PROTOCOL SYNOPSIS

TITLE OF CLINICAL TRIAL:

Phase 3 double-blind placebo-controlled efficacy trial of EVO100 vaginal gel for the prevention of urogenital *Chlamydia trachomatis* and *Neisseria gonorrhea* infection

INVESTIGATIONAL PRODUCT(S):

After a screening period of up to 35 days, women will be randomized to receive either EVO100 or placebo:

EVO100 vaginal gel (previously known as Amphora) is supplied in individually wrapped 5 g single-dose, pre-filled vaginal applicators. EVO100 is a viscous, off white to tan gel of uniform consistency. Its active ingredients are lactic acid United States Pharmacopeia (USP), citric acid USP, and potassium bitartrate USP.

Universal placebo gel (UPG) is an isotonic non-buffering gel, containing 2.7% hydroxyethylcellulose, sorbic acid, sodium hydroxide, sodium chloride, and purified water and supplied in individually wrapped 5 g single-dose, pre-filled vaginal applicators.

CLINICAL PHASE: Phase 3

CLINICAL TRIAL OBJECTIVES:

Primary Objective:

- To evaluate the efficacy of EVO100 vaginal gel in the prevention of urogenital *Chlamydia trachomatis* (CT) and *Neisseria gonorrhea* (GC) infection

Secondary Objectives:

- To assess impact of EVO100 vaginal gel on overall sexual satisfaction and overall product satisfaction over the course of the clinical study
- To evaluate the safety of EVO100

Exploratory Objectives:

- To determine the impact of EVO100 vaginal gel use rate (subject adherence to instructed use) on the efficacy in the combined infections
- To assess other subject satisfaction with EVO100 vaginal gel over the course of the clinical study

OUTCOME MEASURES:

Primary:

- A composite endpoint, defined as a comparison between the proportion of subjects who are defined study successes vs study failures among the intervention groups (EVO100 or placebo) with success defined as subjects completing the trial to Visit 5 without any CT or GC infection.

Secondary:

The secondary outcomes for this study will be assessing the following proportion of subjects:

- with overall sexual satisfaction using the female sexual function index (FSFI) overall sexual

satisfaction question at Visit 5 and not having a CT or GC infection

- with overall sexual satisfaction using the FSFI overall sexual satisfaction question at visit 5
- reporting overall product satisfaction at Visit 5
- Incidence of adverse events (AEs) (descriptive analysis)

Exploratory:

Exploratory assessments include:

- Comparison of compliance with EVO100 vaginal gel usage vs placebo usage during study (rate of product use adherence vs placebo)
- Subgroup analyses of the primary endpoint (the proportion of subjects who are deemed success vs failure) will be performed for the following:
    - Subjects with 0%, >0% and <20%, ≥20%, ≥40%, ≥60%, ≥80% and 100% product use adherence
- Descriptive analysis of failure components defined as failures for the primary endpoint
- Comparison of PROMIS SexFS Satisfaction, Pain and Lubrication subscales with EVO100 vaginal gel usage vs placebo
- Comparison of FSFI Lubrication and Pain subscales with EVO100 vaginal gel usage vs placebo
- Comparison of Patient Global Impression of Change (PGIC) with EVO100 vaginal gel usage vs placebo

CLINICAL TRIAL DESIGN:

This is a Phase 3, double-blind, placebo-controlled study in approximately 90 sites in the United States (US) and European Union (EU) over approximately 16 weeks of use in women age ≥13 years who are at risk of urogenital CT or GC infection.

TREATMENT DURATION:

After a screening period of up to 35 days, women will be randomized to receive either EVO100 or placebo. Each woman will participate in the study until she has completed 16 weeks of treatment or observation or tests positive for CT or GC infection. This will include women who discontinue treatment but continue other study assessments to Visit 5. The intervention period is defined as Visits 1 to 5. There will be a follow-up visit (Visit 6) 4 weeks after the last intervention visit. Visits 5 and 6 will be combined for subjects who discontinue the study early. These periods are outlined in the Schedule of Assessments (Table 1). The protocol-defined period of observation is 20 weeks.

