simplex virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine device
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LB	Lactobacillus
LDH	Lactate dehydrogenase
LSIL	Low grade squamous intraepithelial lesion
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MITT	Modified Intent-to-Treat
N-9	Nonoxynol-9
NAAT	Nucleic acid amplification testing
NDA	New Drug Application
OTC	Over-the-counter
Pap test	Papanicolaou test
RBC	Red blood cell
SAE	Serious adverse event
SOP	Standard operating procedure
STI	Sexually transmitted infection
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event

Abbreviation	Definition
Tel	Telephone/Telephone contact
UMC	Uppsala Monitoring Centre
USP	United States Pharmacopeia
UTI	Urinary tract infection
WBC	White blood cell
WHO	World Health Organization

1 INTRODUCTION

Unintended pregnancies are a significant concern throughout the world and are often associated with adverse maternal and child outcomes.[1,2] Despite recent declines, unintended pregnancy remains a widespread problem, as an estimated 2.8 million unintended pregnancies occur annually in the US, representing 45% of all pregnancies.

The 14% of women at risk who do not practice contraception at all, or who have gaps of a month or more during the year, account for 54% of all unintended pregnancies. According to research conducted by the Centers for Disease Control and Prevention (CDC), approximately 40% of women surveyed after unintended birth who were not using contraception at the time of conception noted one of the following three reasons for nonuse: did not expect to have sex, worried about side effects of birth control, or male partner didn't want to use birth control (17.3%, 14.1%, and 8.0%, respectively).[1] Therefore, for certain women, an ideal product might be one that takes effect immediately, lacks systemic side effects, and is female controlled. This would be consistent with research indicating a preference by some women for short-acting, on-demand contraceptives that are easily reversible.[3,4]

Amphora® contraceptive vaginal gel (Amphora) is a novel, non-hormonal, surfactant-free, contraceptive developed to have acidifying, bioadhesive, and viscosity-retaining properties to provide effective acidification of the male ejaculate in the vagina and to form a long-lasting layer of gel over the vaginal and cervical surfaces.[5,6] As Amphora is non-hormonal, it may be a viable option for women who are reluctant to use hormonal contraceptives due to side effects or for whom hormonal contraceptives are contraindicated, which represents approximately 13%-16% of the population.[7,8] Amphora is also intended to help fill a gap in the contraceptive landscape for women who prefer a rapidly reversible, non-daily and/or on-demand contraception, experience allergy or sensitivity to nonoxynol-9 (N-9), or do not want to rely on a partner's collaboration. Compatibility studies indicate that Amphora can safely be used concomitantly with barrier methods,[9,10,11] such as diaphragms and condoms, which provides reassurance considering evidence suggesting that some women prefer to use multiple types of contraceptives simultaneously.[12] As there is no other method currently available that has all the unique characteristics of Amphora, it will expand the contraceptive options currently available to women.

This Phase III study is designed to further confirm the safety and effectiveness of Amphora demonstrated in a previous Phase III study.

2 STUDY OBJECTIVES

2.1 Primary

- To evaluate the contraceptive efficacy of Amphora over seven cycles of use

2.2 Secondary

- To evaluate the contraceptive efficacy of Amphora as measured by the Pearl Index
- To evaluate the safety of Amphora over seven cycles of use

- To assess pregnancy outcomes

2.3 Exploratory

- To assess subject satisfaction (including sexual satisfaction) with Amphora over seven cycles of use
- To assess pregnancy intendedness for subjects treated with Amphora over seven cycles of use
- To assess dosing time deviations for study drug-associated pregnancies

3 INVESTIGATORS, INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE, EVOFEM, INC., AND PAREXEL PERSONNEL

3.1 Investigators and Institutional Review Board

The multicenter clinical study described in this protocol will be conducted in compliance with the 1996 revision of the Declaration of Helsinki,[13] International Conference on Harmonisation (ICH) Consolidated Good Clinical Practice (GCP) (E6), and all applicable FDA regulations. This clinical study will be conducted under contracts administered by Evofem, Inc. (the Sponsor) with clinical monitoring, data handling, statistical analyses, and study report production performed by PAREXEL or designees. The study will be conducted at approximately 100 clinical sites in the US. A complete list of Investigators, Sub-Investigators, and Coordinators, and their affiliations will be maintained in the Trial Master File. A recognized Institutional Review Board (IRB) must consider and give approval and continuing review for all participating clinical sites.

3.2 Clinical Research Organization

PAREXEL International
195 West Street
Waltham, MA 02541
USA
Phone: +1 781 487 9900
Fax: +1 781 487 0525

Adverse Event Reporting
Refer to Section 5.4.4.

3.3 Clinical Study Period

Each woman will participate until she has been treated for seven on-study menstrual cycles. The cycle in which enrollment occurs is Cycle 0 (Figure 1). If the time from enrollment to the subject's next menstrual period is ≥21 days, the subject's seven study cycles will be Cycles 0-6 (Figure 1a). If the time from enrollment to the subject's next menstrual period is <21 days, the subject's seven study cycles will be Cycles 1-7 (Figure 1b). The final visit to the clinical site will take place 14 to 30 days after the seventh study cycle or after the end of treatment if the subject discontinues treatment prematurely. If a pregnancy is deemed to have occurred on-treatment and

the subject discontinues or is lost to follow up, attempts will be made to follow such pregnancies (up to three attempts followed by a certified letter). AEs considered to be possibly related to study drug will be followed to resolution or, for chronic conditions, deemed stable, even if this occurs beyond the study period. The last electronic Case Report Form (eCRF) should be completed within two weeks of the final assessment.

4 STUDY DESIGN

The proposed study design is a single-arm, open-label, Phase III study in approximately 100 sites in the US over seven cycles of use in women aged 18 to 35 years who are at risk of pregnancy. The primary endpoint is the seven-cycle cumulative pregnancy rate as calculated using the KM method. Secondary endpoints proposed include efficacy as measured by the Pearl Index, AEs, and pregnancy outcomes. In addition, exploratory endpoints proposed include subject satisfaction, sexual satisfaction, pregnancy intendedness, and dosing time deviations for Amphora and associated pregnancies. Safety will be measured by reported AEs.

Through assessments including pelvic examination, laboratory procedures, and medical and gynecological history, subjects will be screened for eligibility in order to enroll approximately 1349 subjects into the study. After a screening period of up to 60 days, enrolled women will receive study drug. Each woman will participate in the study until after she has completed treatment during seven study cycles, as described in Section 3.3. Criteria to determine whether an individual cycle is evaluable for efficacy are described in Section 9.8. Women who have individual cycles that do not meet the criteria for an evaluable cycle will not have those cycles replaced by subsequent cycles in order to provide a total of seven evaluable cycles.

Subjects will be expected to attend five visits: Screening (Visit 1), Enrollment (Visit 2), Visit 3 (during the second study cycle), Visit 4 (during either the fifth or sixth study cycle), and Visit 5 (14 to 30 days after seventh study cycle) as described in Section 5.1. In addition, subjects will be contacted by telephone by the clinical site staff between Visits 3 and 4 to monitor AEs, concomitant medications, sexual activity, use of backup contraception, compliance with use of the study drug and electronic diary (eDiary), need for an unscheduled visit, and confirmation of contact information. In the event that the subject reports any significant gynecological symptoms or any symptoms indicative of a possible UTI, she will be asked to contact the clinical site for possible evaluation. During further unscheduled safety visits, the Investigator may perform a gynecological exam and appropriate laboratory tests, and provide appropriate treatment as necessary.

An independent expert Pregnancy Review Committee will review all confirmed pregnancies. The Pregnancy Review Committee will determine if the pregnancy occurred on treatment (defined as date of conception between enrollment and <8 days after final study drug use) or not on treatment (defined as date of conception prior to enrollment or ≥8 days following final study drug use), or whether there is insufficient information for adjudication. Subjects with an on-treatment pregnancy will discontinue drug but remain in the study for follow-up.

4.1 Subject Selection

Subjects will be treated and followed as outpatients.

