

---

**Phase 2B/3 double-blinded placebo-controlled efficacy trial of  
AMPHORA® gel for the prevention of acquisition of urogenital  
*Chlamydia trachomatis* infection**

**Protocol Number: EVO-003**

**Sponsor:**

Evoform, Inc.  
12400 High Bluff Drive, Suite 600  
San Diego, CA 92130

**CRO:**

ICON Government and Public Health Solutions (GPHS)  
1265 Ridge Road  
Hinckley, OH 44233

**Investigational Product:**

AMPHORA (L-lactic acid, citric acid and potassium bitartrate)  
Vaginal Gel 1.8%/1%/0.4%

**IND Number: 128092**

**Protocol Version Number:**

Version 6.0  
**January 25, 2019**

---

### **Statement of Compliance**

This study will be carried out in accordance with the US Code of Federal Regulations (CFR), local regulations, and Good Clinical Practice (GCP) as required by the following:

- 21 CFR 50, 21 CFR 56, and 21 CFR 312
- International Council for Harmonisation (ICH E6); 62 Federal Register 25691 (1997)

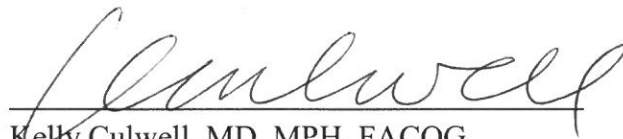
All individuals responsible for the design and conduct of this study have completed Human Subjects Protection Training and are qualified to be conducting research prior to the enrollment of any subjects. CVs for all Investigators and Sub-Investigators participating in this study are on file in a central facility (21 CFR 312.23 [a] [6] [iii] [b] edition).

---

**Protocol Signature Page**

**Phase 2B/3 double-blinded placebo-controlled efficacy trial of  
AMPHORA® gel for the prevention of acquisition of urogenital  
*Chlamydia trachomatis* infection**

The signature below constitutes approval of this protocol and the attachments and provides the required assurances that this study will be conducted according to all stipulations of the protocol, including all the statements regarding confidentiality, and according to local legal and regulatory requirements, and applicable US Food and Drug Administration regulations.



Kelly Culwell, MD, MPH, FACOG  
Evofem, Inc.

25 JAN 2019  
Date

The protocol will be signed by local Investigators who are responsible for the study implementation at his/her specific site, ie, if Investigational New Drug study, the individual who signs the Form FDA 1572.

---

**Signature Page for the Investigator**

**Phase 2B/3 double-blinded placebo-controlled efficacy trial of  
AMPHORA® gel for the prevention of acquisition of urogenital  
*Chlamydia trachomatis* infection**

**Protocol Number:** EVO-003

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 applicable US Food and Drug Administration regulations.

---

Organization Name

---

Investigator Signature

---

Date

---

Print Name

---

## Table of Contents

<b>Protocol Synopsis .....</b>	<b>9</b>
<b>List of Abbreviations .....</b>	<b>15</b>
<b>1 Background Information and Scientific Rationale.....</b>	<b>17</b>
1.1 Background Information.....	17
1.2 Scientific Rationale.....	18
1.3 Study Objectives .....	18
<b>2 Study Design.....</b>	<b>20</b>
2.1 Study Outcome Measures .....	21
2.1.1 Primary Outcome Measures.....	21
2.1.2 Secondary Outcome Measures.....	21
2.1.3 Exploratory Outcome Measures .....	22
2.2 Study Population.....	22
2.3 Study Schedule.....	22
<b>3 Study Enrollment and Retention.....</b>	<b>23</b>
3.1 Inclusion Criteria .....	23
3.2 Exclusion Criteria .....	24
3.3 Prohibited Medications .....	25
3.4 Randomization .....	25
3.5 Blinding.....	26
3.6 Withdrawal.....	26
3.6.1 Reasons for Withdrawal.....	26
3.6.2 Handling of Withdrawal .....	27
3.6.3 Handling Subjects Lost to Follow-up .....	27
3.6.4 Replacement of Subjects Lost to Follow-up and Withdrawal .....	28
3.7 Subject Completion.....	28
3.8 Termination of the Study .....	28
<b>4 Study Products .....</b>	<b>29</b>
4.1 Study Products Description.....	29
4.1.1 Formulation and Packaging .....	29
4.1.2 Product Supply.....	30
4.1.3 Product Storage, Stability, and Expiration.....	30
4.1.4 Preparation .....	30
4.1.5 Distribution to Subjects/Return of Unused Product and Used Applicators ..	30
4.1.6 Administration .....	30
<b>5 Study Procedures/Evaluations.....</b>	<b>32</b>
5.1 Written Informed Consent .....	32
5.2 Inclusion/Exclusion Criteria .....	32
5.3 Evaluation of Eligibility Criteria .....	32

5.4	Demographics .....	32
5.5	Clinical Evaluations .....	33
5.5.1	Medical History .....	33
5.5.2	Vital Signs.....	33
5.5.3	Gynecologic Examinations .....	33
5.5.4	Concomitant Medications .....	33
5.5.5	Height and Weight .....	33
5.6	Laboratory Evaluations.....	34
5.6.1	Pregnancy Testing.....	34
5.6.2	Vaginal pH Testing.....	34
5.6.3	Nucleic Acid Amplification Tests for <i>Chlamydia trachomatis</i> / <i>Neisseria gonorrhoeae</i> .....	34
5.6.4	Staining of Used Applicators .....	34
5.7	Subject eDiaries .....	35
5.8	Procedures by Visit.....	35
5.8.1	Screening (Visit 0; Weeks -6-0) .....	35
5.8.2	Rescreening.....	36
5.8.3	Enrollment/Visit 1 (Week 0 ±7 days) .....	36
5.8.4	Visits 2 Through 4 (Weeks 4-12 ±7 days).....	37
5.8.5	Visit 5 (Week 16 ±7 days) .....	37
5.8.6	Post-intervention Follow-up Visit/Visit 6 (Week 20 ±7 days) .....	38
5.9	Unscheduled Visit(s).....	38
5.10	Early Termination .....	38
5.11	Clinical Laboratory Specimen Preparation, Handling and Storage .....	38
<b>6</b>	<b>Safety Reporting and Safety Monitoring.....</b>	<b>40</b>
6.1	Responsibilities .....	40
6.2	Definitions.....	40
6.3	Safety Reporting Requirements .....	41
6.3.1	Reporting Interval .....	41
6.3.2	Notification of the Sponsor of Serious Adverse Events .....	42
6.3.3	Regulatory Reporting for Studies Conducted Under Investigational New Drug Application .....	42
6.4	Investigator's Assessment of Adverse Events .....	42
6.4.1	Assessment of Severity .....	43
6.4.2	Adverse Event Outcome Measures .....	45
6.5	Study-related Adverse Events.....	45
6.6	Other Safety Considerations .....	45
6.6.1	Follow-up of Adverse Events .....	46
6.6.2	Pregnancy.....	46
<b>7</b>	<b>Clinical Monitoring/Site Monitoring Plan.....</b>	<b>48</b>

---

<b>8</b>	<b>Statistical Considerations</b>	<b>49</b>
8.1	Study Hypotheses	49
8.2	Sample Size Considerations	49
8.3	Final Analysis Plan	49
8.3.1	Analysis Populations	49
8.3.2	Randomization and Stratification	50
8.3.3	Procedures for Handling Missing, Unused, and Spurious Data	50
8.3.4	General Statistical Considerations	50
8.4	Planned Statistical Methodology	50
8.4.1	Data Analysis for Efficacy	50
8.4.2	Data Analysis for Safety	51
8.4.3	Analyses for Exploratory Objectives and Endpoints	51
<b>9</b>	<b>Data Handling/Recordkeeping/Source Documents</b>	<b>52</b>
9.1	Data Capture Methods	52
9.2	Types of Data	52
9.3	Study Records Retention	52
9.4	Source Documents	53
9.5	Protocol Deviations	53
<b>10</b>	<b>Quality Control and Quality Assurance</b>	<b>54</b>
<b>11</b>	<b>Ethics/Protection of Human Subjects</b>	<b>55</b>
11.1	Ethical Standard	55
11.2	Institutional Review Board	55
<b>12</b>	<b>Informed Consent Process</b>	<b>56</b>
12.1	Subject Confidentiality	56
<b>13</b>	<b>Confidentiality Policy</b>	<b>57</b>
<b>14</b>	<b>Publication Policy</b>	<b>58</b>
<b>15</b>	<b>Summary of Changes</b>	<b>59</b>
<b>16</b>	<b>Literature References</b>	<b>62</b>
<b>17</b>	<b>Appendices</b>	<b>64</b>
Appendix A.	Grading of Study-related Adverse Events	64
Appendix B.	Study-related Adverse Events	65
Appendix C.	Study Product Instructions for Use	66
Appendix D.	Subject Satisfaction with Product	69
Appendix E.	Subject Sexual Satisfaction	70
Appendix F.	Sexual Function Questionnaire (SFQ)	71
Appendix G.	Female Sexual Function Index (FSFI)	72

---

## List of Tables

Table 1	Schedule of Assessments .....	13
Table 2	Study Product Dosing .....	29
Table 3	Summary of Changes.....	59

## List of Figures

Figure 1	Schematic Flow of Study Design.....	14
----------	-------------------------------------	----

## PROTOCOL SYNOPSIS

**TITLE OF CLINICAL TRIAL:**

Phase 2B/3 double-blinded placebo-controlled efficacy trial of AMPHORA® gel for the prevention of acquisition of urogenital *Chlamydia trachomatis* infection

**INVESTIGATIONAL PRODUCT(S):**

Eligible subjects will receive:

AMPHORA vaginal gel, 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 2B/3**CLINICAL TRIAL OBJECTIVES:****Primary:**

- To determine if intravaginal AMPHORA gel reduces the risk of urogenital *Chlamydia trachomatis* (CT) infection

**Secondary:**

- To determine if intravaginal AMPHORA gel reduces the risk of urogenital *Neisseria gonorrhoeae* (GC) infection

**Exploratory:**

- To determine if AMPHORA gel use rate (subject adherence to instructed use) has an effect on proportion of subjects who experience at least one CT or GC infection during the study intervention period
- To assess subject satisfaction (including sexual satisfaction) with AMPHORA gel over the course of the clinical study

**OUTCOME MEASURES:****Primary:**

- Proportion of subjects who experience at least one urogenital CT infection during the study intervention period (incident infection of CT)

**Secondary:**

- Proportion of subjects who experience at least one urogenital GC infection during the study intervention period (incident infection of GC)

***Exploratory:***

- Compliance with AMPHORA usage during study (rate of product use adherence)
- Sensitivity analyses of the primary parameter (proportion of subjects who experience at least one CT or GC infection during the study intervention period) will be performed for the following:
  - Subjects with  $\geq 20\%$ ,  $\geq 40\%$ ,  $\geq 60\%$ ,  $\geq 80\%$  and 100% product use adherence
- Subject satisfaction
- Sexual satisfaction

**CLINICAL TRIAL DESIGN:**

This is a Phase 2B/3 double-blind, placebo-controlled study in approximately 50 sites in the United States (US) over approximately 16 weeks of use in women aged 18 to 45 years who are at risk of urogenital re-infection

**TREATMENT DURATION:**

After a screening period of up to 45 days, women will be randomized to receive either AMPHORA or placebo. Each woman will participate in the study until after she has completed 16 weeks of treatment. The final visit to the clinical site will take place 4 weeks after the end of treatment even if the subject discontinues treatment prematurely

**SAMPLE SIZE:**

A sample of approximately 844 women will receive AMPHORA or placebo

**STUDY POPULATION:**

***Study Sites:***

The study will be conducted at up to 50 clinical sites in the US. Subjects will be selected for the study according to the eligibility criteria detailed below

***Inclusion Criteria:***

1. Healthy female subjects between 18 and 45 years of age, inclusive
2. Ability to understand the consent process and procedures
3. Subjects agree to be available for all study visits
4. Written informed consent in accordance with institutional guidelines
5. Negative pregnancy test
6. Negative CT and GC nucleic acid amplification test (NAAT) at screening or positive CT or GC NAAT and receives standard of care (SOC) treatment prior to enrollment
7. Agree to use a woman-controlled method of contraception that is not directly delivered to the vaginal mucosa (with the exception of a vaginal ring) throughout the duration of the study, such as oral contraceptives, birth control implants, intrauterine devices (IUDs), or tubal ligation. Condom use only is not an acceptable form of contraception for this study
8. Able and willing to comply with all study procedures

9. Documented (as part of a retrievable medical record) diagnosis of CT or GC infection within 16 weeks prior to enrollment. Acceptable documentation will include:
  - Lab reports confirming CT/GC infection OR
  - Third party clinic note confirming previous CT/GC infection and indicating the date of diagnosis and/or date of treatment
10. Reports vaginal sexual intercourse with a male partner at least three times per month in the previous month and anticipates vaginal sexual intercourse regularly for the duration of the study
11. Agree to abstain from douching or any form of vaginal suppository use (other than investigational product) during course of study