SAMPLE SIZE:

Assuming a two-sided alpha of 0.05, the failure rate for control subjects to be 32.5%, and the failure rate for the treatment subjects to be 25.5%, a sample of 881 subjects per treatment arm is needed (1762 subjects overall) to achieve 90% power. Anticipating approximately 5% of subjects will have non-negative CT/GC results in enrollment based on the Phase 2B/3 study data, this yields a sample size of 1856 women.

ANALYSIS POPULATION:

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 be the analysis population for the primary endpoint and will consist of all randomized subjects who are negative for chlamydia and gonorrhea at enrollment and are provided with study product. Lastly, the safety population will be based on subjects with documented use of any 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.

STUDY POPULATION:

Study Sites:

The study will be conducted at up to 90 clinical sites in the US and/or EU. Subjects will be selected for the study according to the eligibility criteria detailed below.

Inclusion Criteria:

1. Subjects must meet both of the following criteria:
   a. Healthy female subjects at least 13 years of age with a urogenital CT and/or GC infection (documented in a retrievable medical record) within the 16 weeks prior to enrollment and one or more of the additional risk factors included in point ii below:
      i. Acceptable documentation will include:
         1. Laboratory report(s) confirming CT and/or GC infection
         2. Copy of clinic note from the date of diagnosis confirming CT and/or GC infection and indicating the date of diagnosis and/or date of treatment
         3. Evidence of dispensed medication (from pharmacy records or clinic notes) for antibiotic therapy used for treatment of CT and/or GC
      ii. PLUS one or more of the following additional risk factor(s):
         1. 13 to 24 years of age at the screening visit
         2. New sex partner within the past 12 weeks (84 days)
         3. More than one current sex partner
         4. Knowledge that current sex partner has multiple partners
         5. Partner with known sexually transmitted infection (STI)
         6. Inconsistent condom use among persons who are not in a mutually monogamous relationship
   b. If medical record of previous infection cannot be obtained within two weeks of screening date, following three documented attempts to obtain the medical records, subjects may be enrolled only if they have two or more of the following risk factors, in addition to self-reported history of infection within 16 weeks prior to enrollment:
      i. 13 to 24 years of age at the screening visit
      ii. New sex partner within the past 12 weeks (84 days)
      iii. More than one current sex partner
      iv. Knowledge that current sex partner has multiple partners
      v. Partner with known STI
      vi. Inconsistent condom use among persons who are not in a mutually monogamous relationship