4.1.1 Inclusion Criteria

To enroll in the clinical study, potential subjects **must:**

1. Be healthy women, who are sexually active, at risk of pregnancy, and desiring contraception.
2. Be within the age range of 18 to 35 years old (inclusive) at enrollment.
3. In the opinion of the Investigator, be at low risk for both HIV and STIs based on review of high risk behaviors and exposures according to the Centers for Disease Control Sexually Transmitted Infections (STI) Guideline.
4. At the time of enrollment, have a single male sex partner for ≥3 months.
5. Have a negative urine pregnancy test at enrollment.
6. Have a normal, cyclic menses with a usual length of 21 to 35 days over the last two cycles or at least two consecutive spontaneous menses (21 to 35 days in length) since delivery, abortion, or after discontinuing hormonal contraception or hormonal therapy prior to the date of consent. In addition:
   a. If the subject recently discontinued breastfeeding, she must have demonstrated return to regular cycling and have had at least three consecutive, spontaneous menses post-lactation prior to the date of consent.
   b. If the subject received prior administration of injectable contraceptives (e.g., depot-medroxyprogesterone acetate [DMPA], Depo-Provera), there must be at least 10 months since the last injection and the subject must have had at least two consecutive, spontaneous menses prior to the date of consent.
   c. If a contraceptive implant was recently removed, the subject must have had at least two consecutive, spontaneous menses prior to the date of consent.
   d. If an intrauterine device (IUD) was recently removed, the subject must have had at least one spontaneous menstrual period following removal and prior to the date of consent.
7. Be willing to engage in at least three acts of heterosexual vaginal intercourse per cycle.
8. Be willing to use the study drug as the only method of contraception over the course of the study (with the exception of emergency contraception [EC] in the event a subject engages in vaginal intercourse but believes that the study drug was not used properly or she is at risk for pregnancy for any other reason).
9. Be capable of using the study drug properly and agree to comply with all study directions and requirements, including retaining the wrappers and returning them to the clinical site at the next study visit.
10. Be willing to keep a daily eDiary to record coital information, study drug use information, use of concomitant medications including other vaginal products and other contraceptives, menses, and sign and symptom data for the subject or as reported to her by her partner.
11. Agree not to participate in any other clinical studies during the course of the study.
12. Be capable and willing to give written informed consent to participate in the study

4.1.2 Exclusion Criteria

To enroll in the clinical study, potential subjects **must not**:

1. Have had three or more UTIs in the past year from the date of consent.

2. Have a UTI by urine culture, chlamydia, gonorrhea, or symptomatic yeast vaginitis or symptomatic BV diagnosed by wet mount, trichomoniasis, unless treated and proof of cure is documented within the screening period.
3. Have used vaginal or systemic antibiotics or antifungals within 14 days prior to enrollment, with the exception of vaginal or systemic antibiotics or antifungals completed for the treatment of a UTI, BV, or yeast vaginitis diagnosed at screening within seven days of the Enrollment Visit.
4. Have a history of any recurrent vaginal infections/disorders (either greater than or equal to four times in the past year or greater than or equal to three times in the previous six months from the date of consent).
5. Be pregnant, have a suspected pregnancy, or desire to become pregnant during the course of the study.
6. Have a history of diagnosed infertility or of conditions that may lead to infertility, without subsequent non-assisted reproductive technology intrauterine pregnancy.
7. Have any maternal contraindications to pregnancy (medical condition) or chronic use of medications for which significant evidence of fetal risk exists.
8. Have known or screen test-positive for HIV infection.
9. Have three or more outbreaks of genital HSV within the last year from the date of consent or be receiving suppressive therapy.
10. Have visible genital condylomata (warts).
11. Be lactating or breastfeeding.
12. Have any clinically significant abnormal finding on physical examination including pelvic examination or baseline laboratory assessments which in the opinion of the Investigator, precludes study participation.
13. Have clinically significant signs of vaginal or cervical irritation on pelvic examination.
14. Be planning to have any (e.g., diagnostic or therapeutic) vaginal or cervical procedures during the period of the study.
15. Have an abnormal Pap test based on the following criteria:
    a. Pap test in the past 12 months from the date of screening with atypical squamous cells of undetermined significance (ASC-US) unless at least one of the following criteria is met:
        i. Less than 21 years of age.
        ii. A repeat Pap test at least six months later was normal.
        iii. Reflex HPV testing was performed and was negative for high-risk HPV.
        iv. A colposcopy (with or without biopsy) found no evidence of dysplasia requiring treatment, or treatment was performed and follow-up at least six months after the treatment showed no evidence of disease.
    b. Pap test in the past 12 months from the date of screening with low grade squamous intraepithelial lesion (LSIL) unless at least one of the following criteria is met:
        i. Less than 21 years of age.
        ii. A colposcopy (with or without biopsy) found no evidence of dysplasia requiring treatment, or treatment was performed and follow-up at least six months after the treatment showed no evidence of disease.
    c. Pap test in the past 12 months from the date of screening with atypical squamous cells in which high grade squamous intraepithelial lesion cannot be excluded (ASC-H), atypical glandular cells, high grade squamous intraepithelial lesion (HSIL), or ≥30 years old who are cytology-negative and HPV 16- or HPV 18-positive unless colposcopy and/or

treatment was performed and follow-up at least six months after the colposcopy and/or treatment showed no evidence of disease.

d. Pap test in the past 12 months with malignant cells.

16. Consume (on average) more than three drinks of an alcoholic beverage per day.
17. In the opinion of the Investigator, have a history of substance abuse in the last 12 months.
18. Have taken an investigational drug or used an investigational device within the past 30 days from the date of consent.
19. In the opinion of the Investigator, have issues or concerns that may compromise the safety of the subject, impact the subject's compliance with the protocol requirements, or confound the reliability of the data acquired.
20. Be an Evofem, PAREXEL, or clinical site employee regardless of direct involvement in research activities, or their close relative.

4.1.3 Screen Failures

Subjects who completed the informed consent process but do not meet all eligibility criteria within the 60-day screening period will be screen failures. Screen failure subjects may be rescreened two additional times at the Investigator's discretion, following approval by the Sponsor/PAREXEL. There must be a minimum of two weeks between each rescreening. Each time a subject is rescreened, a new informed consent form (ICF) must be signed.

All screening procedures and laboratory tests (CBC, chemistry, urinalysis, urine culture, chlamydia, gonorrhea, urine pregnancy test) will be repeated upon rescreening. HIV test will not be repeated if the original test still falls within the 60-day screening window. The subject must meet all eligibility criteria prior to enrollment.

The screen failure must be registered in the interactive web response system (IWRS). Upon rescreening, the subject will be assigned a new screening number in the IWRS. A link between the previous screening number and the new screening number will be created in the IWRS and the electronic data capture (EDC) system.

If a blood sample must be redrawn (e.g., due to sample handling problems, breakage or sample integrity), this is not considered a rescreening.

Further details regarding the procedure for rescreening may be found in the Site Reference Manual (SRM).

4.2 Informed Consent Process

The principles of informed consent will be implemented according to the 1996 revision of the Declaration of Helsinki, ICH Consolidated GCP (E6), and applicable FDA regulations.

It is the Investigator's responsibility to ensure that each subject is provided an explanation of the details contained in the Informed Consent Form (ICF) prior to the individual signing and dating the form certifying voluntary participation in the study. The Investigator will not undertake any eligibility testing for the study until valid consent has been obtained. If required by the IRB a witness (impartial observer to the informed consent process) must also sign and date the ICF. The signed and dated ICF must be retained by the Investigator as part of the study records. The subject is to also receive a copy of the ICF after signatures by the Investigator or his/her designees.

4.3 Screening and Enrollment Procedures

Each subject who provides informed consent at the Screening Visit (Visit 1) will be assigned a screening number by the IWRS. The Investigator (or designee) must ensure that the subject is eligible to participate in the study before enrollment and the Coordinator must verify subject eligibility with the Investigator (or designee) prior to enrollment and/or dispensing study drug.

Study drug will be labeled with a unique code.

Further details can be found in the IWRS User Manual.

4.4 Study Drug Use

Eligible subjects will receive study drug to use as their method of contraception while engaging in vaginal sexual intercourse. Study drug will be provided in a prefilled applicator containing 5-grams of drug.

Subjects will be instructed to administer a single pre-filled applicator of study drug intravaginally a maximum of one hour before each episode of vaginal intercourse. Additional applications of study drug should be administered before each additional act of vaginal intercourse regardless of the time of the last application (e.g., if vaginal intercourse occurs more than once in a day). If more than one hour passes before starting intercourse, an additional application of study gel must be applied.

Subjects should be encouraged not to douche during the study; however, if douching does occur, the subject should wait at least six hours after the last act of intercourse and should record the product used as a concomitant medication in the eDiary. Similarly, subjects should be advised not to use lubricants or other vaginal preparations before or during intercourse. If use does occur, it should be recorded in the eDiary and as a concomitant medication.

4.5 Study Drug Packaging and Storage

The study drug will be provided in pre-filled applicators. Each clinical site will receive a supply sufficient for the anticipated number of study participants.

Each subject will receive a supply of pre-filled applicators as well as detailed instructions for administering the study drug. While at the clinical site, study drug must be stored within the appropriate temperature range and secured in a limited-access area. Once distributed, subjects will be asked to store the study drug at room temperature and not to refrigerate or freeze it. The clinical site is not permitted to release supplies of the study drug for distribution by any person not named as an Investigator for the study or to provide these supplies to persons not enrolled in the study.

4.6 Drug Accountability

Study drug will be shipped by PAREXEL or its designee to each clinical site after the receipt and acceptance of all necessary regulatory documents. The Investigator is responsible for maintaining accurate accountability records throughout the study. Each dispensing must be documented in the EDC system. At each study visit, the subject will be provided with a minimum of 1 carton of study drug containing 10 pre-filled applicators.

Subjects should return all unused pre-filled applicators at each study visit; for used or partially used product, only the wrapper should be returned at each study visit. Return of these items will be recorded in the EDC system. The clinical site must account for and properly document all study drug returned by subjects during each visit. In order to receive additional shipments of study drug, a request from the clinical site must be emailed or faxed to their study monitor or the designated contact.

The Investigator is responsible for returning all unused study drug to the Sponsor/PAREXEL for disposal. Alternatively, unused study drug may be disposed of by the clinical site staff at the discretion of the Sponsor/PAREXEL. The Investigator must verify that all unused drug supplies have been returned by the subject and that no remaining supplies are in the Investigator's possession.

4.7 Laboratory Procedures

Laboratory procedures will be performed as described in the Laboratory Manual at either the local laboratory or central laboratory.