***Exclusion Criteria:***

1. Participation in any study with an investigational compound or device within 30 days prior to signing informed consent
2. In the opinion of the Investigator, has a history of substance or alcohol abuse in the last 12 months
3. In the opinion of the Investigator, has issues, conditions, 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
4. Is an Evoform, ICON GPHS, or clinical site employee regardless of direct involvement in research activities, or their close relative
5. Pregnant (or actively trying to become pregnant), or breastfeeding
6. Women who have undergone a total hysterectomy (had uterus and cervix removed)
7. Inability to provide informed consent
8. Has a history or expectation of noncompliance with medications or intervention protocol
9. Have engaged in sexual vaginal intercourse or douching, or used of any form of vaginal suppository or intravaginal device (with the exception of contraceptive vaginal ring or tampons) for 24 hours prior to enrollment (may be enrolled at a later date if all other criteria are met)
10. Menstruating at enrollment (may be enrolled at a later date if all other criteria are met)
11. Is currently being treated, or have been treated, for a period of 21 days prior to enrollment, with specific antibiotics known to be used for the treatment of CT or GC:
  - Azithromycin
  - Erythromycin
  - Tetracycline
  - Minocycline
  - Doxycycline
  - Levofloxacin

- Ofloxacin
  - Ceftriaxone
  - Cefixime
12. In the opinion of the Investigator, has signs/symptoms that indicate persistence of chlamydia or gonorrhea infection diagnosed at screening, new interval infection, and/or a failure to comply with or complete the prescribed treatment regimen following a positive screening NAAT
  13. Women who regularly use douches, vaginal medications, products, or suppositories
  14. Women who are currently using contraceptive products that are directly delivered to the vaginal mucosa (with the exception of contraceptive vaginal ring), such as diaphragms, spermicides, or any vaginally applied or inserted products containing nonoxynol-9 (N-9)
  15. Children, pregnant women, prisoners, and other vulnerable populations

**Table 1 Schedule of Assessments**

Study Visit (V)	Screening <sup>(1)</sup>	Intervention Period; AMPHORA gel N=422, Placebo gel N=422					Post-Intervention Follow-up/Visit 6
		Enrollment/ Visit 1 <sup>(2)</sup>	Visit 2 <sup>(2)</sup>	Visit 3 <sup>(2)</sup>	Visit 4 <sup>(2)</sup>	Visit 5/Early Termination <sup>(2,3)</sup>	
Study Week	-6-0 (-45-0 days)	0 <sup>(4)</sup>	4 <sup>(4)</sup>	8 <sup>(4)</sup>	12 <sup>(4)</sup>	16 <sup>(4)</sup>	20
Investigational Product Dispensed		X	X	X	X		
Informed Consent/HIPAA	X						
Inclusion/Exclusion	X	X					
Concomitant Medications	X	X	X	X	X	X	X
AE Assessment		X	X	X	X	X	X
Medical/Sexual History	X	X					
Last Menstrual Period		X					
Physical Exam		X					
Targeted Physical Exam			[X]	[X]	[X]	[X]	[X]
Body Weight/Height		X					
Vital Signs		X					
Gynecologic Exam		X					
Urine HCG (females)		X	X	X	X	X	X
Vaginal pH		X					
Self-collected CT/GC NAAT	X		X	X	X	X	X <sup>3</sup>
Clinician-collected CT/GC NAAT		X					
eDiary Setup		X					
eDiary Review			X	X	X	X	X
Inspection of Returned Investigational Product			X	X	X	X	
Staining of Used Applicators			X	X	X	X	
Subject Satisfaction with Product						X	
Subject Sexual Satisfaction						X	
Female Sexual Function Index (FSFI)		X				X	
Sexual Function Questionnaire		X				X	

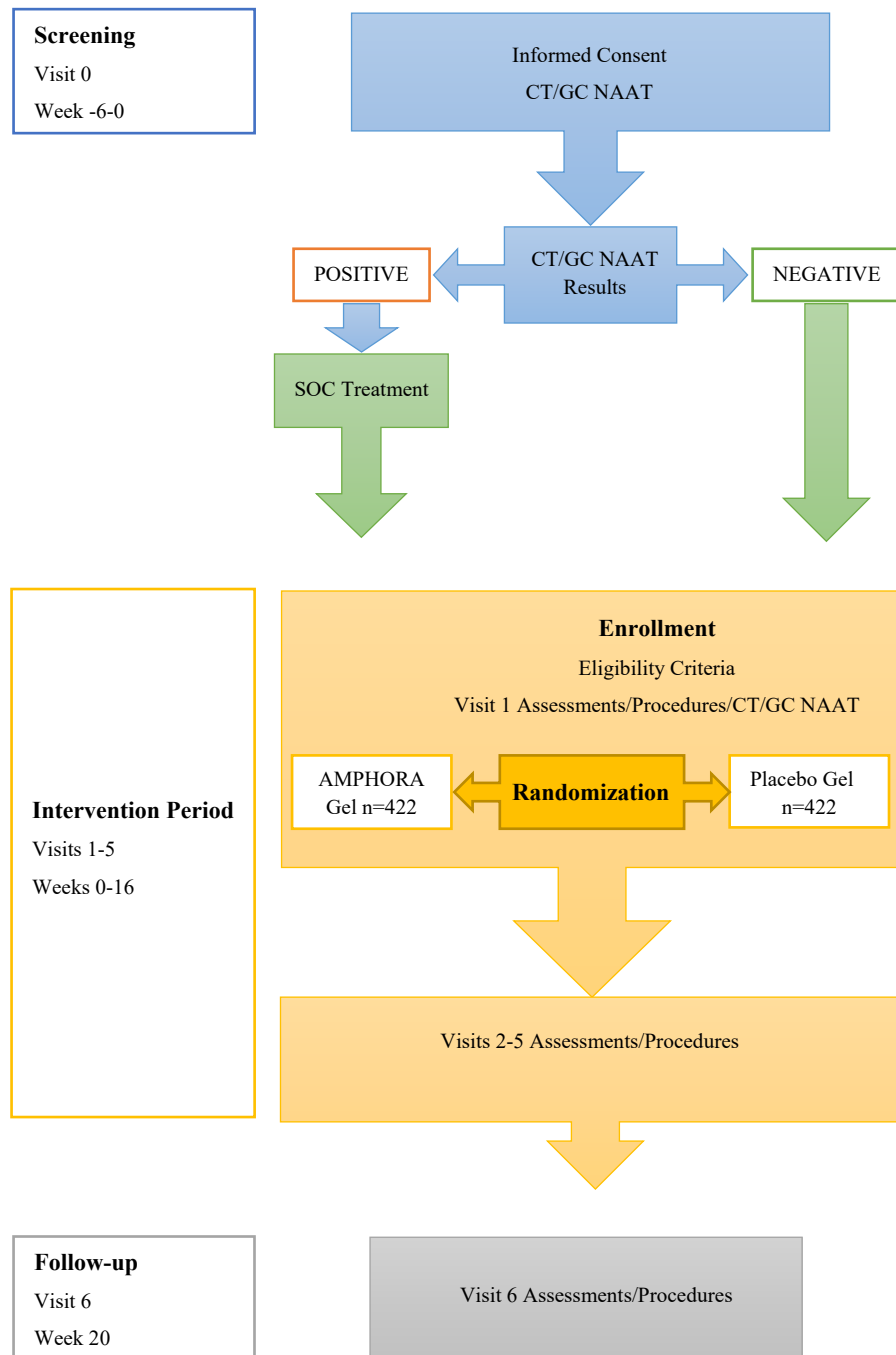
<sup>(1)</sup>Screening period may be up to 45 days. Subjects will be asked to return 7 days after Screening Visit. If subjects NAAT results are positive, they will be first treated by SOC then will return 3-4 weeks after Screening Visit (at least 21 days after treatment) for Enrollment/Visit 1. If the screening period extends past 45 days, subjects will not be enrolled and will need to be rescreened.

<sup>(2)</sup> Subjects must be asked to abstain from vaginal intercourse in the 24 hours preceding Study Visits 2 through 5.

<sup>(3)</sup> CT/GC NAAT testing is not required at this visit if subject was discontinued due to positive NAAT. For early termination, procedures for V5 should be followed with CT/GC NAAT testing required.

<sup>(4)</sup> Subjects will be asked to return  $\pm$  7 days within each visit window.

**Figure 1 Schematic Flow of Study Design**



## LIST OF ABBREVIATIONS

ADL	Activities of daily living
AE	Adverse event
BV	Bacterial vaginosis
CFR	US Code of Federal Regulations
CQMP	Clinical Quality Management Plan
CRA	Clinical Research Associate
CRF	Case report form
CRO	Contract research organization
CT	<i>Chlamydia trachomatis</i>
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic case report form
EDC	Electronic data capture
eDiary	Electronic diary
FDA	US Food and Drug Administration
FDAAA	US Food and Drug Administration Amendments Act
FSFI	Female Sexual Function Index
G (g)	Gram
GC	<i>Neisseria gonorrhoeae</i>
GCP	Good Clinical Practice
GPHS	ICON Government and Public Health Solutions
HDPE	High-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
IFU	Inclusion forming units
IND	Investigational New Drug Application
IRB	Institutional review board
ITT	Intention-to-treat
IUD	Intrauterine device
IWRS	Interactive Web Response System
LB	<i>Lactobacillus</i> species
MedDRA	Medical Dictionary for Regulatory Activities®
mITT	Modified Intention-to-Treat
MOP	Manual of Procedures
N-9	Nonoxynol-9
N	Number (typically refers to subjects)

NAAT	Nucleic acid amplification test
NCI	National Cancer Institute
PID	Pelvic inflammatory disease
Placebo	Inactive substance which may resemble an active agent but has no medical value
QA	Quality assurance
QC	Quality control
SAE	Serious adverse event
SAS	Statistical analysis software
SFQ	Sexual Function Questionnaire
SOC	Standard of care
SOP	Standard operating procedure
STI	Sexually transmitted infection
TEAE	Treatment-emergent adverse event
uHCG	Urine $\beta$ -human chorionic gonadotropin
UMC	Uppsala Monitoring Centre
UPG	Universal placebo gel
US	United States
USP	United States Pharmacopeia
WHO	World Health Organization

---

## 1 Background Information and Scientific Rationale

### 1.1 Background Information

*Chlamydia trachomatis* (CT) infection remains the most frequently reported infectious disease in the United States (US) (1). Several sequelae can result from CT infection in women, the most serious of which include pelvic inflammatory disease (PID) and scarring of the fallopian tubes, ovaries, endometrial lining, and occasionally, adjacent perineum, which increases the risk of future ectopic pregnancy and tubal infertility. These consequences are the main reason that CT infection is estimated to be the costliest of all non-viral sexually transmitted infections (STIs) (2).

An acidic vaginal pH and colonization with *Lactobacillus* species (LB) are two proven components of the multiple defense mechanisms active against infection in the lower female genital tract (3). These species are thought to play key protective roles by producing various bacteriostatic and bactericidal compounds (4), (5), (6). A lower vaginal pH may inhibit STIs, including CT infection (7). In vitro studies have shown that exposure to vaginal secretions at lower pH significantly inhibits CT replication (7), (8). In another experiment, the growth of CT within epithelial cells was inhibited by acidic pH (9).

A prospective case-controlled study found an association between CT infection and higher vaginal pH (median pH of 4.5 in CT and 4.0 in controls, respectively), independent of any other factors (10). The study included 144 cases of CT infections and 145 controls. Sixty-two (62) of the women with CT were diagnosed with concurrent STIs (bacterial vaginosis [BV], genital warts, *Neisseria gonorrhoeae* [GC], trichomoniasis, and candidiasis). However, even when the analyses were restricted to the 82 cases that did not have any other concurrent STI, vaginal pH remained higher in those cases than in the controls. In univariate analyses, cases were over six times as likely as controls to have a pH >4.5. This study, in itself, was unable to answer whether lower vaginal pH reduces risk of acquisition of urogenital CT infection, and further study is needed. However, the results of this study lead to the hypothesis that reduction of vaginal pH (through treatment) in asymptomatic women with conditions that are known to increase vaginal pH (such as BV), may help to prevent CT infection, particularly in those at increased risk of infection.

A recent study of 61 women exposed to GC through an infected partner was conducted at the Baltimore City Health Department STI clinics and showed that 100% of the women whose vaginal pH was  $\geq 5.0$  were subsequently infected with GC versus 40% of the women whose pH was <5.0 (when measured within 5 days of GC exposure) (11). Additionally, pH-dependent risk was independent of BV as diagnosed by Amsel criteria. These data suggest that modification of vaginal pH could be used clinically to reduce risk of GC infection in women.

In summary, the interplay between vaginal pH and the naturally occurring human vaginal microbiota represents an important relationship which has been linked to increased risk for STIs, including CT and GC (12), (13), (14), (15), (16), (17), (18), (19), (20), (21).