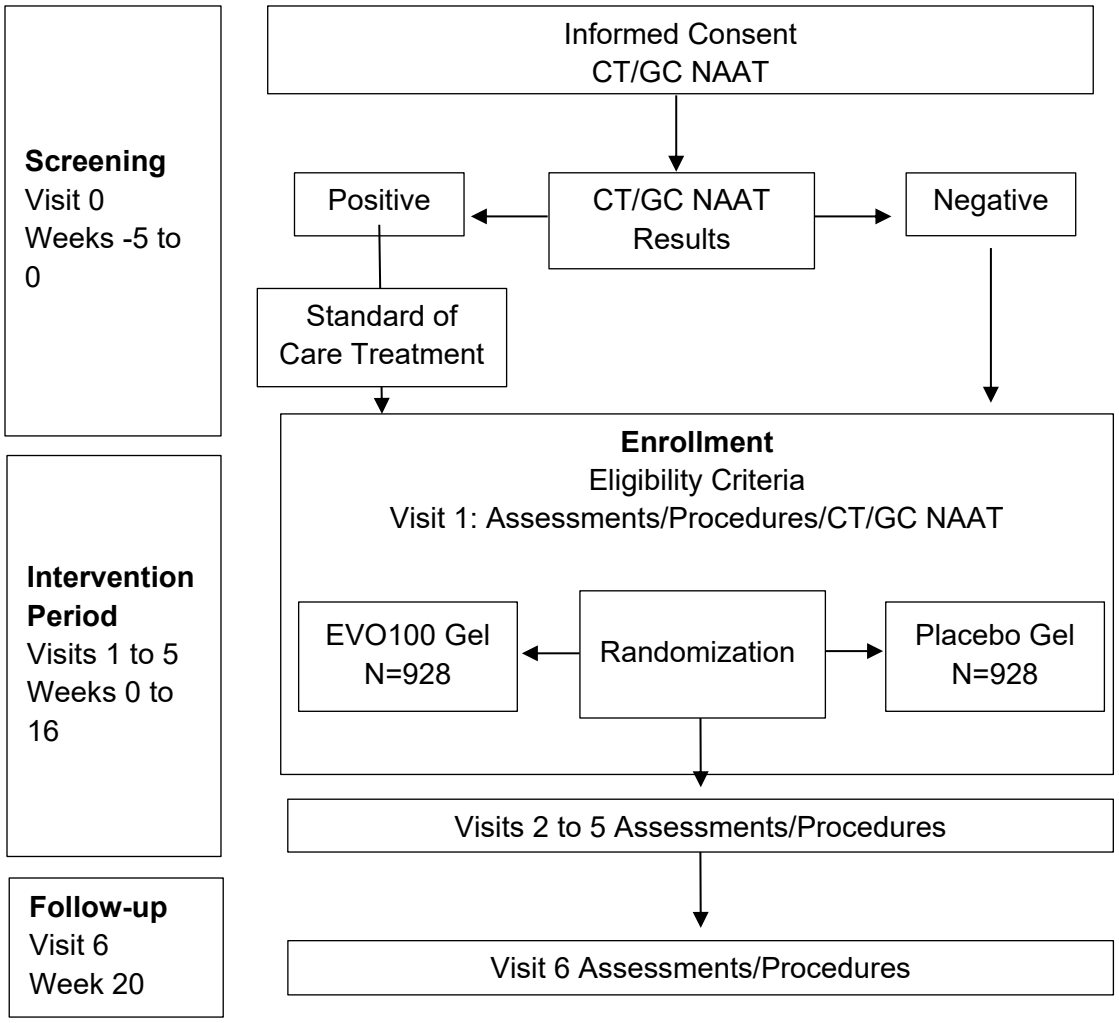
2. Ability to understand the consent process and procedures. For minors, the ability to obtain consent from parents/legal guardian and assent by minor subjects as applicable according to local regulations.
3. Agree to be available for all study visits including Visit 5 and follow-up Visit 6 and comply with follow-up on staff appointment reminders
4. Negative pregnancy test
5. Negative CT and GC nucleic acid amplification test (NAAT) at screening or positive CT or GC NAAT and receives standard of care (SOC according to CDC or World Health Organization [WHO] guidelines) treatment prior to enrollment with subsequent negative CT and GC NAAT testing at enrollment visit
6. 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
7. Able and willing to comply with all study procedures, including the use of eDiaries and reporting of all Adverse Events and concomitant medications.
8. 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
9. 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. Used Phexxi (lactic acid, citric acid, and potassium bitartrate) as a contraceptive vaginal gel within 7 days prior to enrollment (may be enrolled at a later date if all other criteria are met).
3. In the opinion of the Investigator, has a history of substance or alcohol abuse in the last 12 months
4. 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
5. Is a close relative of or is an Evofem, approved contract research organization (CRO), ICON, or clinical site employee regardless of direct involvement in research activities
6. Pregnant (or actively trying to become pregnant) or breastfeeding
7. Women who have undergone a total hysterectomy (had uterus and cervix removed). However, women with subtotal hysterectomy with an intact cervix may be enrolled
8. Inability to provide informed consent or assent
9. Has a history or expectation of noncompliance with medications or intervention protocol
10. Has 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)

11. Menstruating at enrollment (may be enrolled at a later date if all other criteria are met)
12. Is currently being treated, or has been treated, for a period of 21 days prior to enrollment, with any antibiotics. Note: Subjects will not be discontinued from study treatment post-randomization if treated with antibiotics for an infection other than CT or GC.
13. In the opinion of the Investigator, has signs/symptoms that indicate persistence of CT or GC 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
14. Women who regularly use douches, vaginal medications, vaginal products, or suppositories who do not agree to stop these products for the duration of the study
15. 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) or Phexxi (lactic acid, citric acid and potassium bitartrate)
16. Vulnerable populations, including children <13 years of age, pregnant women, prisoners, institutionalized persons, persons without decisional capacity, persons without phone and/or without domicile (homeless).

Figure 1 Schematic Flow of Study Design



Abbreviations: CT = *Chlamydia trachomatis*, GC = *Neisseria gonorrhea*, NAAT = nucleic acid amplification test