Table 2: Location for Laboratory Procedures

Local Laboratory or Site	Central Laboratory
Dipstick urinalysis (study test kit to be provided)	CBC differential
Urine culture	Clinical chemistry
Urine pregnancy test (study test kit provided)	Serum pregnancy test
Pap test	HIV
Wet Mount Analysis	Chlamydia
Vaginal pH	Gonorrhea

Urine pregnancy test:

Clinical sites will be provided with urine pregnancy test kits, and urine pregnancy testing will be performed locally by the clinical site in accordance with the schedule of assessments.

Urine dipstick and culture:

Urine for urinalysis will be obtained as a clean-catch specimen. Dipstick urinalysis will be performed using study test kit provided. Urine culture will be performed locally by the clinical sites under usual procedures for such tests.

A clinical diagnosis of a symptomatic UTI will be made at the clinical site using the following criteria:

- complaint of urinary symptoms;
- 1+ for analytes of blood, leukocyte esterase, protein or nitrites; and
- a minimum bacterial count of 10,000 colony-forming units (CFU)/mL with the presence of uropathogen.

A symptomatic UTI may also be diagnosed by the presence of symptoms and a ≥100,000 CFU/mL presence of uropathogen without a positive leukocyte esterase by dipstick. A clinical diagnosis of an asymptomatic UTI will be made at the clinical site using the following criteria: absence of symptoms and a bacterial count of ≥100,000 CFU/mL with the presence of uropathogen.

Pap tests:

Pap tests will be analyzed locally at the laboratory chosen by the clinical site.

Wet Mount Analysis (monilia, BV, trichomonas) and Vaginal pH:

For symptomatic women only, wet mount analysis for the presence of monilia, BV, and trichomonas will be performed locally at the clinical site. Clinical diagnosis of BV will be made at the clinical site following Amsel's criteria with at least three of the following four findings confirmed:

- homogeneous, thin, white discharge that smoothly coats the vaginal walls;
- clue cells ≥20% (e.g., vaginal epithelial cells studded with adherent coccobacilli) on microscopic examination;
- pH of vaginal fluid >4.5; or
- a fishy odor of vaginal discharge before or after addition of 10% KOH (i.e., the whiff test).

Central Laboratory:

Serum pregnancy tests:

Beta-human chorionic gonadotropin (β-hCG) testing will be performed at a central laboratory on serum samples at the Enrollment Visit and Visit 5/Exit Visit. In addition, subjects who report a positive urine home pregnancy test or have a documented positive urine human chorionic gonadotropin (hCG) test performed at the site after enrollment should have a serum quantitative β-hCG test performed at the central laboratory, preferably on the same day as the urine pregnancy test.

CBC differential (CBC diff), clinical chemistry:

Blood samples will be collected in accordance with the schedule of assessments for CBC diff and clinical chemistry testing at a central laboratory. CBC diff and clinical chemistry laboratory assessments are provided in Appendix B.

HIV, chlamydia, gonorrhea:

Blood samples for HIV testing will be collected in accordance with the schedule of assessments.

Assessments for the diagnosis of chlamydia and gonorrhea will be performed by a central laboratory using a urine sample (not clean-catch) or vaginal swab.

5 STUDY PROCEDURES

5.1 Study Visits

5.1.1 Screening Visit (Visit 1)

Women who present to the clinical site for gynecologic care will be asked to participate in the study. Informed consent must be obtained prior to any study-specific procedures being performed. Please refer to Table 1 for a schedule of study assessments to be performed. The Screening Visit procedures do not have to be completed on a single day if more time is necessary (e.g., if a subject has a condition that requires treatment, as described below, or is menstruating).

The following events will occur at the Screening Visit:

- Obtain signed and dated informed consent and give a copy to potential subject
- Review inclusion/exclusion criteria
- Collect demographic information (age, race, ethnicity)
- Collect medical, gynecological, and pregnancy history. Gynecological history will include the start date of last menstrual period
- Vital signs (height, weight, and blood pressure)
- Record pre-trial medications (inquire about subject self-medication for suspected UTIs, including any herbal or natural supplements), present use and 6-month history
- Record history of contraceptive use in the past year

- Physical exam including assessment of heart, lungs, and abdomen, and a breast exam at the discretion of the Investigator
- Gynecological exam including assessment of the vulva, vaginal wall, cervix, adnexae, and uterus by speculum and bimanual exam. Wet mount and vaginal pH for monilia, BV, and trichomonas will be performed only for symptomatic women.
- Pap test (unless results performed ≤ 12 months prior to the Screening Visit are obtained)
- Vaginal swab or urine sample taken for chlamydia and gonorrhea tests
- Blood sample collection for CBC diff, clinical chemistry, and HIV test
- Urine pregnancy test
- Dipstick urinalysis (only to be performed if the subject presents to the center with urinary symptoms)
- Urine culture
- Review partner risk of HIV and STIs (according to CDC guidelines) to the best of the potential subject's knowledge
- Confirm subject contact information
- The Enrollment Visit will be performed upon confirmation that all eligibility criteria have been met

If the subject presents at the Screening Visit and is diagnosed with chlamydia or gonorrhea, and all other eligibility criteria are met, she will be treated and allowed to enter the study after proof of cure is documented and it is at least 21 days since treatment. Test of cure is recommended 3-4 weeks after completing treatment for chlamydia or gonorrhea.[14]

If the subject presents at the Screening Visit and is diagnosed with a UTI, symptomatic BV, or symptomatic yeast vaginitis, and all other eligibility criteria are met, she will be prescribed appropriate treatment and allowed to enter the study after proof of cure is documented and it is at least seven days since treatment. Test of cure is recommended seven days after completing treatment for a UTI. Dipstick urinalysis will be repeated at the Enrollment Visit, which should be scheduled for seven or more days after the subject completes the treatment prescribed for the UTI.

5.1.2 Enrollment Visit (Visit 2)

If the subject meets all eligibility criteria, she will be scheduled for an Enrollment Visit within 60 days of the date of consent. If Screening Visit procedures are performed over more than one day, the Enrollment Visit will be scheduled within 60 days of the first the date of consent. Proof of cure must be documented for subjects diagnosed at the Screening Visit with UTI, symptomatic BV, trichomoniasis, symptomatic yeast vaginitis, chlamydia, or gonorrhea.

At the Enrollment Visit, the following will occur:

- Verify that all eligibility criteria have been met
- Review medical and gynecological history; update start date of last menstrual period

- Update pre-trial medications and record concomitant medications (inquire about subject self-medication for suspected UTIs, including any herbal or natural supplements)
- Update history of contraceptive use within the past year
- Vital signs (weight and blood pressure only)
- Urine pregnancy test
- Serum quantitative β-hCG pregnancy test
- Dipstick urinalysis (if 1+ or greater for any analyte of blood, leukocyte esterase, protein, or nitrite results are positive, the urine should be sent for urine culture and microscopic urinalysis.
    - If the Enrollment Visit dipstick urinalysis is negative, the subject can be enrolled.
    - If the Enrollment Visit dipstick urinalysis test is positive, the subject may not be enrolled in the study at this visit and a urine culture will be performed.
        - If the urine culture is positive, the subject will be a screen failure and can be rescreened. If a UTI is diagnosed, the subject cannot be enrolled until proof of cure is documented.
        - If the urine culture is negative, the subject may return and be enrolled in the study.
- Perform gynecological exam, including assessment of the vulva, vaginal wall, cervix, adnexae, and uterus (bimanual and speculum). Wet mount and vaginal pH for monilia, BV, and trichomonas will be performed only for symptomatic women.
- Administer questionnaires to assess subject satisfaction with most recent birth control method, sexual satisfaction, and pregnancy intendedness
- Dispense study drug to subject (enough to last until next scheduled visit)
- Provide instructions on how to use the study drug
- Dispense eDiary and provide instructions on how to use it
- Record AEs
- Provide emergency contact information to study participant
- Remind subjects of their right to use EC during the study
- Encourage subjects not to have intercourse, use the study drug, or place anything in the vagina within 24 hours of the next scheduled clinical site visit
- Schedule the next study visit
- Confirm subject contact information
- Update medical history

Subjects will be instructed to contact the clinical site as soon as possible if any of the following occur:

- She is about to run out of study drug.

- Her period is late by one week or more or she suspects she might be pregnant for any reason.
- She suspects she might have a UTI, vaginal infection, BV or sexually transmitted infection or has sought care at another facility for a UTI, vaginal infection or vaginosis including BV, or sexually transmitted infection.
- She experiences any medical problem, whether or not she thinks it is related to the study drug.
- She has any questions about using the study product or about the study.
- She wishes to stop using the study drug as her method of contraception or to discontinue from the study.
- She misses or expects to miss a scheduled visit.
- She experiences any technical difficulty with the eDiary. See Section 5.6 for eDiary instructions.