## 1.2 Scientific Rationale

AMPHORA is an acid-buffering vaginal gel (pH 3.5) containing three active ingredients (L-lactic acid, citric acid, and potassium bitartrate). It is currently in development as a contraceptive to be applied intravaginally before sexual intercourse. During development, it was found to have in vitro activity against GC, as well as BV-associated microbes, without having a detrimental effect on beneficial native LB and to inhibit *Trichomonas vaginalis* under both aerobic and anaerobic conditions (Investigator's Brochure, 2016). This has led to further development as a microbicide to lessen the risk of, or prevent acquisition of, STIs.

Subsequent studies done on AMPHORA in the animal model support further in vivo microbicide research. AMPHORA with and without nonoxynol-9 (N-9) was applied vaginally to Swiss Webster mice before inoculation of 15  $\mu$ L  $10^4$  or  $10^5$  inclusion forming units [IFU] CT. AMPHORA was found to provide protection against upper genital tract infection in 88% to 100% of the animals, whereas the other four vaginal gel products tested protected only 0% to 38% of the animals. It was also determined that the addition of 5% N-9 to AMPHORA did not enhance its protective effect at the usual challenge inoculum (22).

In another murine study, AMPHORA displayed significant protection against transmission of GC with only one of 17 mice treated having positive culture results compared with 13 of 15 untreated control mice. Of the six topical microbicide agents tested, AMPHORA was the most highly active against GC in vitro; a 0.625% solution of this product inhibited six of the seven GC strains (23).

Low adherence to product use is an ongoing challenge in vaginal microbicide studies, though recent analysis of study data has produced baseline predictors of high adherence (24). A recent prospective study on sexual risk behavior and incident STIs included a substudy that showed use of cell phone-based e-diaries assisted in achieving an enhanced subject compliance rate of 89.7% (25).

## 1.3 Study Objectives

**Primary:** To determine if intravaginal AMPHORA reduces the risk of urogenital *Chlamydia trachomatis* (CT) infection

**Secondary:** To determine if intravaginal AMPHORA reduces the risk of urogenital *Neisseria gonorrhoeae* (GC) infection

---

**Exploratory:**

- To determine if AMPHORA use rate (subject adherence to instructed use) has an effect on proportion of subjects who experience at least one CT or GC infection during the study intervention period
- To assess subject satisfaction (including sexual satisfaction) with AMPHORA over the course of the clinical study

---

## 2 Study Design

Eight hundred forty-four (844) women, ages 18 to 45, who have had a documented urogenital chlamydia or gonorrhea infection at any time over the 16 weeks preceding the Enrollment Visit, or found to be positive at Screening Visit will be enrolled. A high prevalence of *Chlamydia trachomatis* infection has been observed in those who were treated for urogenital chlamydial infection during the preceding several months. The second infection may result from re-infection through an untreated partner or exposure through a new partner. By including only women who have had a CT infection within the past 16 weeks, this study targets those at high risk for infection (1), (26).

Regardless of whether a potential subject agrees to participate in the study, subjects should be treated according to each site's routine standard of care (SOC) for STI prevention which should follow the prevention strategies recommended by the Centers for Disease Control and Prevention (<https://www.cdc.gov/std/tg2015/clinical.htm>). These strategies include client-centered STI prevention counseling addressing subject's individual risk factors and advice on the correct and consistent use of male condoms to prevent STIs and human immunodeficiency virus (HIV), as well as condom provision if part of the site's SOC. Those who agree to participate (ie, subjects who provide informed consent) should be treated according to SOC prior to and throughout the study period as necessary.

Subjects will be tested for current GC/CT infection by nucleic acid amplification test (NAAT) via vaginal swab. Those negative for current infection will be enrolled. Those who test positive for CT/GC infection will receive SOC treatment. To meet eligibility criteria, these subjects will not be enrolled until 3 to 4 weeks after screening (at least 21 days after treatment).

Eligible participants will be enrolled and randomized 1:1 (422 subjects per treatment arm) to either AMPHORA or placebo; 5 g of AMPHORA or placebo will be supplied in pre-filled, single-dose applicators. A baseline vaginal pH and a full gynecologic exam (speculum) will be obtained at enrollment.

Subjects are instructed to apply AMPHORA or placebo gel immediately before or up to one hour prior to coitus for the duration of the 16-week intervention period. AMPHORA or placebo is to be re-applied in the same manner for each occurrence of sexual intercourse. Subjects will keep an electronic diary (eDiary) to document and track sexual activity and product use.

Every 4 weeks (5 visits), all subjects will return to the clinic for repeat CT/GC NAAT (vaginal swab), urine pregnancy (urinary human chorionic gonadotrophin [uHCG]) testing, eDiary review, and return of used and unused investigational product. Applicators will be visually inspected for use and staining will be performed to confirm vaginal insertion of used (empty) applicators. At Visits 2 to 4, subjects will be re-supplied with AMPHORA or placebo gel. At Visit 5, subjects will

return used and unused investigational product and continue to use their eDiaries but will not be resupplied with AMPHORA or placebo gel.

Subjects will return for a follow-up visit 4 weeks after the intervention period. At this time, CT/GC NAAT (vaginal swab), pregnancy (uHCG) testing, and eDiary review will be performed.

## **Screening and Eligibility**

Subjects who consent may be screened if they have a known case of CT or GC within 16 weeks of enrollment, or suspicion of current CT or GC infection (subsequently confirmed with NAAT test at Screening Visit). Subjects randomized within 45 days of initial screening do not need to be re-screened.

## **Intervention and Follow-up Period**

The intervention period is defined as Visits 1 to 5. There is one follow-up visit (Visit 6) 4 weeks after the last intervention visit. These periods are outlined in the Schedule of Assessments (Table 1). The protocol-defined period of observation is 20 weeks.

## **Safety Follow-up After Protocol-defined Period of Observation**

This period includes safety follow-up as required by Good Clinical Practice (GCP) and standard clinical study practice. Adverse events (AEs) determined to be at least possibly related to the investigational product continuing after the final study visit (Visit 6) will be followed until resolution or stable status as determined by the Investigator. Applicable information is found in Section 6.3.

## **2.1 Study Outcome Measures**

### **2.1.1 Primary Outcome Measures**

The primary objective of this study is to demonstrate the superior efficacy of AMPHORA compared with placebo for the prevention of urogenital CT infection. The primary efficacy endpoint is the proportion of subjects who experience at least one CT infection during the study intervention period (incident infection of CT).

### **2.1.2 Secondary Outcome Measures**

The secondary outcome will measure the proportion of subjects who experience at least one urogenital GC infection during the study intervention period (incident infection of GC).

---

### 2.1.3 Exploratory Outcome Measures

Exploratory assessments include:

- AMPHORA usage during the study (rate of product use adherence) and sensitivity analyses of the primary parameter (proportion of subjects who experience at least one CT or GC infection during the study intervention period) and subjects with  $\geq 20\%$ ,  $\geq 40\%$ ,  $\geq 60\%$ ,  $\geq 80\%$ , and 100% product use adherence
- Assessing subject satisfaction (including sexual satisfaction) with AMPHORA over the course of the clinical study

## 2.2 Study Population

Approximately 1055 women who have had a documented CT or GC vaginal infection at any time over the 16 weeks preceding enrollment, or suspicion of current CT or GC infection (subsequently confirmed with NAAT test at Screening Visit), will be screened to identify 844 healthy female subjects who are eligible to participate.

## 2.3 Study Schedule

**Schedule for individual subjects:** Individual subjects will participate in the study for up to 24 weeks. The study Schedule of Assessments (Table 1) and the description of procedures involving study subjects, by study visit, is provided in Section 5.8.

---

### **3 Study Enrollment and Retention**

No study procedures will be performed until informed consent is obtained. Eight hundred forty-four (844) healthy female subjects, ages 18 to 45, will be enrolled.

Subjects will be recruited through institutional review board (IRB)-approved materials, database queries, and word of mouth. Children, pregnant women, prisoners, and other vulnerable populations will not be enrolled.

Screening will begin with the Investigator or designee providing an overview of the study to the potential subject. Subjects will be excluded if they do not understand the protocol and participation requirements and/or if they are unable, unlikely, or unwilling to comply with gel application as directed, eDiary recording, or follow-up visit attendance. All subjects who consent will be assigned a screening number.

All eligibility criteria must be met for inclusion into the study; no waivers will be granted.

In this study, subjects will be encouraged to strive for 100% product use adherence; however, emphasis will be placed on accurate and forthright eDiary recording of each coital event noting use or non-use of the product and any circumstance that may have impacted their decision to use or not use as directed under the study. Adherence to product use will be measured using a combination of eDiary reporting and number/inspection/staining of returned investigational product/gel applicators.

Study retention strategies will include clear explanations during enrollment of the study schedule and procedures and financial payment and/or reimbursements. Study staff will be actively involved in engaging subjects and implementing systems for appointment reminders and follow-up with missed visits.

#### **3.1 Inclusion Criteria**

1. Healthy female subjects between 18 and 45 years of age, inclusive
2. Ability to understand the consent process and procedures
3. Subjects agree to be available for all study visits
4. Written informed consent in accordance with institutional guidelines
5. Negative pregnancy test
6. Negative CT and GC NAAT at screening or positive CT or GC NAAT and receives SOC treatment prior to enrollment
7. Agree to use a woman-controlled method of contraception that is not directly delivered to the vaginal mucosa (with the exception of a vaginal ring) throughout the duration of the study, such as oral contraceptives, birth control implants, intrauterine

- devices (IUDs), or tubal ligation. Condom use only is not an acceptable form of contraception for this study
8. Able and willing to comply with all study procedures
  9. Documented (as part of a retrievable medical record) CT or GC infection within 16 weeks prior to enrollment. Acceptable documentation will include:
    - Lab reports confirming CT/GC infection OR
    - Third party clinic note confirming previous CT/GC infection and indicating the date of diagnosis and/or date of treatment
  10. Reports vaginal sexual intercourse with a male partner at least three times per month in the previous month and anticipates vaginal sexual intercourse regularly for the duration of the study
  11. Agree to abstain from douching or any form of vaginal suppository use (other than investigational product) during course of study

### **3.2 Exclusion Criteria**

1. Participation in any study with an investigational compound or device within 30 days prior to signing informed consent
2. In the opinion of the Investigator, has a history of substance or alcohol abuse in the last 12 months
3. In the opinion of the Investigator, has issues, conditions, 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
4. Is an Evoform, ICON GPHS, or clinical site employee regardless of direct involvement in research activities, or their close relative
5. Pregnant (or actively trying to become pregnant), or breastfeeding
6. Women who have undergone a total hysterectomy (had uterus and cervix removed)
7. Inability to provide informed consent
8. Has a history or expectation of noncompliance with medications or intervention protocol
9. Has engaged in sexual vaginal intercourse or douching, or used any form of vaginal suppository or intravaginal device (with the exception of contraceptive vaginal ring or tampons) for 24 hours prior to enrollment (may be enrolled at a later date if all other criteria are met)
10. Menstruating at enrollment (may be enrolled at a later date if all other criteria are met)
11. Is currently being treated, or have been treated, for a period of 21 days prior to enrollment, with specific antibiotics known to be used for the treatment of CT or GC:
  - Azithromycin

- 
- Erythromycin
  - Tetracycline
  - Minocycline
  - Doxycycline
  - Levofloxacin
  - Ofloxacin
  - Ceftriaxone
  - Cefixime
12. In the opinion of the Investigator, has signs/symptoms that indicate persistence of chlamydia or gonorrhea infection diagnosed at screening, new interval infection and/or a failure to comply with or complete the prescribed treatment regimen following a positive screening NAAT
  13. Women who regularly use douches, vaginal medications, products, or suppositories
  14. Women who are currently using contraceptive products that are directly delivered to the vaginal mucosa, such as diaphragms, spermicides, or any vaginally applied or inserted products containing N-9
  15. Children, pregnant women, prisoners, and other vulnerable populations

### **3.3 Prohibited Medications**

Subjects must not be currently taking or applying, or have taken or applied, for a period of 21 days prior to enrollment, antibiotics with activity against CT or GC. The following antibiotics meet these criteria:

- Azithromycin
- Erythromycin
- Tetracycline
- Minocycline
- Doxycycline
- Levofloxacin
- Ofloxacin
- Ceftriaxone
- Cefixime

### **3.4 Randomization**

This is a Phase 2B/3 placebo-controlled randomized study with 422 subjects per intervention arm, for a total of 844 subjects. The 844 subjects will be randomized using an Interactive Web Response System (IWRS) in a 1:1 fashion across the two intervention groups, AMPHORA or

placebo. Randomization will be stratified by site, and all documentation of this procedure and output will be saved with the IWRS vendor until the end of the study. Randomization will occur following enrollment and prior to issuance of investigational product to subjects.

### **3.5 Blinding**

Investigators and subjects in both intervention groups will remain blinded to their intervention assignment (AMPHORA or placebo) over the entire duration of the study (double-blind). The Sponsor, Evoform, Inc., will prepare the investigational product as well as placebo and supply these products in ready-to-dispense status.

Any request from the Investigator for information about treatment administered to study subjects must be approved by the Medical Monitor.

If the code must be broken in the case of an emergency for subsequent management of a subject, the Investigator must provide a written request with record of the circumstances surrounding the event, including the purpose, date, and personnel involved. Emergency unblinding will be available by using the IWRS. An emergency treatment disclosure is a reportable event that must be reported to the Medical Monitor within 24 hours of the event.

Otherwise, blinding will not be broken until all subjects have completed the final study visit and the database has been locked and approved.

### **3.6 Withdrawal**

#### **3.6.1 Reasons for Withdrawal**

A study subject will be discontinued from participation in the study for:

- Development of any [exclusion criteria](#)
- Positive GC/CT NAAT testing at enrollment
- Pregnancy or breastfeeding
- Request by subject to terminate participation
- Subject is no longer sexually active on a regular basis, ie, records no sexual activity for two or more cycles
- Requirement for prohibited treatment (see [exclusion criteria](#)) during the intervention period
- Intervention-related toxicity
- Lost to follow-up
- Request of primary care provider

- Request of the IRB/ethics committee, US Food and Drug Administration (FDA), or Sponsor
- Subject is no longer able to attend study visits and/or comply with study procedures
- The subject's well-being, based on the opinion of the Investigator

### **3.6.2 Handling of Withdrawal**

If a subject is withdrawn from participation, the reason(s) for discontinuation must be documented in the source documents and electronic case report forms (eCRFs). The procedures for Visit 5 should be followed for the Early Termination Visit. Subjects who withdraw or are withdrawn from the study who received any amount of the investigational product will be encouraged to return to the clinic for a final visit to complete the post-intervention follow-up visit (all procedures from Visit 6). If an AE or serious adverse event (SAE) has occurred, every effort will be made to undertake protocol-specified safety follow-up procedures, and the subject will be encouraged to receive appropriate care under medical supervision until the symptoms of any AE resolve or the subject's condition becomes stable.

### **3.6.3 Handling Subjects Lost to Follow-up**

The study design has incorporated primary, secondary, and tertiary strategies for reducing the number of subjects lost to follow-up. Primary strategies include having sites: 1) fully inform subjects of study visit details prior to randomization, 2) addressing subjects' expectations on study participation, 3) motivating subjects to adhere to follow-up visits and research protocols, and 4) utilizing eDiaries for data entry and review. Secondary strategies include: 1) scheduling all visits around subjects' availability which are within the visit window, 2) providing a visit reminder ahead of time, and 3) reviewing data for missed and overdue follow-up visits. Tertiary strategies include: 1) discussing subjects' difficulty in adhering to study protocol and answering any questions they might have and 2) continuing attempts to reach subjects lost to follow-up and recording all contact attempts.

A subject will be considered as lost to follow-up if participation in study activities is not continued after:

- Three attempts at telephone contact without success following missed study assessment timepoint, followed by
- Issuance of a certified letter to last documented address of subject, and no response within 7 days of mailing

Documentation of lost to follow-up status will be maintained in the subject's case report form (CRF) and in source documents. The reason(s) for the lost to follow-up, if known, and the appropriate timelines for subject-study site correspondence will be captured along with the study site's attempts to reach the subject. Lastly, all proper procedures of sending certified letter of

---

discontinuation from study based on lost to follow-up status and a recommendation to come in for a discontinuation visit to determine safety of the subject will be followed by the study site. The conditions and plans for replacement of subjects lost to follow-up are described in Section 3.6.3.

### **3.6.4 Replacement of Subjects Lost to Follow-up and Withdrawal**

An enrolled subject will be considered lost to follow-up or withdrawn as described in Section 3.6.3 at any point prior to Visit 6 (post-intervention follow-up visit). Subjects will not be replaced in this study.

### **3.7 Subject Completion**

An enrolled subject will be considered a study completer once any of the following three criterion is met:

1. Finishes all study visits without experiencing a urogenital CT or GC infection
2. Experiences urogenital CT infection
3. Experiences urogenital GC infection

### **3.8 Termination of the Study**

The study may be terminated at the discretion of the Sponsor. The study may also be terminated at a study site after discussion with the Sponsor. The reason for termination will be documented.

## 4 Study Products

### 4.1 Study Products Description

There are two study products used over the course of the intervention period for this study:

1) AMPHORA and 2) placebo.

#### AMPHORA

AMPHORA is in development as a vaginally administered contraceptive gel and microbicide agent. AMPHORA is an acid-buffering gel (pH 3.5) containing three active ingredients (L-lactic acid 1.8%, citric acid 1%, and potassium bitartrate 0.4%) and the following non-active ingredients: benzoic acid, alginic acid, xanthan gum, glycerin, and water.

#### Placebo (Universal Placebo Gel)

The placebo used in this study is universal placebo gel (UPG). UPG is an isotonic non-buffering gel, with pH adjusted to 4.5 and containing 2.7% hydroxyethylcellulose, sorbic acid, sodium hydroxide, sodium chloride, and purified water. In clinical studies, UPG has been proven safe and acceptable when used up to twice daily for 14 days (27).

**Table 2 Study Product Dosing**

Intervention Group	AMPHORA	Placebo
Group A	422 subjects, 5 g dose applied up to 1 hour prior to coitus	N/A
Group B	N/A	422 subjects, 5 g dose applied up to 1 hour prior to coitus

#### 4.1.1 Formulation and Packaging

For this study, pre-filled, single-use applicators will be used. The AMPHORA and placebo gels will be filled (5 g) into identical single-dose applicators consisting of an injection molded opaque white high-density polyethylene (HDPE) barrel with a rounded distal end for easy insertion. A thermoplastic rubber piston will be inserted at the opposite end of the barrel. This component will seal the end of the barrel to keep the contents stable over time and also functions as the applicator piston when in use. A HDPE plunger rod will be packaged alongside of the barrel within an aluminum overwrap. Product will be dispensed as a box of 10 overwrapped applicators with used applicator return bags and instructions for use.

---

#### **4.1.2 Product Supply**

AMPHORA and placebo will be supplied by the Sponsor, Evoform, Inc., 12400 High Bluff Drive, Suite 600, San Diego, CA 92130.

#### **4.1.3 Product Storage, Stability, and Expiration**

The investigational product should be stored at room temperature (15°C-30°C). The investigational product will be maintained and dispensed by site research staff.

#### **4.1.4 Preparation**

The investigational product is supplied ready for use. No preparation is necessary.

#### **4.1.5 Distribution to Subjects/Return of Unused Product and Used Applicators**

Following screening, enrollment, and randomization, subjects will be issued a 4-week supply of investigational product based on the individual subject's projected usage. Each investigational product box contains 10 applicators. A subject could receive up to three boxes at a study visit during the intervention period. Subjects will be asked how many prefilled applicators they need, based on their number of sexual encounters per 4 weeks. At Visits 2 to 4 each, during the intervention period, subjects will return all unused product and used applicators packaged individually in plastic return bags provided and will be issued a new 4-week supply of investigational product based on projected usage. Unopened kits may be redispensed to the same subject, as appropriate. Subjects may be issued additional investigational product, as needed, should their supply be exhausted prior to the next study visit; however, excessive product usage should be brought to the attention of the Investigator and Sponsor. At Visit 5, subjects will return all unused product and used applicators.

#### **4.1.6 Administration**

AMPHORA and placebo will be intravaginally administered by the subject in exactly the same manner. To administer, the plunger rod is inserted into the piston end of the barrel engaging the piston. The cap is removed from the distal end of the barrel; the barrel is then inserted into the subject's vagina (distal end first). The plunger rod is pushed into the barrel, subsequently moving the piston and gel toward the open end of the barrel. Only the gel will leave the barrel.

Detailed instructions for administration are included as **Appendix C** and supplied to the subject with the investigational product. Subjects will be trained in investigational product application prior to issuance.

---

#### **4.1.7 Product Accountability**

The Investigator will keep a record of the dates and amounts of investigational product received, the amount dispensed to study subjects, the amount returned from subjects at each visit (unused and used applicators) and the amount in inventory (not issued). These records should include the dates, quantities, and batch/serial numbers or kit numbers.

The Investigator will record drug accountability on a Drug Disposition Log, which will be monitored and confirmed by the Clinical Research Associate (CRA). Upon completion of the study and final drug accountability monitoring visit, all unused study medication will be returned to Evofem, Inc., or, if instructed by Evofem, Inc., unused investigational product may be destroyed onsite according to the site's standard operating procedures (SOPs).

---

## **5 Study Procedures/Evaluations**

Subjects will undergo the following study procedures as indicated in this section and according to the Schedule of Assessments (Table 1). All equipment used should be calibrated and undergo routine calibration, as appropriate.

### **5.1 Written Informed Consent**

A written informed consent will be obtained from all study participants before start of any study activities. The Informed Consent specifies, in lay and culturally appropriate language, all expectations from the participant including duration of study, number of doses and visits, procedures at each visit, safety documentation (including subject diary), use of contraceptives, restrictions on intravaginal product or device use, sampling plan, potential risks, stipend for participation in study, and relevant research scope.

All study-related questions by the subject should be responded to before completion of the Informed Consent. The subject will be provided ample time to consider their potential participation, including time to consult with friends, family, and primary care provider if desired. The completed Informed Consent form will be verified for its proper completion. A signed copy of the Informed Consent will be provided to the subject and the original will be kept on file in the subject's study file.

### **5.2 Inclusion/Exclusion Criteria**

Participants will meet all the stated [inclusion criteria](#) and not possess any of the [exclusion criteria](#) to be eligible to participate in this study. Only subjects that are eligible based on the study inclusion and exclusion criteria will be enrolled in the study.

### **5.3 Evaluation of Eligibility Criteria**

The Investigator will evaluate whether a subject meets the study's inclusion/exclusion criteria at screening and enrollment and before administering any study product. The Investigator will be responsible for ensuring that the evaluation of eligibility criteria is addressed for all subjects enrolled in the study.

### **5.4 Demographics**

Demographics data will be collected from all study participants, including date of birth, race, and ethnicity.

---

## 5.5 Clinical Evaluations

All clinical procedures summarized in this section will be performed according to the site's SOC SOPs.

### 5.5.1 Medical History

A detailed medical/surgical/gynecologic/sexual history will be obtained. Changes in medical history, if applicable, will be reviewed at each visit.

A review of body systems will be performed by the Investigator to screen for exclusion criteria.

Subjects will be asked about current drug and alcohol use by the Investigator for evaluating eligibility.

### 5.5.2 Vital Signs

Vital signs, including blood pressure, heart rate, and body temperature, will be measured and recorded. Vital sign measurements will be obtained after the subject has been sitting quietly for at least 5 minutes. When taking an oral temperature, assure the subject has not had any recent hot or cold beverages or has recently smoked, including e-cigarettes. The Investigator should use clinical judgment when characterizing bradycardia among health subjects, eg, conditioned athletes.

### 5.5.3 Gynecologic Examinations

A full gynecologic examination (speculum) will be performed **after** swab for vaginal pH is collected.

Targeted physical and/or gynecologic examination (speculum), will be performed at any subsequent or unscheduled visit if necessary due to an AE.

### 5.5.4 Concomitant Medications

Concomitant medications that will be taken during the study, including all over-the-counter medications, vitamins, and nutritional supplements, will be recorded and should include at a minimum: start date, stop date or continuing, and indication/reason.

### 5.5.5 Height and Weight

Body weight and height will be recorded.

---

## 5.6 Laboratory Evaluations

Specimens collected for NAATs will be processed by the sites and shipped to a central laboratory for testing. All other laboratory testing and staining of used applicators will be performed onsite.

### 5.6.1 Pregnancy Testing

Subjects of reproductive potential, including those with history of tubal ligation, will be required to provide a urine specimen to be tested for uHCG. This test will be performed at each site using the SOC testing materials and procedure.

Negative results must be obtained prior to dosing. Women who test positive for pregnancy will be excluded from participating in this study and be referred for follow-up as per clinic protocol (see Section 6.6.2 Pregnancy).

### 5.6.2 Vaginal pH Testing

Swab for vaginal pH reading is collected prior to introduction of speculum for gynecologic exam. Specimen collection and vaginal pH testing procedures is detailed in the Manual of Procedures (MOP).

### 5.6.3 Nucleic Acid Amplification Tests for *Chlamydia trachomatis*/*Neisseria gonorrhoeae*

All women will have vaginal swabs collected all visits (screening, enrollment, and each intervention visit and follow-up visit) for NAATs. Swabs will be collected by clinician when speculum exams are performed; otherwise vaginal swabs will be self-collected by subject while in clinic. Specimens will be collected using the specific collection/transport kit materials and package insert instructions as designated by the central laboratory. Specimens will be shipped to the central laboratory according to procedure and as included in the MOP. All positive results will be reported to the study site for follow-up.

### 5.6.4 Staining of Used Applicators

Sites will collect returned unused product and used applicators at each study visit. Site staff is responsible to visually inspect unused study product to confirm package seal is intact/not broken. If the seal is broken the applicator should be assessed for use (appears full of gel and unused). The used applicators will be tested onsite to validate vaginal insertion by using staining with trypan blue. Staff performing staining procedures will be trained and procedures will be detailed in the MOP.