5.1.3 Visit 3 and Visit 4

Subjects will return to the clinical site for Visit 3 (during the second study cycle) and for Visit 4 (during either the fifth or sixth study cycle). The following events will occur during these interim visits:

- Vital signs (weight and blood pressure only)
- Gynecological exam including assessment of the vulva, vaginal wall, cervix, adnexae, and uterus (bimanual and speculum); wet mount and vaginal pH for monilia, BV, and trichomonas will be performed only for symptomatic women
- Urine pregnancy test (if positive, serum sample is collected to be sent to central laboratory for a serum quantitative β-hCG test [Section 4.7]), bimanual exam for uterine sizing, and transvaginal ultrasound, preferably on the same day
- Dipstick urinalysis (if analytes are 1+ positive or greater for blood, leukocyte esterase, or protein, or nitrite results are positive, the urine will be sent for urine culture and microscopic analysis)
- Perform chlamydia and gonorrhea tests only if the subject indicates that she has changed sexual partners or is symptomatic. If, according to the subject, her partner has been diagnosed or is being treated, she should be assessed per clinical site standard.
- Administer questionnaires to assess subject satisfaction with study drug, sexual satisfaction, and pregnancy intendedness
- Review eDiary data report for completeness and accuracy, and assess the need for subject re-training in eDiary use
- Review study drug adherence data
- Review backup contraception use and sexual activity

- Collect unused study drug and unused applicators, and record study drug accountability information
- Re-supply study drug, as necessary
- Record concomitant medications (including any herbal or natural supplements)
- Record AEs
- Remind subjects of their right to use EC during the study
- Encourage subjects not to have intercourse, use the study drug, or place anything in the vagina within 24 hours of the next scheduled clinical site visit
- Visit 4 only: discuss post-study contraception with the subject to be started after completion of cycle 7 and before Visit 5/Exit Visit
- Schedule the next clinical site visit
- Confirm subject contact information

If the subject presents to an interim visit and is diagnosed with a UTI, symptomatic BV, trichomoniasis or symptomatic yeast vaginitis, she will be treated and allowed to continue in the study. All diagnosed or suspected conditions will be noted in the EDC system.

Based on gynecologic exam at each visit, investigators will note the presence or absence of vulvar, vaginal, or cervical findings (as defined in Section 5.4.3), including epithelial disruption, or areas of obvious erythema; these will be assessed as either not present, mild, moderate, or severe; the presence or absence of bleeding, petechiae, or sloughing will also be recorded on the gynecological exam eCRF. These findings will be reported as an AE if considered by the Investigator to be a clinically significant change from baseline, defined as an at least one level increase in severity of the finding from baseline.

If, during the eDiary review, the clinical site detects any pattern of incorrect or inconsistent drug usage, the subject will again be provided with proper usage instructions for the study drug. In addition, the eDiary data report will be reviewed to ensure that it does not contain reports of any signs or symptoms related to drug use. If a sign or symptom is reported in the subject eDiary that warrants follow-up, the subject may be contacted for further information as necessary and may be asked to return to the clinical site for evaluation and/or treatment.

At each interim visit, all subjects will be reminded to contact the clinical site as soon as possible if any of the following occur:

- She is about to run out of study drug.
- Her period is late by one week or more or she suspects she might be pregnant for any reason.
- She suspects she might have a UTI or has sought care at another facility for a UTI, vaginal infection, or vaginosis, including BV, or sexually transmitted infection.
- She experiences any medical problem, whether or not related to the study drug.
- She has any questions about using the study drug or about the study.

- She wishes to stop using the study drug as her method of contraception or to discontinue from the study.
- She misses or expects to miss a scheduled visit.
- She experiences any technical difficulty with the eDiary.
- The clinical site should contact the subject within one business day if a notification is received that the subject has missed an eDiary entry.

5.1.4 Visit 5 (Treatment Exit)

Subjects will return to the clinical site 14-30 days after the seventh study cycle for exit from the study (Visit 5; Treatment Exit Visit). The following study activities will occur at this visit. In addition, these procedures should also be performed any time a subject discontinues the study prematurely.

- Vital signs (weight and blood pressure only)
- Perform physical examination (heart, lungs, and abdomen, and a breast exam at the discretion of the Investigator)
- Gynecological examination, including assessment of the vulva, vaginal wall, cervix, adnexae, and uterus. Wet mount for monilia, BV, and trichomonas will be performed only for symptomatic women.
- Perform chlamydia and gonorrhea tests only if the subject indicates that she has changed sexual partners or is symptomatic. If, according to the subject, her partner has been diagnosed or is being treated, she should be assessed per clinical site standard.
- CBC diff and chemistry panels to be sent to central laboratory for analysis
- Urine pregnancy test (if the test is positive and the pregnancy is deemed to be on-treatment, the subject should not be discontinued from the study but should have pregnancy assessments)
- Serum quantitative β-hCG pregnancy test
- Dipstick urinalysis (only to be performed if the subject presents to the center with urinary symptoms)
- Urine culture
- Administer questionnaires to assess subject satisfaction with study drug, sexual satisfaction, and pregnancy intendedness
- Review eDiary data report for completeness and accuracy
- Review study drug use adherence data
- Review backup contraception use and sexual activity
- Collect unused study drug and wrappers, and record drug accountability information
- Record concomitant medications (including any herbal or natural supplements)
- Record AEs

- Discuss post-study contraception with the subject
- For subjects who are discontinuing early from the study, the clinical site personnel should provide counseling about alternative methods of birth control and referral, as applicable

Investigators will note the presence or absence of vulvar, vaginal, or cervical findings (as defined in Section 5.4.3), including epithelial disruption, or areas of obvious erythema; these will be assessed as either not present, mild, moderate, or severe; the presence or absence of bleeding, petechiae, or sloughing will also be recorded on the gynecological exam eCRF and reported as an AE if considered by the Investigator to be a clinically significant change from baseline, defined as an at least one level increase in severity of the finding from baseline.

eDiary data reports will be reviewed to ensure that they do not contain any reported signs or symptoms related to drug use. If a sign or symptom is reported in the subject diary that warrants follow-up, the subject may be contacted for further information as necessary and may be asked to return to the clinical site for evaluation and/or treatment.

5.1.5 Contact Between Visits

Subjects will be contacted by telephone by the clinical site staff between Visits 3 and 4. All such contacts and attempts should be documented in the subject's source file. Between-visit contact is to include the following assessments:

- Record AEs
- Record concomitant medications (including any herbal or natural supplements)
- Review eDiary data reports for completeness and accuracy, and assess the need for subject re-training in eDiary use
- Review study drug adherence data
- Review backup contraception use and sexual activity
- Confirm subject has sufficient supply of study drug
- Identify any other issues; plan an unscheduled visit, if necessary
- Confirm subject contact information

5.1.6 Unscheduled Safety Visits

In the event that the subject reports any significant gynecological symptoms or any symptoms indicative of a possible UTI, she will be asked to contact the clinical site for evaluation. During unscheduled safety visits, the Investigator may perform a gynecological exam and appropriate laboratory tests and provide appropriate treatment as necessary. Subjects should be discouraged from any self-medication with vaginal products; rather, they should visit the clinical site for assessment and treatment. Similarly, subjects should be discouraged, but not prohibited, from seeking treatment for suspected UTIs or other vaginal infections at facilities other than the clinical site.

Based on the results of the gynecological exam and laboratory tests, if the Investigator determines that the subject should be discontinued, the Treatment Exit procedures (as detailed in Section 5.1.4) will be performed and the subject will be discontinued from the study. In addition, if at any time during the study a subject misses her period or suspects that she may be pregnant, she should call the clinical site to schedule a urine pregnancy test.

5.2 Emergency Contraception

In the event a subject engages in vaginal intercourse but believes that the study drug was not used properly or if she feels she is at risk for pregnancy for any other reason, she is eligible to request a prescription for EC or obtain her own as OTC. The individual clinical sites will provide EC in accordance with the standard of care of the clinical site. Any time EC use occurs, the date of usage as well as the reason for usage should be recorded as a concomitant medication in the source and the EDC system as well as the eDiary.

5.3 Pre-Trial and Concomitant Medications

At the Screening Visit and Enrollment Visit, the study subjects will be asked to report medications and health products that were taken at the time of screening and prior to enrollment, including any herbal or natural supplements, over the past six months. The subject's contraceptive use within the past year will also be recorded at these study visits.

The use of concomitant medications and health products will also be queried in the eDiary, at Visits 2-5 and during the between-visit contact. If vaginal symptoms are present, the subject should visit the clinical site for evaluation and treatment as indicated. Subjects should be instructed to abstain from any vaginal self-medication. All medications and health products taken by the participant during the course of the study, including all vaginal preparations and any medication given for the treatment of any AE must be recorded in the EDC system.

Subjects should be encouraged not to douche during the study; however, if douching does occur, the subject should wait to douche until at least six hours after the last act of intercourse and should record the product used as a concomitant medication in the eDiary. Similarly, subjects should be advised not to use any lubricants or vaginal preparations before or during intercourse. If use does occur, it should be recorded in the eDiary and as a concomitant medication.

5.4 Adverse Events

5.4.1 Collection of Adverse Events

It is the responsibility of the Investigator to collect all AEs (both serious and non-serious) derived by spontaneous, unsolicited reports of subjects, by observation, and by routine open questionings, e.g., "How have you felt since I last saw you?"

5.4.2 Definitions

For the purposes of this study, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered related.

All AEs, including intercurrent illnesses, occurring during the study will be documented in the EDC system. Illnesses that existed before entry into the study will not be considered AEs unless they worsen during the treatment period. All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, reported by subject), must be documented.

Pre-existing conditions will be recorded in the EDC system on the appropriate page (e.g., Medical History)

AE data should be collected from enrollment until Visit 5 (14-30 days after the seventh study cycle) or early termination from the study. Those events that occur between the Screening Visit and enrollment will be analyzed as medical history. A treatment-emergent AE (TEAE) will be defined as an AE that begins or that worsens in severity after at least one dose of study drug has been administered. All AEs considered at least possibly related to study drug will be followed until resolution or, for chronic conditions, until deemed stable.

5.4.3 Assessment of Adverse Events

Each AE will be assessed by the Investigator for seriousness, intensity, and causality using the following definitions:

Seriousness

A serious AE (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening; this means that the patient is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event(s) that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the patient or require intervention to prevent the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Medical and scientific judgment should be exercised in deciding whether a case is serious and whether expedited reporting is appropriate.

Intensity

Investigators should assess the severity of AEs according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. In general, CTCAE severity grades are:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL) (Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.)
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Causality

The Investigator will assess the causality/relationship between the study drug and the AE and record that assessment in the EDC system. The most likely cause of an AE (e.g., concomitant disease, concomitant medication, other) will be indicated in the EDC system with details of the concomitant disease or medication or other cause.

The causal relationship of the AE to study drug will be described per World Health Organization (WHO) Uppsala Monitoring Centre (UMC) causality categories[15]:

- Certain/Definite:
  - Event or laboratory test abnormality, with plausible time relationship to drug intake
  - Cannot be explained by disease or other drugs
  - Response to withdrawal plausible (pharmacologically, pathologically)
  - Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon)
  - Rechallenge satisfactory
- Probable/Likely:
  - Event or laboratory test abnormality, with plausible time relationship to drug intake
  - Unlikely to be attributed to disease or other drugs
  - Response to withdrawal clinically reasonable
  - Rechallenge not required
- Possible:
  - Event or laboratory test abnormality, with plausible time relationship to drug intake
  - Could also be explained by disease or other drugs
  - Information on drug withdrawal may be lacking or unclear
- Unlikely:
  - Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)

  - Disease or other drugs provide plausible explanations

- Not assessable:
  - Report suggesting an adverse reaction
  - Cannot be judged because information is insufficient or contradictory
  - Data cannot be supplemented or verified

Genitourinary Side Effects

Genitourinary (GU) side effects (including vaginal burning, vaginal itching, vaginal pain, and other unexpected vaginal symptoms) will be collected in the eDiary each time the study drug is used and will be recorded at AEs. Subjects will note the time of drug administration, time of sexual intercourse and if they had any side effect (including severity, duration, and resolution).

Unexpected vaginal bleeding or spotting will be recorded as AEs; however, expected menstrual-related bleeding and/or spotting will not.

Vulvar, Vaginal, or Cervical Side Effects

An adaptation of the *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, Addendum 1 – Female Genital Grading Table for Use in Microbicide Studies* will be used by the investigator to grade changes from baseline in vulvar, vaginal or cervical findings noted during the gynecologic exam and determine if they are considered significant, as defined as at least one grade increase from baseline. These should be reported as AEs. The Female Genital Grading Table for Use in Microbicide Studies was developed for use in protocols involving topical application of products to the female genital tract. Although developed specifically for microbicide studies, it is applicable to other protocols as well to ensure data consistency across sites.

Table 3: Vulvar, Vaginal, or Cervical Individual Signs/Symptoms Grading Table

Parameter	Grade 0 Normal	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe
Epithelial disruption	None	Blisters, ulcerations, superficial disruptions with minimal impact on life – no treatment needed	Blisters, ulcerations, large disruptions – treatment indicated	Severe epithelial disruption with hospitalization indicated
Erythema	None	Erythema covering <50% of surface	Erythema covering ≥50% of surface	Severe erythema with hospitalization indicated
Parameter	**Grade 0**	**Grade 1**		
Bleeding	None	Present		
Petechiae	None	Present		
Sloughing	None	Present		

Recording Adverse Events

AE reporting will extend from enrollment until Visit 5 (14-30 days after the seventh study cycle). AEs occurring after Visit 5 should be reported to PAREXEL by the Investigator if the Investigator considers there is a causal relationship with the study drug.

All AEs, regardless of the relationship to study drug, will be recorded in the EDC system.

All AE reports should contain a brief description of the event, date and time of onset, date and time of resolution, intensity, treatment required, relationship to study drug, action taken with the study drug, outcome, and whether the event is classified as serious.

AEs reported as ongoing at the last study visit will be listed as ongoing as of the last study date, and time of resolution will be marked as Not Applicable.

5.4.4 Reporting Serious Adverse Events

The Investigator must report any SAEs to PAREXEL Medical Services within 24 hours of becoming aware of the event.

The Investigator and the Sponsor/PAREXEL will review each SAE report and the Sponsor/PAREXEL will evaluate the seriousness and the causal relationship of the event to study treatment. In addition, the Sponsor/PAREXEL will evaluate the expectedness according to the Investigator Brochure. Based on the assessment of the event, a decision will be made concerning the need for further action.

All SAEs will be recorded from enrollment until Visit 5. SAEs occurring after Visit 5 and coming to the attention of the Investigator must be reported only if they are considered (in the opinion of the Investigator) causally related to the investigational drug.

Clinical sites should complete the SAE form and fax the documents to PAREXEL Medical Services using the PAREXEL SAE fax number below:

(781) 434-5957

or

Complete the SAE report form and submit it to PAREXEL Medical Services via email using the email address below:

NorthAmerica_Medical@parexel.com

and/or

If the clinical site is unable to complete the SAE form to report the event within 24 hours of its knowledge of the event, the Investigator may report the SAE over the telephone via the SAE answering service, and then provide the completed SAE form via **fax/email**. If questions arise

regarding the reporting procedures or the specifics of the reporting of an event, sites may call the following number:

(781) 434-5010

5.4.5 Follow-Up of Adverse Events

All AEs experienced by a subject, deemed to be possibly related to study product, will be monitored until the AE has resolved. Any abnormal laboratory values deemed to be possibly related to study product will be monitored until they have returned to baseline or stabilized at a level acceptable to the Investigator and Medical Monitor, until there is a satisfactory explanation for the changes observed, until the subject is lost to follow-up, or until the subject has died.

5.4.6 Pregnancy

For the purposes of this study, pregnancy is not considered an AE. The pregnancy must be reported using the Pregnancy Notification Form to PAREXEL Medical Services within 24 hours of Investigator awareness (contact details in Section 5.4.4). Details on pregnancy determination and follow-up are provided in Section 6.6. Miscarriage is not considered an AE, unless meeting the SAE criteria (Section 5.4.3).

5.5 Questionnaires

Questionnaires will be used to evaluate subject satisfaction with the study drug (Appendix C), subject sexual satisfaction (Appendix D-Appendix F), and pregnancy intendedness (Appendix G) in accordance with the schedule of assessments.

5.6 Electronic Diary

Subjects will keep a daily eDiary to record coital information; study drug use information; use of concomitant medications, including other vaginal products and other contraceptives; menses; and sign and symptom data for the subject or as reported to her by her partner. If the subject has not completed the daily eDiary at any time, the site, PAREXEL, and the Sponsor will be notified via email, and the site will contact the subject for follow-up. Subjects will be allowed to retroactively enter data up to the predefined lock-out. Compliance reports will be available in real time and will be reviewed by the site at each visit, via telephone contact, and as needed based on eDiary alerts.

6 STUDY CONDUCT

6.1 Deviation from the Protocol

The Investigator should not deviate from the protocol except when necessary to protect the subject's immediate safety or welfare. In the event that the Investigator or the subject deviates from the protocol, documentation should be provided to PAREXEL within two business days of Investigator awareness detailing the circumstances of the deviation. Certain protocol deviations may be considered as protocol violation and could require the subject to be terminated early from

the study. It is the responsibility of the clinical sites to also report all protocol deviations/violations to their IRB as required under their IRB approval.

6.2 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents must be approved by an IRB. The site must document that all ethical and legal requirements have been met before the first subject is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the Sponsor (and in many cases the FDA), and receive IRB approval prior to implementation as appropriate. Amendments cannot be implemented until the investigator is officially notified of the change by the Sponsor/PAREXEL. All amendments will be distributed to all investigational sites, with appropriate instructions for implementation.

6.3 Confidentiality

All study findings and documents are confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor/PAREXEL.

The anonymity of participating subjects must be maintained. During screening and after enrollment, coded subject numbers will be used to identify subjects in the EDC system and in other documents submitted to PAREXEL, and on all laboratory specimens in order to maintain subject confidentiality. Documents not to be submitted to PAREXEL that identify the subject (e.g., the signed ICF) must be maintained in confidence by the Investigator.

6.4 Discontinuation of Subjects

A subject will be considered to have completed the study after she has completed seven on-study menstrual cycles (Section 3.3), the final visit has been performed, and the appropriate set of data has been collected and entered in the EDC system. A subject will be considered to have prematurely discontinued if she fails to remain in the study for seven on-study menstrual cycles and returns for Visit 5. Subjects who become pregnant while participating in the study are not considered to be discontinued unless they choose to no longer participate or are otherwise lost to follow up per Section 6.6. Subjects may withdraw from the study at any time without penalty and for any reason without prejudice to future medical care.