---

## 5.7 Subject eDiaries

Each subject will be provided with a secure validated eDiary software application downloaded to their personal cellular telephone or tablet to collect, at minimum, subject-reported sexual activity and study product use data. The eDiary application will be de-identified using the subject number assigned at the time of screening; research staff will receive, and review data identified only by the subject number throughout the course of the study.

The Investigator or designee will ensure each subject is trained in the importance of the eDiary and on its use. The instruction on maintaining the eDiary should include fields that must be completed and how the subject should record data within them. All eDiary entries will be reviewed on a regular basis, with subjects at each follow-up visit. Study sites must encourage eDiary recording by subjects via text messaging or direct contact with subjects. All eDiary entries will become part of the subjects' study record.

## 5.8 Procedures by Visit

### 5.8.1 Screening (Visit 0; Weeks -6-0)

Subjects who wish to participate in the study will be asked to sign and date the Informed Consent and HIPAA forms prior to any study-specific procedures. All subjects will be provided with a copy of their own signed and dated Informed Consent form. The Investigator must keep a subject screening log, subject enrollment log, and subject identification log for identifying all subjects having signed Informed Consent and HIPAA forms.

The following will be recorded by research staff in the source documents and CRF, as required:

1. Informed consent and HIPAA forms completed
2. Demographic data
3. Evaluation of inclusion and exclusion criteria
4. Medical/surgical/gynecologic/sexual history
5. Concomitant medication: all medications taken will be recorded in standard data collection forms with attention to drug route, daily dose, duration, start date, stop date, and indications
6. Self-collected vaginal swab for CT and GC NAATs

Subjects will be asked to return to the clinic after receipt of negative CT and GC NAAT results, preferably in 1 week  $\pm$  7 days for enrollment. Enrollment must be completed within 45 days of screening.

If NAAT results are positive, subjects must be treated according to SOC prior to enrollment. To meet eligibility criteria, these subjects will not be enrolled until 3 to 4 weeks after screening (at least 21 days after treatment).

---

### 5.8.2 Rescreening

Subjects do not need to be rescreened if enrollment is within 45 days of initial screening. If more than 45 days, Informed Consent and Screening Visit assessments/procedures should be repeated.

### 5.8.3 Enrollment/Visit 1 (Week 0 ±7 days)

Subjects must be asked to abstain from vaginal intercourse in the 24 hours preceding Study Visit 1. The following will be recorded by research staff in the source documents and CRF:

1. Evaluation of inclusion and exclusion criteria
2. Evaluation of eligibility criteria
3. Demographic data
4. Completed Female Sexual Function Index (FSFI) and Sexual Function Questionnaire (SFQ)
5. Updated Medical/surgical/gynecologic/sexual history
6. Last menstrual period (date, if known)
7. Concomitant medication: all medications taken will be recorded in standard data collection forms with attention to drug route, daily dose, duration, start date, stop date and indications
8. Body height and weight
9. Vital sign measurements (blood pressure, heart rate, temperature)
10. Physical exam
11. Pregnancy test (urine)
12. Vaginal pH\*
13. Clinician-collected vaginal swab for CT and GC NAATs
14. Gynecologic examination\* (speculum, performed by clinician)
15. Randomization and issuance of study product (4-week supply based subject estimation of projected use)
16. Instructions on eDiary setup and use

*\*Swab for vaginal pH reading is collected prior to introduction of speculum for gynecologic exam.*

Should subject be menstruating at time of scheduled visit, the visit may be rescheduled during the 7-day visit window, if possible.

Randomization, training, and verification of subject understanding, competency, and willingness to administer study product as directed is documented prior to issuance of study product.

If a subject's CT/GC NAAT results are positive at the enrollment visit, the subject should be immediately terminated from the study, IP accountability conducted, and all used/unused kits

returned to the clinic. An Early Termination Visit should be performed to complete all procedures indicated for Visit 5 with the exception of repeat GC/CT NAAT testing. The subject should have SOC treatment for the infection and should be encouraged to return for a post-intervention follow-up visit approximately 4 weeks  $\pm$  7 days from Early Termination Visit or last IP use.

#### **5.8.4 Visits 2 Through 4 (Weeks 4-12 $\pm$ 7 days)**

Subjects must be asked to abstain from vaginal intercourse in the 24 hours preceding Study Visits 2 through 4. The following will be performed, and research staff will record results in the source documents and CRF:

1. Changes in the following since Screening Visit:
  - a. AEs
  - b. Concomitant medications
2. Pregnancy test (urine)
3. Self-collected vaginal swab for CT and GC NAATs
4. Targeted physical exam, if needed based on symptoms
5. Subject diary review (sexual activity, product use since last visit)
6. Return of all unused study product and used applicators
7. Issuance of additional study product (4-week supply based on prior month's usage or per subject estimation of projected use)

#### **5.8.5 Visit 5 (Week 16 $\pm$ 7 days)**

Subjects must be asked to abstain from vaginal intercourse in the 24 hours preceding Study Visit 5. The following will be performed, and research staff will record results in the source documents and CRF:

1. Changes in the following since last visit:
  - a. AEs
  - b. Concomitant medications
2. Pregnancy test (urine)
3. Self-collected vaginal swab for CT and GC NAATs
4. Targeted physical exam, as needed, based on symptoms
5. Subject diary review (sexual activity, product use since last visit)
6. Completed FSFI, SFQ, subject satisfaction with product, and subject sexual satisfaction questionnaires

---

7. Return of all unused study product and used applicators

**5.8.6 Post-intervention Follow-up Visit/Visit 6 (Week 20 ±7 days)**

The following will be performed, and research staff will record results in the source documents and CRF:

1. Changes in the following since last visit:
  - a. AEs
  - b. Concomitant medications
2. Pregnancy test (urine)
3. Self-collected vaginal swab for CT and GC NAATs. This is not required for subjects who were withdrawn due to positive CT or GC NAAT
4. Targeted physical exam, as needed based on symptoms
5. Subject diary review (sexual activity since last visit)

**5.9 Unscheduled Visit(s)**

The subject will be asked to return to the study site for evaluation if she develops symptoms or signs of illness and needs to be evaluated between scheduled visits. A targeted physical examination, as dictated by the symptoms, will be performed. Safety or other laboratory tests will be obtained as deemed necessary by the Investigator. Findings will be documented in the source documents and eCRF for unscheduled visits. AE assessment (including SAEs) will be recorded in the source documents and eCRF.

Subjects will be asked to contact the study site to obtain additional study product should their monthly supply be depleted in advance of their next scheduled visit.

**5.10 Early Termination**

If a subject who has received study product withdraws or is withdrawn, an early termination visit will be conducted if the subject is willing. All activities listed for Visit 5 will be carried out unless medically contraindicated. CT and GC NAAT is not required at the Early Termination Visit if subject is being withdrawn due to positive GC or CT NAAT.

**5.11 Clinical Laboratory Specimen Preparation, Handling and Storage**

All laboratory specimens collected during study visits will be collected and processed by a trained study research team member, following site SOPs, MOPs, and all applicable site and local safety committee safety guidelines. All samples collected for uHCG will be tested onsite.

---

Vaginal swab specimens collected for NAATs will be processed, stored, and shipped to the central laboratory for testing as described in the MOP.

Returned applicators will be collected from subjects at each visit. Trained study staff will perform staining on used applicators onsite as described in the MOP.

---

## **6 Safety Reporting and Safety Monitoring**

Since this clinical study is being conducted exclusively in the US, FDA regulations including safety monitoring and reporting responsibilities of Sponsor and Investigators must be followed to ensure the safety and protection of human subjects and accuracy of the data collected.

### **6.1 Responsibilities**

Investigators participating in this clinical study are required to:

- Evaluate subject safety including assessment of AEs for seriousness, severity, and causality
- Notify the ICON GPHS Medical Monitor of SAEs within 24 hours of becoming aware of them
- Provide detailed written reports, including necessary documentation requested by the Sponsor or IRB, promptly following immediate initial reports
- Inform the IRB of AEs as required by applicable regulatory requirements

### **6.2 Definitions**

#### **Adverse Event (AE)**

Any untoward medical occurrence in a clinical investigation subject who has received a study product intervention and that does not necessarily have to have a causal relationship with the study product. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a study medicinal product, whether or not considered related to the study medicinal product.

#### **Serious Adverse Event (SAE)**

An SAE is any adverse event that results in any of the following outcomes:

- Death
- Life-threatening (immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability or incapacity
- Congenital anomaly/birth defect

- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

The term “life-threatening” in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

The term “hospitalization” describes a period of at least 24 hours. Overnight stay for observation, treatment at an emergency room or treatment on an outpatient basis does not constitute a hospitalization. However, medical judgment must always be exercised and when in doubt the case should be considered serious.

### **Non-serious Adverse Event**

A non-serious AE is any AE which does not fulfill the definition of an SAE.

### **Treatment-emergent Adverse Event (TEAE)**

A TEAE is any AE occurring after the application of the study product and within the time of residual product effect, or pre-existing medical condition that worsens in intensity after the application of study product and within the time of residual product effect. The time of residual product effect is 7 days after the dose of the study product, when the effect of the product is still considered to be present based on change of vaginal pH from baseline.

### **Unexpected Adverse Reaction**

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigational New Drug (IND) Safety Data; see Investigator’s Brochure).

## **6.3 Safety Reporting Requirements**

### **6.3.1 Reporting Interval**

All AEs and SAEs will be collected and recorded following randomization.

The Investigators will follow all AEs that are deemed at least possibly related to investigational product and SAEs until resolution (return to pre-intervention status or stabilization of conditions deemed as chronic), even if this extends beyond the study-reporting period.

---

A subject will be considered as lost to follow-up if participation in AE assessment is not continued after:

- Three unsuccessful attempts at telephone contact (separated by at least 24 hours) following missed AE assessment visit or telephone consultation; followed by
- Issuance of a certified letter to last documented address of subject, and no response within 7 days of mailing

At any time after the completion of the study, if an Investigator becomes aware of an SAE that is suspected to be related to the investigational product, the Investigator will report the event to ICON GPHS within 24 hours of awareness. The Investigator will ensure that the appropriate IRB has been notified of the reported SAE in a timely manner per internal IRB reporting requirements.

### **6.3.2 Notification of the Sponsor of Serious Adverse Events**

Any AE that meets a protocol-defined serious criterion, must be submitted within 24 hours of site awareness.

The Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

Other supporting documentation of the event requested by the Medical Monitor should be provided.

The Sponsor will be notified of any unexpected SAE with suspicion of being related to study drug. In addition, the Sponsor will be informed of any study procedure-related SAE which may warrant a change of any study procedure or halting of the study.

### **6.3.3 Regulatory Reporting for Studies Conducted Under Investigational New Drug Application**

The Sponsor is responsible to report both serious and unexpected events that are associated with investigational product(s) to the FDA within the required timelines as specified in 21 CFR 312.32 (fatal and life-threatening events within 7 calendar days by phone or fax and all other SAEs in writing within 15 calendar days). All serious events designated as “not associated” to investigational product(s) will be reported to the FDA at least annually in a summary format.

## **6.4 Investigator’s Assessment of Adverse Events**

The determination of seriousness, severity, and causality will be made by a site Investigator.

---

### 6.4.1 Assessment of Severity

Each AE will be assessed by the Investigator with regard to the following categories:

#### Seriousness

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening; this means that the subject is at risk of death at the time of the event, and 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 that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of 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 electronic data capture (EDC) system. The most likely cause of an AE (eg, 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:

- Certain
  - 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 (ie, an objective and specific medical disorder or a recognized pharmacological phenomenon)
  - Rechallenge satisfactory, if necessary
- Probable/Likely:
  - Event or laboratory test abnormality, with reasonable 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
- Conditional/Unclassified:
  - Event or laboratory test abnormality
  - More data for proper assessment needed, or
  - Additional data under examination

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

#### **6.4.2 Adverse Event Outcome Measures**

The outcome of all AEs will be reported based on the following definitions, independent of whether they are serious or non-serious AEs, their severity, or their relationship to the investigational product:

- Recovered: fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first study-related activity after the subject signed the informed consent
- Recovering: the condition is improving and the subject is expected to recover from the event. This term should only be used when the subject has completed the study
- Recovered with sequelae: as a result of the AE, the subject suffered persistent and significant disability/incapacity (eg, became blind, deaf, paralyzed). Any AE recovered with sequelae should be rated as an SAE
- Not recovered
- Fatal
- Unknown: this term should only be used in cases where the subject is lost to follow-up

#### **6.5 Study-related Adverse Events**

See **Appendix A** for descriptions and grading criteria for anticipated study-related AEs. All AEs will be documented on the standard AE forms. AE forms for cutaneous AE grade 3 or higher will be sent to the Medical Monitor within 24 hours of awareness (non-serious or serious).

The reporting of an AE grade 3 or higher will prompt follow-up diagnostic work-up (eg, physical examinations, vital signs, descriptive assessment, subject diary, and clinical laboratory work). If the cutaneous AE is grade 3, subjects will be seen twice weekly until the severity is reduced to grade 2 or less at two consecutive follow-up visits (1 week) and not getting worse.