Subjects must be discontinued from the study for any of the following reasons:

- Withdrawal of consent
- Emergence of condition(s) such that, in the opinion of the Investigator, continuation in the study would negatively impact the health of the subject or would jeopardize the validity of the data collected (e.g., development of a condition that would have prevented her entry into the study according to the inclusion or exclusion criteria that could affect the study data)
- Any confirmed STI (other than HPV or trichomoniasis)

- Subject lost to follow-up
- If subject stops using study drug as her method of contraception
- Study terminated (Section 6.5)

Subjects may be discontinued prematurely from treatment for other reasons at the Investigator's discretion. Investigators considering subject discontinuation should contact the Sponsor/PAREXEL to discuss the specific case prior to withdrawal of the subject.

In all instances of premature discontinuation, the reason will be recorded in the EDC system. If withdrawal from the study is due to an AE, this information will also be recorded in the EDC system. In addition, all subjects who terminate early from the study will be asked to undergo the Treatment Exit Visit procedures (Section 5.1.4) regardless of the reason for discontinuation.

Every effort must be made to follow up with subjects who terminate with a study drug-related AE(s) to determine the outcome of the AE(s).

Subject Discontinuation Due to Non-Adherence

Due to the risk of non-adherence-related pregnancy, subject discontinuation should be considered for non-adherence (unless a specific reason is given by the subject that can be corrected in the next cycle). Investigators considering subject discontinuation for the following reasons should contact the Sponsor/PAREXEL to discuss the specific case prior to withdrawal of the subject.

1. Subjects with repeated failure over the course of one cycle to enter eDiary data, such that assessments of study medication compliance, sexual activity, and use of backup contraception are not possible.
2. Subjects missing >50% doses/month for two consecutive months by self-report in eDiary.
3. If an enrolled subject misses a scheduled appointment, she should be contacted within 24 hours to reschedule the clinical site visit as soon as possible. After waiting one business day for the subject to respond, the clinical site should make additional attempt(s) to contact the subject. If the subject is not reached within two additional business days, a certified letter must be sent asking the subject to contact the clinical site. If the subject fails to respond within 24 hours after receipt of the certified letter is confirmed, she will be considered lost to follow-up and the last date of contact with the subject will be recorded as the date of discontinuation. The certified letter receipt will be filed with the Investigator's copy of the subject's source document. If the subject re-contacts the clinical site prior to being discontinued, and extenuating circumstances exist, the subject may be allowed to continue in the study with Sponsor/PAREXEL approval.
4. For subjects with the following, the Investigator should discuss the specific circumstances leading to the event with the subject and Sponsor/PAREXEL:
    - Two consecutive cycles with no sexual activity
    - Two consecutive cycles with use of backup contraception

6.5 Premature Termination of the Study

If the Investigator or the Sponsor/PAREXEL becomes aware of conditions or events that suggest the study poses a possible hazard to subjects, the study may be terminated after appropriate consultation among the relevant parties. The study may also be terminated early at the Sponsor's discretion for reasons other than subject safety.

Conditions that may warrant termination include, but are not limited to:

- The discovery of a significant or unacceptable risk to the subjects enrolled in the study.
- Failure to enroll subjects at an acceptable rate.
- A decision on the part of the Sponsor to suspend or discontinue development of the study drug.

6.6 Pregnancy Determination/Pregnancy Review Committee

If urine pregnancy testing performed at the clinical site during post-enrollment scheduled or unscheduled visits is positive, samples for serum quantitative β-hCG will be collected and sent for assessment by the central laboratory and pelvic examination for assessment of uterine size will be performed, preferably during the same study visit. Pelvic ultrasound (transvaginal if ≤12 weeks estimated gestation) will be performed as promptly as possible, preferably the same day as the positive urine pregnancy test is identified. The study drug must be discontinued immediately upon confirmation of a pregnancy, and the subject will remain in the study for pregnancy assessments.

At enrollment, if the urine pregnancy test is negative and the serum β-hCG is borderline or positive, then the participant must be discontinued from the study and the reason for discontinuation will be protocol deviation, no pregnancy assessments as described below will be performed as part of the study, the pregnancy will not be followed, and the pregnancy will not be assessed by the Pregnancy Review Committee.

Repeat evaluations (e.g., repeat ultrasound if initial ultrasound done prior to presence of gestational sac and/or crown rump length for dating) will be done as necessary to increase the accuracy of the determination of the estimated date of conception. Subjects who become pregnant while participating in the study should not be discontinued and, for those who choose to no longer participate or are lost to follow up, attempts should be made to continue to follow the pregnancy (up to three attempts followed by a certified letter), unless the Sponsor/PAREXEL has determined that sufficient information is available or will not become available.

Any subject who reports a positive home pregnancy test must be evaluated at the site as soon as possible (e.g., the same day) for serum pregnancy testing, pelvic examination, and pelvic ultrasound (transvaginal if estimated gestational age is ≤12 weeks at the time of the visit).

An independent expert Pregnancy Review Committee will review all confirmed pregnancies. Details of the membership and responsibilities of the Pregnancy Review Committee are defined in the Pregnancy Review Committee Charter. The Pregnancy Review Committee will determine if the pregnancy occurred on-treatment (defined as date of conception between enrollment to <8

days after final study drug use) or not on-treatment (defined as date of conception prior to enrollment or after ≥8 days following final study drug use), or whether there is insufficient information for adjudication.

For confirmed pregnancies, the date of conception will be assessed from the following:

- First trimester transvaginal ultrasound (considered the most accurate; later ultrasounds will not be used for redating)
- Estimate based on pelvic and/or abdominal examination or pregnancy outcome
- eDiary information (e.g., last menstrual period and sexual activity)
- Quantitative β-hCG determination
- Urine hCG (date of last negative and first positive)
- Investigator estimation in the absence of above criteria

Subjects who become pregnant during the on-treatment period will be instructed to immediately stop use of study product, informed of pregnancy options, and referred for appropriate care. Subjects who become pregnant while participating in the study will be continued to be followed. If they are lost to follow-up, then attempts will be made to contact the subject as described above. Reports of pregnancy outcome will be requested by the Investigator from the attending physician or subject. Pregnancy outcome data will include the rates of spontaneous abortion, stillbirth, and live preterm and full-term births. If a subject has a spontaneous abortion or ectopic pregnancy this will not be considered as an AE or SAE unless it meets one of the SAE criteria indicated in Section 5.4.3. In addition, congenital malformations and anomalies will be recorded and summarized.

7 STUDY MONITORING AND DOCUMENTATION

7.1 Clinical Monitoring, Quality Control, and Quality Assurance

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded in the EDC system for this study must be consistent with the subjects' source documentation (i.e., medical records).

The Investigator and Sub-Investigators will allow representatives from the Sponsor/PAREXEL direct access to all eCRFs, source documents, and corresponding portions of the medical records for each participant at mutually convenient times for periodic review during the study and after the study has been completed. The monitoring visits provide the opportunity to:

- Initiate the clinical site.
- Evaluate the progress of the study.
- Verify the accuracy and completeness of the eCRFs/EDC system.
- Ensure that all protocol requirements, applicable local regulations, and Investigators' obligations are being fulfilled.
- Resolve any inconsistencies in the study records.
- Close out the study at the clinical site.

In addition to routine monitoring, site audits may be performed. The purpose of such audits will be to be to evaluate study conduct and compliance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirements. If an audit is performed, the clinical site must provide the auditors with direct access to all relevant records and documentation related to the study.

8 DATA MANAGEMENT

8.1 Database Management and Quality Control

All data generated by the clinical site personnel will be captured electronically at each study center using an EDC system. Data from external sources (such as laboratory data) will be imported into the database by the site. Once the clinical data have been submitted to the central server at the independent data center, changes to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

If additional changes are needed or questions arise, PAREXEL will raise a query in the EDC system. The appropriate staff at the clinical site will answer queries sent to the Investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the eCRF page.

The specific procedures to be used for data entry and query resolution using the EDC system will be provided to the clinical site in a training manual. In addition, clinical site personnel will receive training on the EDC system.

8.2 Case Report Forms and Source Documentation

All data obtained during this study should be entered in EDC system promptly. All source documents from which EDC entries are derived should be placed in the subject's medical records. Measurements for which source documents are usually available include laboratory assessments. The original EDC entries for each subject may be checked against source documents at the clinical site during a monitoring visit or audit.

After review by the site monitor, completed EDC entries will be forwarded to PAREXEL. Instances of missing or uninterpretable data will be discussed with the Investigator for resolution.

8.3 Data Collection

The Investigators (and appropriately authorized staff) will be given access to an online web-based EDC system. This system is specifically designed for the collection of the clinical data in electronic format. Access and right to the EDC system will be carefully controlled and configured according to each individual's role throughout the study. In general, only the Investigator and authorized staff will be able to enter data and make corrections in the EDC system.

The EDC system should be completed for each subject included in the study and should reflect the latest observations on the subjects participating in the study. Therefore, the EDC entries are to be completed as soon as possible during or immediately after the subject's visit or assessment. The Investigator must verify that all data entries in the EDC system are accurate and correct. If some assessments cannot be done, or if certain information is unavailable, not applicable or unknown, the Investigator should indicate this in the EDC system.

Computerized data-check programs and manual checks will identify any clinical data discrepancies for resolution.