#### **6.6 Other Safety Considerations**

Any significant worsening or new findings noted during post-intervention follow-up visit or any other potential safety assessments performed during the study, whether or not they are required by the protocol, should be recorded on the appropriate AE form.

---

### 6.6.1 Follow-up of Adverse Events

During and following a subject's participation in a clinical study, the Investigator should ensure that adequate medical care is provided to the subject for any AEs, including clinically significant laboratory values related to the study. The Investigator should inform the subject when medical care is needed for AEs.

The period for reporting new AEs will continue until the post-intervention follow-up visit (final study visit).

All non-serious AEs classified as possibly/probably related to the investigational product must be followed until the subject has recovered and all queries have been resolved. However, cases of chronic conditions can be closed if determined by clinician as stable, with an outcome of "recovering" or "not recovered." If a subject died from another event, these cases can be closed with an outcome of "not recovered."

All other non-serious AEs must be followed until the outcome of the event is "recovering" (for chronic conditions), or until the end of the post-intervention follow-up stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. If a subject died from another event, these cases can be closed with an outcome of "not recovered."

The Investigator must enter follow-up information about non-serious AEs on the AE form within the CRF.

Queries or follow-up requests from ICON GPHS should be responded to within 14 calendar days, unless otherwise specified. The Investigator must forward follow-up information on SAEs to the requestor within 5 calendar days of obtaining the request for follow-up information.

All SAEs must be followed until the outcome of the event is recovered, recovered with sequelae, or fatal and until all queries have been resolved. For cases of chronic conditions and cancer or if the subject dies from another event, follow-up until the outcome categories are "recovered," "recovered with sequelae," or "fatal" is not required, as these cases can be closed with an outcome of "recovering" or "not recovered."

### 6.6.2 Pregnancy

While women of childbearing potential are eligible for the study, they must agree to use an approved form of birth control (see Section 3.1 Inclusion Criteria) over the duration of the study period. Women of childbearing potential are defined as any female who has experienced menarche and who is NOT permanently sterile or postmenopausal. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause. If there is any

---

question that a subject will not be reliable in the adherence to this requirement, they should not be entered into the study.

Study subjects must be instructed to notify the study site Investigator immediately if they suspect pregnancy during the course of the study and for a period of 4 weeks following study discharge. Subjects who become pregnant will be instructed to immediately discontinue study product. The Investigator must report any pregnancy during the study to the Medical Monitor within 14 calendar days of obtaining the information using the Pregnancy Form and the Pregnancy Follow-up Form, respectively. Pregnancy complications must be recorded as AEs or SAEs if meets criteria. If the infant has a congenital anomaly or birth defect, the anomaly or defect must be reported and followed as an SAE.

---

## **7 Clinical Monitoring/Site Monitoring Plan**

Monitoring will be conducted to ensure that human subject rights and well-being are protected, data are accurate, complete, and verifiable from source documents, and the study complies with the protocol/amendment(s), and applicable regulatory requirements.

In order to ensure protocol compliance, monitoring visits will occur at scheduled intervals prior to, during, and at study completion. The visit frequency will be defined in a monitoring plan and communicated to the Investigators.

A separate study-specific monitoring plan will define the monitoring details such as the frequency of monitoring visits and percentage and selection of charts/source documentation to be monitored. An ICON GPHS CRA will be responsible for the clinical monitoring at the study sites. The CRA will operate independently from the study sites and will comply with ICON GPHS SOPs. The CRA will ensure that the Investigators understand the investigational status of the study product, all requirements of the protocol, and his/her regulatory responsibilities as an Investigator. The CRA will visit the clinical site in accordance with the monitoring plan to assess compliance with the protocol, verify accuracy and completeness of the data, perform accountability of study product, and review essential regulatory documents.

The investigational sites will provide direct access to all study-related documents and records maintained by the Investigators, including but not limited to study-related source data for the participants in this study.

The Investigators are ultimately responsible for ensuring that the CRA's findings are addressed.

---

## 8 Statistical Considerations

This section outlines the basic statistical approach for the study. A final statistical analysis plan will be written and approved before the database lock. This plan will specify all statistical methods and plans for analysis.

### 8.1 Study Hypotheses

The hypothesis to be tested in this study is that AMPHORA will prevent the sexual transmission of CT. As noted above, CT infection in women is associated with higher vaginal pH (pH >4.5) (10). This finding is supported by other reports in the literature (7). In addition, a higher vaginal pH has been associated with increased transmission of GC (28). AMPHORA also contains a relatively high concentration of lactic acid (1.8% w/v). Lactobacilli inactivate CT through the production of lactic acid (29). Thus, AMPHORA should reinforce the ability of lactobacilli to maintain healthy levels as well as provide additional lactic acid that may act directly in preventing CT infection.

### 8.2 Sample Size Considerations

The primary analysis is a comparison between proportion of subjects who experience at least one CT infection among the intervention groups (AMPHORA or placebo).

It is assumed that the proportion of subjects experiencing at least one infection of CT during the study period (incident infection of CT) up to Week 16 under placebo will be 22.5%. An incident infection of CT of 13% in the subjects receiving active treatment (ie, a treatment difference of 9.5%) is considered clinically relevant for AMPHORA versus placebo. Using a Chi-square test for the primary endpoint, 253 analyzable subjects per treatment group (506 subjects total in the ITT population) will yield approximately 80% power to detect 9.5% treatment difference with a 2-sided 5% type I error rate (SAS 9.3 PROC POWER). Assuming that 20% of the total enrolled subjects will be lost to follow-up, 15% will be re-infected with GC (making them ineligible for the primary endpoint analysis), and 5% will be deemed ineligible for analysis due to antibiotic use, the total sample size planned for this study is 844 subjects.

### 8.3 Final Analysis Plan

#### 8.3.1 Analysis Populations

This study will utilize three analysis populations: Intention-to-Treat (ITT), modified Intention-to-Treat (mITT), and safety.

The ITT population will consist of all randomized subjects. The mITT population will consist of all randomized subjects who are negative for chlamydia and gonorrhea at enrollment and report

use of study product prior to at least one coital event. Lastly, the safety population will be based on subjects who applied any amount of study product.

Analyses using the ITT and mITT populations will be performed based on the treatment randomized. Meanwhile, safety analyses will be based on the treatment received.

### **8.3.2 Randomization and Stratification**

A randomized study group assignment schema, stratified by study site, will be developed using SAS, release 9.3 or higher.

### **8.3.3 Procedures for Handling Missing, Unused, and Spurious Data**

All analyses will be based on data as observed in the study. No imputations will be performed for data that are missing or spurious.

Given the need to provide treatment to subjects who become infected with CT and/or GC, not all subjects will be evaluable for each endpoint since the use of antibiotics would treat both possible infections. Therefore, the subjects analyzed for the primary efficacy endpoint are those that are infected with CT or who complete the study with no re-infections. Likewise, the subjects analyzed for the secondary efficacy endpoint are those that are infected with GC or who complete the study with no re-infections.

### **8.3.4 General Statistical Considerations**

All subjects that enter the study will be accounted for in the final clinical report, whether or not they are included in the analysis. All reasons for exclusion will be documented for those subjects.

For continuous variables, descriptive statistics will include the number of non-missing values, mean, standard deviation, median, minimum, and maximum. For categorical variables, descriptive statistics will include counts and percentages per category.

Baseline values for all parameters will be the most recent value prior to administration of study product or speculum exam.

## **8.4 Planned Statistical Methodology**

### **8.4.1 Data Analysis for Efficacy**

For the primary analysis, the proportion of subjects who experience at least one CT infection will be compared between the intervention groups (AMPHORA or placebo) using a Chi-square test.

The primary efficacy analysis will be completed using the subjects deemed analyzable (see Section 8.2) from the mITT population.

The primary statistical hypothesis being tested is that there is no difference in the proportion of subjects with CT infections in the AMPHORA intervention group versus placebo. In statistical terms:

$$H_0: p_{\text{AMPHORA}} = p_{\text{placebo}}, H_A: p_{\text{AMPHORA}} \neq p_{\text{placebo}}$$

where  $p_{\text{AMPHORA}}$  and  $p_{\text{placebo}}$  denote the proportion of subjects with CT infections during the study while on AMPHORA or placebo, respectively. Denominators for percentages are number of subjects in the mITT population in each intervention group. To test superiority over placebo, the incident infection of CT will be compared against placebo based on a Chi-square test. The estimated difference in proportions, 95% confidence interval, and p-value will be presented. A two-sided 5% type I error rate ( $\alpha=0.05$ ) will be used.

Similar analyses will be performed for incident infection of GC.

#### 8.4.2 Data Analysis for Safety

All AEs will be coded using the Medical Dictionary for Regulatory Activities® (MedDRA) v17.0 or higher. The incidence of AEs (new or worsened) will be summarized by primary system organ class, preferred term, severity, and relationship to study intervention. The incidence of death, SAEs, and AEs leading to discontinuation will be summarized separately by primary system organ class and preferred term.

#### 8.4.3 Analyses for Exploratory Objectives and Endpoints

Adherence with AMPHORA usage during study (rate of product use adherence) will be measured by inspection/analysis of returned gel applicators and eDiary data. Summary statistics of adherence overall and by intervention group will be provided.

Based on the adherence rate for each subject, sensitivity analyses will be conducted in the same manner as the primary and secondary endpoint analyses to examine if the level of re-infection between treatment groups differs for  $\geq 20\%$ ,  $\geq 40\%$ ,  $\geq 60\%$ ,  $\geq 80\%$ , and 100% adherence rates. These sensitivity analyses will be performed on the mITT population.

Subject satisfaction with the study drug (including sexual satisfaction in **Appendix E**) will be summarized using frequency and percentage.

Subject sexual satisfaction will be measured utilizing baseline and follow-up questions on the impact of study drug on sexual function with the SFQ and item 10 on the FSFI. These scores and responses will be summarized using frequency and percentage.

---

## **9 Data Handling/Recordkeeping/Source Documents**

It is each Investigator's responsibility to ensure that all team members appropriately handle all data and related documentation. All subject information, including source documents and laboratory reports, must be reviewed by the Investigator and clinical team and submitted to the ICON GPHS Data Management Team via eCRF. ICON GPHS Data Management will work with the Investigators and CRAs to develop a data management plan, including eCRF creation and instructions for the study to establish, maintain, and update the study data effectively. Clinical data will be entered directly from the source documents to the data management system within 72 hours of study activity to maintain up-to-date information on all clinical and laboratory data. There will be ongoing processing of data and quality checks. CRAs will be responsible for source verification of the eCRFs.

Data security is of paramount concern. A comprehensive IT Systems Security Plan with a disaster recovery plan is in place to safeguard data systems related to this clinical study.

### **9.1 Data Capture Methods**

Clinical data (including AEs and concomitant medications) will be entered into the Clinical Studio EDC system. This system is a 21 CFR 11-compliant internet data entry system provided by the ICON GPHS Data Coordinating Center. Only those who are trained and delegated the responsibility by the Investigator (with delegation documented on the signature delegation log) will collect and enter data. The data system includes password protection and internal quality checks, such as heuristic checks, to identify data that appear inconsistent, incomplete, or inaccurate.

### **9.2 Types of Data**

Data for this study will include reported symptoms, AEs, clinical laboratory data, adherence with AMPHORA usage from eDiary data and applicator staining, and clinician-obtained baseline pH values.

Clinical data will be entered directly from the source documents. CRAs will perform source verification and query generation. CRAs will work with the Data Manager and site personnel to freeze data prior to analysis. AEs, medical history, and medications will be coded using MedDRA v17.0 (or higher) and WHO drug dictionaries.

### **9.3 Study Records Retention**

Each study site will maintain appropriate medical and research records for this study, in compliance with ICH E6 R1 Section 4.9, regulatory and institutional requirements for the

protection of confidentiality of subjects. The study site will permit authorized representatives of Evofem, Inc., ICON GPHS, and regulatory agencies to examine (and when required by applicable law, copy) clinical records for the purposes of clinical site monitoring, quality assurance reviews, audits, and evaluation of the study safety and progress. A site master file will be maintained to include essential documents.

Study documents will be retained for a minimum of two years after the last marketing application approval or two years from the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period, if required by local regulations. No record will be destroyed without the written consent of Evofem, Inc.

#### **9.4 Source Documents**

The source document is defined as the first place the data are recorded, eg, hard copy paper and/or electronic forms, laboratory printouts, and medical records. The study sites may use study-specific paper data collection forms that mirror each EDC form to enter data from the source (the subject's chart, eDiary data, or other medical records) onto the form provided. Clinical and research laboratory reports will be printed from the laboratory system and utilized as source documents. Clinical data will be entered directly from the source documents to the data management system within 72 hours of study activity to maintain up-to-date information on all clinical and laboratory data protocol deviations.

#### **9.5 Protocol Deviations**

A protocol deviation is any noncompliance with the clinical study protocol or GCP requirements. The noncompliance may be either on the part of the subject, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

Investigation of the protocol deviations will be conducted by the study team, especially the Investigator, to assess whether the deviation is due to a subject-specific issue, or whether there is an underlying structural or operational aspect of the research process and protocol which may require correction or revision.

It is the responsibility of the Investigator to use continuous vigilance to identify and report deviations by entering the information into the clinical database within three working days of identification of the protocol deviation or of the scheduled protocol-required activity.

Appropriate reporting forms must be maintained in the regulatory file as well as in the subject's source document. The Investigator is responsible for ensuring all study staff understand the IRB reporting guidelines and adhere to all related requirements and documentation. A cumulative list of protocol deviations will be reported in the clinical study report.

Refer also to Section 10 Quality Control and Quality Assurance.

---

## **10                      Quality Control and Quality Assurance**

The Clinical Quality Management Plan (CQMP) is developed by ICON GPHS. The CQMP outlines quality control (QC) and quality assurance (QA) processes to be applied to protocol activities at the clinical sites.

The ICON GPHS QA Specialist will develop, implement, and oversee all functions of the CQMP. The Investigators are responsible for the oversight and implementation of the CQMP at their respective clinical sites. The site roles and responsibilities are to submit protocol deviation logs, AE/SAEs, and screening and enrollment logs within required time intervals.

The QC of study-related records will be performed by the site's clinical staff. Prior to data entry, study visit documentation will be reviewed for accuracy and completeness.

Through periodic verification of data collected for this protocol, ICON GPHS QA activities document compliance with GCP standards, human subjects' protections, and applicable federal regulations governing the use of investigational products. Key quality indicators, as detailed in the CQMP and applicable to the protocol, will be examined in each subject record selected for QA review.

Study records will remain onsite in a secure location. The clinical site will permit ICON GPHS, the Sponsor, and other applicable regulatory authorities access to study-related records.

---

## **11 Ethics/Protection of Human Subjects**

### **11.1 Ethical Standard**

The study sites will ensure compliance with the legal and ethical obligations for the conduct of clinical research involving human subjects, with the key regulations and ethical standards implemented as follows:

- Title 21 CFR 50, Subpart A: General Provisions and Subpart B: Informed Consent, FDA
- Title 21 CFR 56, Subparts A-E: Institutional Review Boards
- FDA Information Sheets: Guidance for IRBs and Clinical Investigators, 1998 Update
- International Conference on Harmonisation GCP (ICH E6 R1): Consolidated Guideline, June 1996
- The Belmont Report

### **11.2 Institutional Review Board**

Prior to initiation of the study, the study protocol, investigator brochure, sample informed consent form, and any other documents that pertain to subject information and recruitment methods such as advertisements, will be submitted to a centralized and/or local IRB. Any other information that may be requested by the IRB for review and approval will also be submitted.

Approval from the IRB for all subsequent protocol amendments and changes to the informed consent form will be obtained. The IRB will be notified of protocol deviations as well as AEs and SAEs occurring at the site, in accordance with regulatory requirements.

Each IRB will review and approve the study protocol and subject informed consent form. After approval by the committee, the following documentation must be sent to the study manager or designee before the study commences:

- Confirmation of IRB approval of the protocol
- Confirmation of IRB approval of the informed consent form and applicable addenda
- A list of IRB members, their representative capacity, and their affiliation (a Health and Human Services General Assurance number will suffice)

---

## **12 Informed Consent Process**

The informed consent process will be initiated before a volunteer agrees to participate in the study and should continue throughout the individual's study participation. The subject will sign the informed consent document before any procedures are undertaken for the study. A copy of the signed informed consent/assent document will be given to the subject or the legal guardian for their records. The consent will explain that subjects may withdraw consent at any time throughout the course of the study. Extensive explanation and discussion of risks and possible benefits of this investigation will be provided to the subjects in understandable language. Adequate time will be provided to ensure that the subject has time to consider and discuss participation in the protocol.

The consent forms will describe in detail the study interventions/products/procedures and risks/benefits associated with participation in the study. The rights and welfare of the subjects will be protected by emphasizing that their access to and the quality of medical care will not be adversely affected if they decline to participate in this study.

### **12.1 Subject Confidentiality**

Subject confidentiality is strictly held in trust by the participating Investigators, their staff, and the Sponsor and their agents. This confidentiality includes documentation, investigation data, subject's clinical information, and all other information generated during participation in the study.

No information concerning the study or the data generated from the study will be released to any unauthorized third party without prior written approval of the Sponsor and the subject.

The study monitor or other authorized representatives of the Sponsor or governmental regulatory agencies may inspect all documents and records required to be maintained by the Investigators, including but not limited to, medical records (office, clinic, or hospital) for the subjects in this study. The clinical study site will permit access to such records.

---

## **13                      Confidentiality Policy**

The information obtained during the conduct of this study is considered confidential and can be used by Evofem, Inc., for regulatory purposes and for the general development of the investigational product. All information supplied by Evofem, Inc., in connection with this study shall remain the sole property of Evofem, Inc., and is to be considered confidential information. No confidential information shall be declared to others without prior written consent from Evofem, Inc. Such information shall not be used except in the performance of this study. The information obtained during this study may be made available to other physicians who are conducting other clinical studies with the investigational product, if deemed necessary by Evofem, Inc.

---

## **14                      Publication Policy**

Evoform, Inc., is the IND Sponsor. Evoform, Inc., will assume responsibility for registering the study in the National Library of Medicine registry (<https://www.clinicaltrials.gov>). In compliance with Public Law 110-85, the FDA Amendments Act of 2007 (FDAAA), Evoform, Inc., will also post results of the study.

## 15 Summary of Changes

**Table 3 Summary of Changes**

Version Number	Effective Date	Summary of Changes
1.0	24 Mar 2017	Original protocol
2.0	19 Sep 2017	<p>Editorial changes and additional detail added throughout</p> <p>Title Page – added CRO information, updated AMPHORA name</p> <p>Signature page for the Investigator added</p> <p>Original Section 2 – Protocol Summary changed to Protocol Synopsis, updated, and moved to front for easier reference</p> <p>Original section 3 – removed (included elsewhere in study documentation)</p> <p>Original Section 4.3 – removed (included in Investigator’s Brochure)</p> <p>Sections renumbered</p> <p>Original Section 5; new Section 2 – added requirement for subjects to be treated to the clinical site’s standard of care for STI prevention including condom provision</p> <p>Original Section 6.2; new Section 3.2 – added/revised exclusion criteria 2, 3, 4, 5, 13, 16</p> <p>Original Section 6.4; new section 3.4 – revised randomization scheme to include IWRS</p> <p>Original Section 6.6.1; new Section 3.6.1 – clarified/expanded reason for withdrawal</p> <p>New Section 3.7 – added completer criteria</p> <p>Original Section 7.1; new section 4.1 – updated the description of AMPHORA, removed intellectual property information</p> <p>Original Section 7.1.5; new Section 4.1.5 – clarified amount of study product to be dispensed at each visit</p> <p>Original Section 8.8; new Section 5.8.1 – revised list of procedures performed</p> <p>Original Section 8.8; new Section 5.8.3, 5.8.4, 5.8.5 – added requirement for subjects to abstain from intercourse 24 hours prior to the visit; removed condom issuance</p> <p>Original Section 9.2; new Section 6.2; removed “Pre-intervention adverse event” definition</p> <p>Original Section 9.4.1 – removed (duplicative)</p>

Version Number	Effective Date	Summary of Changes
		<p>Original Section 9.6.2; new Section 6.6.2 – clarified pregnancy reporting process</p> <p>Original Section 7 – removed (not necessary due to extensive prior clinical testing)</p> <p>Original Section 11.2; new Section 8.2 – increased sample size to 844 subjects</p> <p>Original Section 11.3 – removed (not necessary)</p> <p>Original Section 11.4.3; new Section 8.3.3 – clarified evaluable subjects</p> <p>Original Section 11.5.3; new Section 8.4.3 – clarified exploratory analyses</p> <p>Appendix A – Schedule of Events changed to Schedule of Assessments, updated, and moved to front for easier reference</p> <p>Appendix B – removed (included in Investigator’s Brochure)</p>
2.1	10 Oct 2017	<p>Inclusion criterion #7 and exclusion criterion # 15 were updated to provide clarity on acceptable forms of contraception</p> <p>Section 5.1 – removed statement regarding ICH GCP</p> <p>Section 6.6.2 – included definition of women of childbearing potential</p>
3.0	11 Oct 2017	<p>Inclusion criterion #7 and exclusion criterion #15 were updated to provide clarity on acceptable forms of contraception</p> <p>Section 5.1 – removed statement regarding ICH GCP</p> <p>Section 6.6.2 – included definition of women of childbearing potential</p>
4.0	15 Mar 2018	<p>Inclusion criterion #1, age increased from 18-35 to 18-45</p> <p>Exclusion criterion #2 (consume on average more than three drinks of an alcoholic beverage...) was merged with exclusion criterion #3 (in the opinion of the investigator, has a history of substance or alcohol abuse within that last 12 months)</p> <p>Inclusion criterion #7 modified</p> <p>Exclusion criterion #15 may use NuvaRing</p> <p>Screening period increased from to 30-45 days</p> <p>Sites increased to 50</p> <p>Addition of exploratory measures (subject satisfaction, sexual satisfaction, SFQ, FSFI)</p>

Version Number	Effective Date	Summary of Changes
5.0	13 Aug 2018	<p>Exclusion criterion #11, antibiotic treatment increased to 21 days prior to enrollment to provide consistency throughout the protocol</p> <p>Screening eligibility, increase from 30-45 days modified for consistency</p> <p>Study schedule, location of Schedule of Assessments table clarified</p> <p>Inclusion Criterion #7 modified for consistency throughout the protocol</p> <p>Exclusion Criterion #9 modified for consistency throughout the protocol</p> <p>Prohibited medications, antibiotic treatment increased to 21 days to provide consistency throughout the protocol</p> <p>Appendix D, extra page removed</p>
6.0	21 Jan 2019	<p>Table 1 Schedule of Assessments and Section 3.6.2, clarified that procedures for V5 should be followed for Early Termination.</p> <p>Added CT/GC NAAT testing is not required at V5/Early Termination if termination from the study is due to positive CT/GC NAAT test.</p> <p>Inclusion Criterion #9 clarified and formatting/numbering corrected.</p> <p>Section 3.6 clarified that positive CT/GC NAAT test at enrollment is a reason for withdrawal.</p> <p>Section 5.8.3 updated Termination Visit procedures for positive CT/CG testing at enrollment.</p> <p>Section 5.8.6 updated self-collected vaginal swab for CT and GC NAATs not required for Post-Intervention Follow-up Visit if termination of study is due to positive CT/GC NAAT test.</p> <p>Section 6.4.1 SAE causality – returned to original language.</p> <p>Safety CRO changed to ICON GPHS throughout.</p>

---

## 16 Literature References

1. Centers for Disease Control and Prevention. Sexually Transmitted Disease Treatment Guidelines, 2015. MMWR Recomm Rep. 2015 June 15; 64(3).
2. Owusu-Edusei KJ,HW,TL,ea. The Estimated Direct Medical Cost of Selected Sexually Transmitted Infections in the United States, 2008. Sexually Transmitted Diseases. 2013 Mar; 40(3): p. 197-201.
3. Linhares IM SPLBGPWS. Contemporary perspectives on vaginal pH and lactobacilli. Am J Obstet Gynecol. 2011 Feb; 204(2): p. 120.e1-e5.
4. Boskey E, Cone R, Whaley K, Moench T. Origins of vaginal acidity: High D/L lactate ratio is consistent with bacteria being the primary source. Hum Reprod. 2001; 16: p. 1809-1813.
5. Kaewsrirach J, Peeyananjarassri K, Kongprasertkit J. Selection and identification of anaerobic lactobacilli producing inhibitory compounds against vaginal pathogens. FEMS Imm Med Microbiol. 2006; 8: p. 75-83.
6. Klebanoff J, Hillier L, Eschenbach D. Control of the Microbial Flora of the Vagina by H2O2-Generating Lactobacilli. The Journal of Infectious Disease. 1991; 164: p. 94-100.
7. Yasin B, Pang M, Wagar E, Lehrer R. Examination of Chlamydia trachomatis Infection in Environments Mimicking Normal and Abnormal Vaginal pH. American Sexually Transmitted Diseases Association. 2002; 29(9): p. 514-519.
8. Mahmoud E, Svenssen LO, Olsson SE, Mardh PA. Antichlamydial activity of vaginal secretion. Am J Obstet Gynecol. 1995; 172: p. 1268-72.
9. Schramm N, Bagnell C, Wyrick P. Vesicles Containing Chlamydia trachomatis Serovar L2 Remain above pH 6 within HEC-1B Cells. Infection and Immunity. 1996 Apr; 64(4): p. 1208-14.
10. Das S SCAS. Higher vaginal pH is associated with Chlamydia trachomatis infection in women: a prospective case-controlled study. International Journal of STD & AIDS. 2005 Apr; 16(4): p. 290-293.
11. McLaughlin S, Zenilman J, Ghanem K, Griffiss J. An Algorithm to Identify Neisseria gonorrhoeae Infection in Exposed Women. Poster. ; 2016.
12. Donders G, Bosmans E, Dekeersmaecker A. Pathogenesis of abnormal vaginal bacterial flora. Am J Obstet Gynecol. 2000 Apr; 182(4): p. 872-878.
13. Gupta K, Stapleton A, Hooton T, Roberts P, Fennell C, Stamm W. Inverse Association of H2O2-Producing Lactobacilli and Vaginal Escherichia coli Colonization in Women with Recurrent Urinary Tract Infections. The Journal of Infectious Diseases. 1998; 178: p. 446-50.
14. Pybus V, Onderdonk A. Microbial interactions in the vaginal ecosystem, with emphasis on the pathogenesis of bacterial vaginosis. Microbes and Infection. 1999;: p. 285-292.
15. Chernes T, Meyn L, Krohn M, Lurie J, Hillier S. Association between Acquisition of Herpes Simplex Virus Type 2 in Women and Bacterial Vaginosis. Clinical Infectious Disease. 2003 Aug; 37: p. 319-25.