8.4 Study Documentation

Investigators are responsible for assuring that the essential documents maintained in the Trial Master File at the clinical site are accurate and complete.

8.5 Data Processing

The data-review and data-handling document provided to the site will include specifications for consistency and plausibility checks on data and will also include data-handling rules for obvious data errors.

8.6 Retention of Data

The Investigator will maintain adequate records of the study, including in the EDC system, subjects' medical records, laboratory reports, ICF, drug disposition records, safety reports, information regarding subjects who discontinued, and other pertinent data, for a minimum of 2 years. The Investigator must contact the Sponsor for authorization prior to destruction of any such records, in the event of accidental loss or destruction, or to transfer the records to another location or to the Sponsor

9 STATISTICAL AND ANALYTICAL METHODS

The statistical considerations summarized in this section outline the plan for data analysis of this study. Further details will be provided in the Statistical Analysis Plan (SAP).

9.1 Outcome Evaluations

Primary

- The seven-cycle cumulative pregnancy rate as calculated using the KM method

Secondary

- Efficacy as measured by the Pearl Index

$$\text{Pearl Index} = \frac{\text{Number of Pregnancies} * 365.25 * 100}{\text{Total Number of Days Exposed}}$$

- AEs
- Pregnancy outcome

Exploratory

- Subject satisfaction
- Sexual satisfaction
- Pregnancy intendedness
- Dosing time deviations for study drug-associated pregnancies

9.2 Sample Size

The sample size determination assumes the following:

- Study drug pregnancy percentage: 16.5%
- 26.5% of subjects fail to qualify for the primary efficacy analysis population
- Of the subjects that qualify for the primary efficacy analysis population, the average number of evaluable efficacy cycles per subject: 3.17
- Exponential hazard for:
    - Pregnancy rate first 6 months: 16.5%
    - Drop out month 1: 10%
    - Drop out months 2-6: 38%

With 1349 participants aged 18 through 35 years (inclusive), the study will have 90% power to ensure that the upper limit of the 95% CI of the cumulative seven-cycle pregnancy rate is less than or equal to 21%. The expected number of completers is 515 and the expected number of cycles evaluable for safety is at least 3143.

9.3 Analysis Populations

The following subject populations will be created:

- Intent-to-treat (ITT): All subjects enrolled into the study.
- Safety population: ITT subjects who administer the study drug at least once
- Modified intent-to-treat (MITT): Subjects must meet requirements 1, 2, and 3 simultaneously, and at least one of requirement 4 or requirement 5 to be included in the MITT analysis population:

1. Between 18 to 35 years of age (inclusive) at enrollment
2. Had at least one report of pregnancy status after being enrolled; subjects with a positive serum pregnancy test at enrollment will not be included.
3. ITT subjects whose diaries indicate they had at least one episode of coitus while using the study drug (also referred as "Typical-Use")
4. Had at least one cycle of eDiary without any backup contraception or EC
5. Became pregnant and the pregnancy had a conception date that occurred between enrollment and <8 days after final study drug use

- Efficacy-evaluable (EE): A subset of the MITT population that includes only those subjects whose diaries indicate that they used the study drug correctly for every act of intercourse for at least one menstrual cycle (also referred as "Perfect-Use" or "Per Protocol"). Cycles in which the study drug was used incorrectly for one or more coital acts will be removed, and the correct use cycles will be compressed to provide contiguous cycles of correct use.

The MITT is the primary population for analysis of efficacy. Analyses in the EE population will be considered exploratory only.

9.4 Disposition of Subjects

The number of subjects who are enrolled, treated, attended the various assessments, and who discontinue prematurely from or complete the study will be summarized.

9.5 Demographic and Pre-Treatment Characteristics

Subject demographics and pre-treatment characteristics will be summarized descriptively.

9.6 Treatment Exposure

Exposure to study drug will be summarized by the number of times the treatment is administered, the length of time over which the treatment is used, the number of times the study drug was used per cycle, and the number of cycles in the study.

9.7 Pre-Trial and Concomitant Medications

Concomitant medications include any medication or health product taken during the active study treatment period. Pre-trial medications include any medications taken within 60 days of enrollment, and for one year in the case of contraceptives. The number and percentage of subjects using medications, as captured on the Concomitant Medication eCRF Form, will be tabulated for the safety population. There will be separate tables for pre-trial and concomitant medications. Subjects taking a medication more than once will be only counted once for that medication.

9.8 Analyses of Pregnancy Experience

9.8.1 Primary Efficacy Analysis

The primary efficacy endpoint is the seven-cycle cumulative pregnancy rate as calculated using the KM method. The KM estimate and its 95% CI (based on Greenwood's method) of the seven-cycle cumulative pregnancy probability of women in the MITT population will be calculated.

9.8.1.1 Derivation of the Primary Variable

The primary variable is the number of cycles from enrollment to the first pregnancy within seven cycles, which will be derived in the following steps:

- Imputing the missing dates of cycles: If the eDiary has partial dates for the start/end of a cycle, then the dates will be imputed to be a full date (when possible) based on the start/end dates of cycles that occurred before and after that cycle with partial dates. If multiple cycles in a row occur with partial start/end dates, then it will be assumed the cycles were equal length in order to determine the imputed start/end dates of the cycle.
- Determining the evaluable cycles: Cycles must meet all conditions given below to be considered evaluable cycles:
    - Cycles 0-6 for subjects who are enrolled for at least 21 days prior to the start of her next menses, or Cycles 1-7 for subjects who are enrolled in less than 21 days prior to the start of her next menses;
    - Cycles that are indicated by the eDiary that no backup contraception or EC are used or in which subjects are pregnant;
    - Cycles with length within the range of 21 days to 35 days or in which subjects are pregnant.
    - For EE analyses, cycles in which the eDiaries indicate that study drug was used correctly for every act of intercourse during that cycle.
    - Compressing the evaluable cycles: Evaluable cycles will be compressed to form contiguous evaluable cycles for each subject sequentially.
- Determining the date of conception:
    - The Pregnancy Review Committee will review all confirmed pregnancies and determine if the pregnancy occurred on-treatment (defined as date of conception between enrollment to <8 days after final study product use) or not on‑treatment (defined as date of conception prior to enrollment or after 7 days

following final study product use), or whether there is insufficient information for adjudication.

For confirmed pregnancies, the date of conception will be assessed from the following:

- First trimester transvaginal ultrasound (considered the most accurate; later ultrasounds will not be used for redating)
- Estimate based on pelvic and/or abdominal examination or pregnancy outcome
- eDiary information (e.g., last menstrual period and sexual activity)
- Quantitative β-hCG determination
- Urine hCG (date of last negative and first positive)
- Investigator estimation in the absence of above criteria

- Determining of censoring for cycles to pregnancy: Subjects will be censored from analysis at the earliest of:
  - The estimated date of conception that occurred between enrollment and <8 days after final study drug use
  - The last date at which pregnancy status was known
  - The conclusion of her seventh cycle on-treatment (up to a total of 245 days [or 294 days for the sensitivity analysis, allowing a cycle length range of 21 to 42 days])

9.8.2 Secondary Analysis

Secondary Efficacy Analysis as Measured by the Pearl Index: The Pearl Index and its 95% CI for the MITT population will be calculated. The Pearl Index will be calculated as the percentage of the total number of pregnancies versus the total number of days exposed. The 95% CI will be calculated using normal approximation.

9.8.3 Sensitivity Analyses

Sensitivity Analysis with Respect to the Cycle Range: The primary analysis will be repeated with the cycle length expanded from 21-35 days to 21-42 days.

Sensitivity Analysis of the Dosing Time with Respect to Sexual Intercourse: To evaluate the effect of the dosing time with respect to sexual intercourse, subgroup analyses for the primary analysis will be performed by the dosing time category performed according to the following

dosing time categories with respect to sexual intercourse: < 1 hour, < 1.5 hour, < 2 hours, <2.5 hours, and all cycles (without respect to dosing time).

Sensitivity Analysis with Respect to Completers and Non-completers: To evaluate differences between completers and non-completers the primary analysis will be repeated for just completers. A completer is defined as a woman who becomes pregnant within 7-cycles (inclusive) or who completes the 7 cycles with no pregnancy.

9.9 Safety Parameters

The safety population will be used for all safety summaries. All safety data will be summarized descriptively.

9.9.1 Incidence of Adverse Events

The number (percentage) of subjects with at least one AE will be presented in a frequency table by MedDRA system organ class and per MedDRA "preferred" term. A similar summary will be created for SAEs and AEs leading to discontinuation of study drug use. Summaries will also be presented by relationship to study drug and intensity of AE.

9.9.2 Other Safety Assessments

Changes in other safety parameters such as hematology and clinical chemistry, vital signs, physical examination, gynecological exam, and pregnancy outcome follow up will be summarized using descriptive statistics as appropriate.

9.10 Other Endpoints

9.10.1 Subject Satisfaction

Subject satisfaction with the study drug and subject sexual satisfaction will be summarized using frequency and percentage.

9.10.2 Pregnancy Intendedness

Pregnancy intendedness scale results and change from baseline will be summarized descriptively.

9.11 Protocol Deviations

Deviations from the protocol, including violations of inclusion/exclusion criteria, will be assessed in cooperation with the Sponsor and summarized. Subjects whose diaries indicate that they used the assigned study drug incorrectly for every act of intercourse for every menstrual cycle will be excluded from the EE population. Cycles in which the study drug was used incorrectly for one or more coital acts will be removed, and the correct use cycles will be compressed to provide contiguous cycles of correct use.