16. Martin Jr. H, Richardson B, Nyange P, Lavreys L, Hillier S, Chohan B, et al. Vaginal Lactobacilli, Microbial Flora, and Risk of Human Immunodeficiency Virus Type 1 and Sexually Transmitted Disease Acquisition. *The Journal of Infectious Diseases*. 1990; 180: p. 1863-8.
17. Sobel J. Is There a Protective Role for Vaginal Flora? *Current Infectious Disease Reports*. 1990; 1: p. 379-383.
18. Watts D, Fazarri M, Minkoff H, Hillier S, Sha B, Glesby M, et al. Effects of Bacterial Vaginosis and Other Genital Infections on the Natural History of Human Papillomavirus Infection in HIV-1–Infected and High-Risk HIV-1–Uninfected Women. *The Journal of Infectious Diseases*. 2005; 191: p. 1129-39.
19. Wiesenfeld H, Hillier S, Krohn M, Landers D, Sweet R. Bacterial Vaginosis Is a Strong Predictor of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* Infection. *Clinical Infectious Diseases*. 2003; 36: p. 663-668.
20. Lai S, Hida K, Shukair S, Wang Y, Figueiredo A, Conoe R, et al. Human Immunodeficiency Virus Type 1 Is Trapped by Acidic but Not by Neutralized Human Cervicovaginal Mucus. *Journal of Virology*. 2009 Nov; 83(21): p. 11196-11200.
21. Taha T, Hoover D, Dallabetta G, Kumwenda N, Mtshayile L, Yang LP, et al. Bacterial vaginosis and disturbances of vaginal flora: association with increased acquisition of HIV. *AIDS*. 1998; 12: p. 1699-1706.
22. Pilipenko V, Bourne N, Zaneveld L, Garg S, Waller D, Stanberry L. New Nonoxynol-9 Formulation (ACIDFORM) Significantly Impacts Experimental Genital Chlamydia Infection in a Mouse Model. In ; 1999; Denver.
23. Spencer S, Valentin-Bon I, Whaley K, Jerse A. Inhibition of *Neisseria gonorrhoeae* genital tract infection by leading-candidate topical microbicides in a mouse model. *J Infect Dis*. 2004 Feb; 189: p. 410-419.
24. Friedland B, Stoner M, Chau M, Plagianos M, Govender S, Moror N, et al. Baseline Predictors of High Adherence to a Coitally Dependent Microbicide Gel Based on an Objective Marker of Use: Findings from the Carraguard Phase 3 Trial. In ; 2016. p. 2565-2577.
25. Hensel D, Fortenberry J, Harezlak J, Craig D. The feasibility of cell phone based electronic diaries for STI/HIV research. *BMC Med Res Meth*. 2012; 12: p. 75.
26. Hosenfeld C, Workowski K, Berman S, Zaidi A, Dysoon J, Mosure D, et al. Repeat Infection With Chlamydia and Gonorrhea Among Females: A Systematic Review of the Literature. *Sexually Transmitted Diseases*. 2009 Aug; 36(8): p. 478-489.
27. Schwartz J, Ballagh S, Kwok C, Mauck C, Weiner D, Rencher W, et al. Fourteen-day safety and acceptability study of the universal placebo gel. *Contraception*. 2007; p. 136-141.
28. Das S, Allan S. Higher Vaginal pH Is Associated With *Neisseria gonorrhoeae* and *Chlamydia trachomatis* Infection in a Predominantly White Population. *Sexually Transmitted Diseases*. 2006 Aug; 33(8): p. 527-528.
29. Gong Z, Luna Y, Yu P, Fan H. Lactobacilli Inactivate *Chlamydia trachomatis* through Lactic Acid but Not H<sub>2</sub>O<sub>2</sub>. *PLoS ONE*. 2014; 9(9).

## 17 Appendices

### Appendix A. Grading of Study-related Adverse Events

The table referenced below is a modification of the NCI Common Terminology Criteria for Adverse Events (v4.03, May 2009) tables, adjusted to display common AEs applicable to this study. A grading (severity) scale is provided for each AE term. A brief definition is provided to clarify the meaning of each AE term. Any clinical event deemed by the clinician to be serious or life threatening should be considered a Grade 4 event.

A semi-colon indicates ‘or’ within the description of the grade; a single dash (-) indicates a grade is not available. ADL = Activities of Daily Living.

#### **ESTIMATING SEVERITY GRADE**

For abnormalities NOT found elsewhere in the tables use the scale below to estimate grade of severity:

<b>GRADE 1</b>	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
<b>GRADE 2</b>	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
<b>GRADE 3</b>	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
<b>GRADE 4</b>	Life-threatening consequences; urgent intervention indicated.
<b>GRADE 5</b>	(Death) is not appropriate for some AEs and therefore is not an option.

\*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

\*\*Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

### Appendix B. Study-related Adverse Events

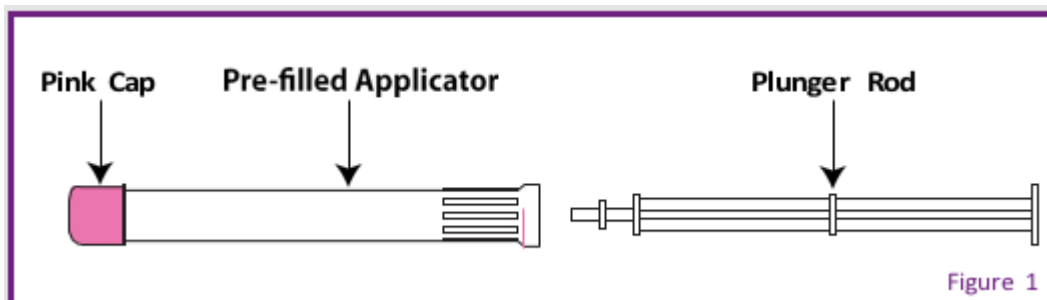
Adverse Event	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
<b>Vaginal inflammation</b> Definition: A disorder characterized by inflammation involving the vagina.	Mild discomfort or pain with edema or redness	Moderate discomfort or pain with edema, redness; limiting instrumental ADL	Severe discomfort or pain and edema, or redness; limiting self-care ADL; small areas of mucosal ulceration	Widespread areas of mucosal ulceration; life-threatening consequences; urgent intervention indicated	Death
<b>Vaginal pain</b> Definition: A disorder characterized by a sensation of marked discomfort in the vagina.	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-	-
<b>Vaginal burning</b> Definition: A disorder characterized by a sensation of marked burning in the vagina.	Mild burning	Moderate burning; limiting instrumental ADL	Severe burning; limiting self-care ADL		
<b>Vaginal pruritus</b> Definition: A disorder characterized by an uncomfortable feeling of itching and burning in the vagina.	Mild	Intense; intermittent; limiting instrumental ADL	Intense; constant; limiting self-care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	-	-

## Appendix C. Study Product Instructions for Use

### How to Use the Study Drug

#### Description

- Each single-use foil pouch contains a pre-filled applicator with a pink cap and a plunger rod (Figure 1).

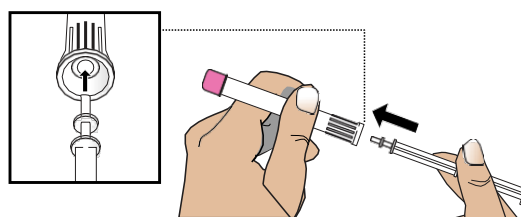


#### Important Use Information

- During your entire time in this study, use the Study Drug every time you have vaginal sex regardless of the time of the last application or even if you have sex more than once in a day. The Study Drug can be used immediately before or up to one hour before vaginal sex.
- If you or your partner develop burning or irritation of the vagina or penis or experience difficult or painful urination, discontinue use and consult your clinical site staff.

#### Instructions for Using the Study Drug

1.
  - Wash your hands with soap and water before opening the foil pouch.
  - Remove the pre-filled applicator and plunger from the foil pouch.
2. Gently insert the pointed end of the plunger into the opening inside the pre-filled applicator until the plunger lightly snaps in place (Figure 2). Be careful not to push the plunger farther after it snaps in place to avoid the release of any Study Drug into the cap.



3.

- Remove the pink cap from the pre-filled applicator (Figure 3). The pre-filled applicator is now ready for use.
- NOTE – space between the Study Drug and end of the applicator is normal.

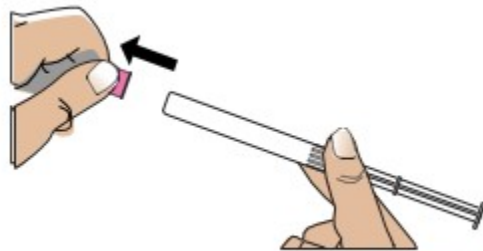


Figure 3

4.

- Hold the applicator at the grooved area closest to the plunger. Gently place the applicator into the opening of your vagina pushing it as far as it will comfortably go, similar to the placement of a tampon (Figure 4).
- NOTE - Lying on your back with your knees up may help with this step.

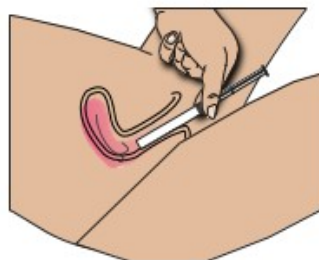


Figure 4

5. Using your index finger, push the plunger all the way into the barrel of the pre-filled applicator until it stops to ensure all the Study Drug has been applied (Figure 5).

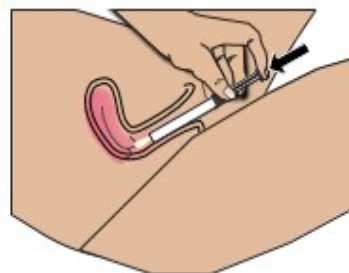


Figure 5

6.

- Gently withdraw the pre-filled applicator (Figure 6). Do not reuse the empty applicator or plunger. Place the used applicator in the resealable plastic bag provided (only one applicator per bag) and return along with all other used and unused applicators to next scheduled visit.
- The Study Drug gel is effective immediately after insertion. Vaginal sex should occur within one hour after insertion.



Figure 6

---

## **Appendix D. Subject Satisfaction with Product**

### **STUDY VISIT 5**

1. How satisfied are you with the study product?
  - a. Very satisfied
  - b. Satisfied
  - c. Somewhat satisfied
  - d. Somewhat dissatisfied
  - e. Dissatisfied
2. How likely is it that you would recommend this study product to a friend who is considering such a product?
  - a. Very likely
  - b. Likely
  - c. Somewhat likely
  - d. Somewhat unlikely
  - e. Unlikely
3. If you were still considered to be at risk of an infection, how likely would you be to continue with the use of this product if it were available after the study?
  - a. Very likely
  - b. Likely
  - c. Somewhat likely
  - d. Somewhat unlikely
  - e. Unlikely

---

## **Appendix E. Subject Sexual Satisfaction**

### **Study Visit 5**

What impact has the study product 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 F. Sexual Function Questionnaire (SFQ)

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, <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	<input type="checkbox"/>
b.	Lack of sexual interest or desire	1	2	3	4	5	<input type="checkbox"/>
c.	Vaginal tightness	1	2	3	4	5	<input type="checkbox"/>
d.	Pain during penetration or intercourse	1	2	3	4	5	<input type="checkbox"/>
e.	Anxiety about your sexual performance	1	2	3	4	5	<input type="checkbox"/>
f.	Unable to orgasm	1	2	3	4	5	<input type="checkbox"/>
g.	Vaginal bleeding or irritation from penetration or intercourse	1	2	3	4	5	<input type="checkbox"/>
h.	Increased sensitivity of your skin to intimate touching	1	2	3	4	5	<input type="checkbox"/>
i.	Sharp pain inside or outside your vagina	1	2	3	4	5	<input type="checkbox"/>
j.	Other problem with sexuality; Please specify:	1	2	3	4	5	<input type="checkbox"/>

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

---

## Appendix G. Female Sexual Function Index (FSFI)

### 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

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***