9.12 Computer Methods

Version 9.3 or later of the SAS® statistical software package will be used to produce all summaries, listings, statistical analyses, and graphical presentations.

10 REVISION HISTORY

Table 4: Summary of Amendments

Version Number	Effective Date	Summary of Changes
1	05 May 2017	Original Protocol
2	08 June 2017	Section 4.1.3: Moved Partner Requirements from the inclusion/exclusion criteria to the screening procedures based on IRB comments Clarifications to partner information collection throughout
3	19 June 2017	Section 5.4.3: Added grading criteria for valvar, vaginal or cervical AEs Section 5.6: Lock-out period statement added for eDiary Section 6.6: Corrected typo in "on-treatment" definition Section 9.1: Revised the Pearl Index formula Section 9.2: Sample size increased from 1157 (85% power) to 1349 (90% power) Section 9.8.3: Added an additional sensitivity analysis Table 1: Clarified footnote "a"
4	01 Nov 2017	Section 6.4 – Clarified that subjects who become pregnant are not discontinued Section 9.2 – Updated the expected number of completers and evaluable cycles for 1394 participants Section 9.8.3 - Adjusted dosing time intervals

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12 APPENDICES

Appendix A: Investigator Obligations

This clinical research study is subject to the regulations of the FDA. The responsibilities imposed upon Investigators by the FDA are summarized in the "Statement of Investigator Form" (Form FDA 1572). This form summarizes the qualifications of each Investigator, his or her obligations in carrying out the research protocol, and expresses his or her willingness to follow FDA regulations with respect to this study.

The Investigator agrees to assume the following responsibilities and signifies his or her agreement by signing the Form FDA 1572:

- To secure prior approval of the study by an appropriate IRB. This board should be constituted in conformity with FDA regulations.
- To report on the progress of the study to the IRB and to submit a final report within three (3) months of the conclusion of data collection.
- To maintain current records of the receipt, dispensing, and disposition of study drug and to return all unused drug to the Sponsor or the Sponsor's designated agent.
- To obtain a valid, fully informed, freely given written consent from each subject who participates in the study.
- To prepare and maintain adequate case histories of all subjects entered into the study, including web-based eCRFs, hospital records, laboratory results, and lab records, and to store these case histories for a minimum of two years following notification by the Sponsor that all investigations have been discontinued or that the FDA has approved the drug or device application.
- To identify all Sub-Investigators who will also supervise drug administration or device implantation.
- To report all AEs/SAEs to the Sponsor or designated agent per Section 5.4.
- To allow inspection or copying by the FDA, Sponsor, or Sponsor's designated agent of case histories and records of drug distribution.

Appendix B: CBC with Differential and Clinical Chemistry

The following central laboratory evaluations will be conducted on blood samples collected per the schedule of assessments:

CBC	Clinical Chemistry
Basophils (absolute count and %)	Albumin
Eosinophils (absolute count and %)	Alkaline phosphatase
Hemoglobin	Aspartate aminotransferase (AST)
Hematocrit	Bicarbonate
Lymphocytes (absolute count and %)	Blood urea nitrogen (BUN)
Mean corpuscular volume (MCV)	Calcium
Mean corpuscular hemoglobin (MCH)	Chloride
Mean corpuscular hemoglobin concentration (MCHC)	Cholesterol
	Glucose
Monocytes (absolute count and %)	Lactate dehydrogenase (LDH)
Neutrophils (absolute count and %)	Phosphorus
Platelet count	Potassium
Red blood cell (RBC)	Total Protein
White blood cell (WBC)	Total Bilirubin
	Sodium
	Uric acid

Appendix C: Subject Satisfaction with Study Drug

Baseline:

How satisfied were you with your most recent birth control method?

a. Very satisfied
b. Satisfied
c. Somewhat satisfied
d. Somewhat dissatisfied
e. Dissatisfied

Study Visits 3-5:

How satisfied are you with your study birth control method?

a. Very satisfied
b. Satisfied
c. Somewhat satisfied
d. Somewhat dissatisfied
e. Dissatisfied

How likely is it that you would recommend this method to a friend who is considering a vaginal contraceptive gel?

a. Very likely
b. Likely
c. Somewhat likely
d. Somewhat unlikely
e. Unlikely

How likely is it that you would recommend this method to a friend who is considering another birth control option?

a. Very likely
b. Likely
c. Somewhat likely
d. Somewhat unlikely
e. Unlikely

How likely would you be to continue this method if it were available after the study?

a. Very likely
b. Likely
c. Somewhat likely
d. Somewhat unlikely
e. Unlikely

Appendix D: Subject Sexual Satisfaction

Baseline:

What impact did your most recent contraceptive method have on your sex life in the last 4 weeks of use?

a. My sex life was a lot better than before
b. My sex life was a little better than before
c. My sex life was no different than before
d. My sex life was a little worse than before
e. My sex life was a lot worse than before

Study Visits 3-5:

What impact has the study contraceptive method had on your sex life since your last study visit?

a. My sex life is a lot better than before
b. My sex life is a little better than before
c. My sex life is no different than before
d. My sex life is a little worse than before
e. My sex life is a lot worse than before

Appendix E: Sexual Function Questionnaire

How frequently in the PAST MONTH have you had the problems listed below?*
ALSO, MARK THE BOX IN THE LAST COLUMN if the problem stops your sexual activity.

		Not at all	Seldom, less than 25% of the time	Sometimes, about 50% of the time	Usually, about 75% of the time	Always	MARK THE BOX IF THE PROBLEM STOPS YOUR SEXUAL ACTIVITY
a.	Vaginal dryness during sexual activity	1	2	3	4	5	☐
b.	Lack of sexual interest or desire	1	2	3	4	5	☐
c.	Vaginal tightness	1	2	3	4	5	☐
d.	Pain during penetration or intercourse	1	2	3	4	5	☐
e.	Anxiety about your sexual performance	1	2	3	4	5	☐
f.	Unable to orgasm	1	2	3	4	5	☐
g.	Vaginal bleeding or irritation from penetration or intercourse	1	2	3	4	5	☐
h.	Increased sensitivity of your skin to intimate touching	1	2	3	4	5	☐
i.	Sharp pain inside or outside your vagina	1	2	3	4	5	☐
j.	Other problem with sexuality; Please specify:	1	2	3	4	5	☐

*Source: Question 10, Sexual Function Questionnaire, Fred Hutchinson Cancer Research Center.

Appendix F: Female Sexual Function Index

Female Sexual Function Index (FSFI) ©

Subject Identifier _____ Date _____

INSTRUCTIONS: These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation and vaginal intercourse.

Sexual intercourse is defined as penile penetration (entry) of the vagina.

Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CHECK ONLY ONE BOX PER QUESTION.

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how **often** did you feel sexual desire or interest?

   ☐ Almost always or always
   ☐ Most times (more than half the time)
   ☐ Sometimes (about half the time)
   ☐ A few times (less than half the time)
   ☐ Almost never or never

2. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?

   ☐ Very high
   ☐ High
   ☐ Moderate
   ☐ Low
   ☐ Very low or none at all

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Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how **often** did you feel sexually aroused ("turned on") during sexual activity or intercourse?

   ☐ No sexual activity
   ☐ Almost always or always
   ☐ Most times (more than half the time)
   ☐ Sometimes (about half the time)
   ☐ A few times (less than half the time)
   ☐ Almost never or never

4. Over the past 4 weeks, how would you rate your **level** of sexual arousal ("turn on") during sexual activity or intercourse?

   ☐ No sexual activity
   ☐ Very high
   ☐ High
   ☐ Moderate
   ☐ Low
   ☐ Very low or none at all

5. Over the past 4 weeks, how **confident** were you about becoming sexually aroused during sexual activity or intercourse?

   ☐ No sexual activity
   ☐ Very high confidence
   ☐ High confidence
   ☐ Moderate confidence
   ☐ Low confidence
   ☐ Very low or no confidence

6. Over the past 4 weeks, how **often** have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

   ☐ No sexual activity
   ☐ Almost always or always
   ☐ Most times (more than half the time)
   ☐ Sometimes (about half the time)
   ☐ A few times (less than half the time)
   ☐ Almost never or never

7. Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

8. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

9. Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

10. Over the past 4 weeks, how **difficult** was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **often** did you reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **difficult** was it for you to reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

13. Over the past 4 weeks, how **satisfied** were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

14. Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

15. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner?

- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life?

- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

17. Over the past 4 weeks, how **often** did you experience discomfort or pain during vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

18. Over the past 4 weeks, how **often** did you experience discomfort or pain following vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

19. Over the past 4 weeks, how would you rate your **level** (degree) of discomfort or pain during or following vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Very high
- ☐ High
- ☐ Moderate
- ☐ Low
- ☐ Very low or none at all

Thank you for completing this questionnaire

Appendix G: Pregnancy Intendedness

1. At baseline and all in-person study visits:
   On a scale of 1-10 (Very unhappy to Very happy), how would you feel if you were to get pregnant?
2. If a subject becomes pregnant at any time during the study:
   On a scale of 1-10 (Very unhappy to Very happy), how do you feel about your pregnancy?