Protocol Title:	Phase 3 double-blind placebo-controlled efficacy trial of EVO100 vaginal gel for the prevention of urogenital *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infection (EVOGUARD)
Protocol Number:	EVO100-311
Protocol Version, Date	Version 4.0, May 26, 2021
Document Version, Date:	Final Version 2.0, April 6, 2022

Prepared by:

Premier Research

On behalf of:

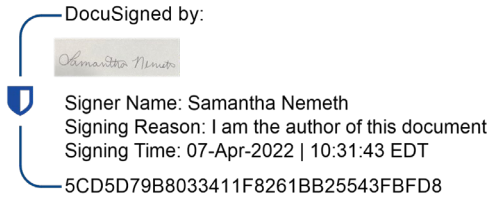
Evofem, Inc.

Confidentiality statement:

- The information provided in this document is strictly confidential.
- The recipients of the SAP must not disclose the confidential information contained within this document or any related information to other persons without the permission of the sponsor.
- In addition, the recipients of the SAP must keep this confidential document in a controlled environment which prevents unauthorized access to the document.

SIGNATURE PAGE

Prepared at Premier Research by:



07-Apr-2022 | 10:33: 8 EDT

Samantha Nemeth, Senior Statistician

Date
(DD Mmm YYYY)

Reviewed at Premier Research by:

07-Apr-2022 | 11:17: 4 EDT

Clint Dart, VP Biostatistics and Programming

Date
(DD Mmm YYYY)

Approved at Evofem, Inc. by:

07-Apr-2022 | 08:32:(2 PDT

Catherine Maher, VP Regulatory Affairs & PV

Date
(DD Mmm YYYY)

REVISION HISTORY

Version/Date	Version name	Section	Changes implemented
Final Version 1.0/ 23-SEP-2020	Initial approved version	N/A	Baseline version
Final Version 2.0/ 06-APR-2022			Additional verbiage for duplicate patients, safety population defined using distributed/returned product, separate secondary endpoints of CT and GC Only, invalid status missing at Visit 5, EMA verbiage, subset analysis regarding documentation status, subset analysis by age group, visit flexibility for handling COVID-19 patients, GU TEAE description, additional subject adherence category, and Table of Contents for Data Displays

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Interval
CSR	Clinical Study Report
CT	Chlamydia trachomatis
eDiary	Electronic Diary
FDA	US Food and Drug Administration
FSFI	Female Sexual Function Index
GC	Neisseria gonorrhoeae
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ITT	Intention to Treat
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-Treat
NAAT	Nucleic Acid Amplification Test
PGIC	Patient Global Impression of Change
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SexFS	Brief Profile Sexual Function and Satisfaction
SOC	System Organ Class
TEAEs	Treatment Emergent AEs
TFLs	Tables Listings and Figures
uHCG	urinary β-human chorionic gonadotrophin
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations and data displays for study protocol EVO100-311 Version 4.0 “Phase 3 double-blind placebo-controlled efficacy trial of EVO100 vaginal gel for the prevention of urogenital Chlamydia trachomatis (CT) and Neisseria gonorrhoeae (GC) infection (EVOGUARD)” dated 26MAY2021 for clinical study report (CSR) analysis. The table of contents and templates for the tables listings and figures (TFLs) will be produced in a separate document.

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

The preparation of this SAP has been based on International Conference on Harmonisation (ICH) E9.

All data analyses and generation of TFLs will be performed using SAS version 9.4 or higher.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate the efficacy of EVO100 vaginal gel in the prevention of urogenital Chlamydia trachomatis (CT) and Neisseria gonorrhoeae (GC) infections.

2.2 Secondary Objective(s)

- To evaluate the safety of EVO100.

2.3 Exploratory Objective(s)

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

3 STUDY DESIGN

3.1 General Study Design

At total of 1730 women, ages ≥18, who had a documented urogenital CT or GC infection or an undocumented self-reported CT or GC infection with risk factors, at any time over the 17 weeks preceding the enrollment visit, or positive at screening visit will be enrolled. A high prevalence of CT infection has been observed in those who were treated for urogenital chlamydial infection during the preceding several months. The second infection may result from infection through an untreated partner or exposure through a new partner. By including only women who have had a CT or GC infection within the past 17 weeks, this study targets those at high risk for infection.

At screening, subjects will be tested for a 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 at screening will receive standard of care treatment. To meet eligibility criteria, these subjects will not be enrolled until 3 to 4 weeks after screening (at least 21 days after treatment).

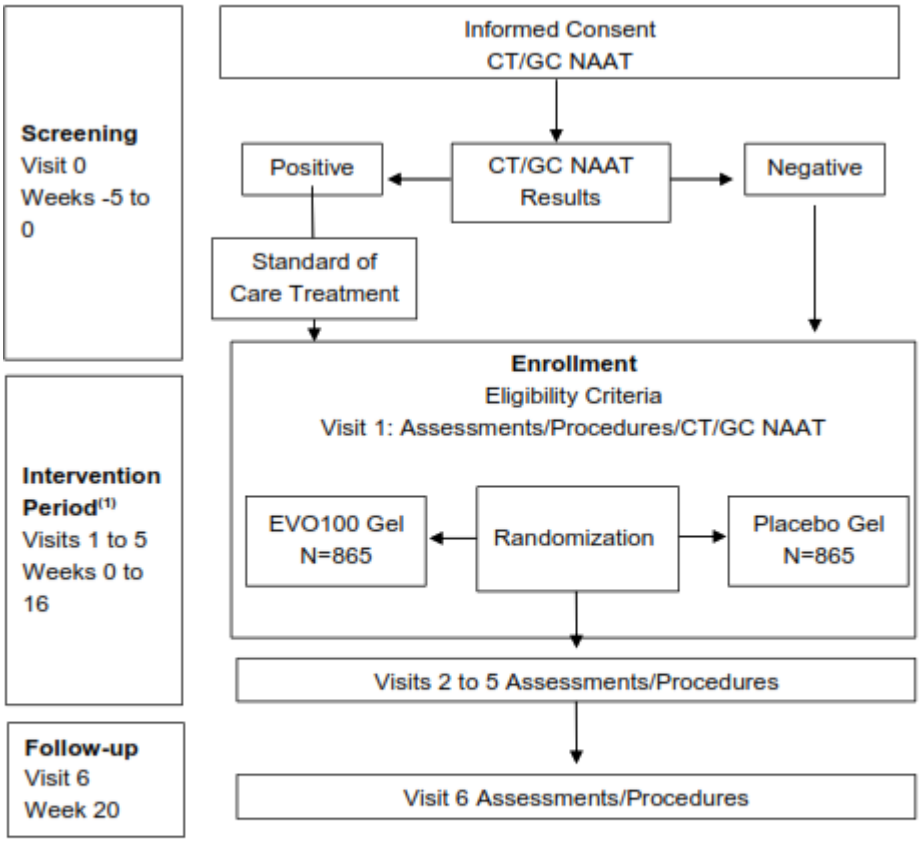
Eligible participants will be enrolled and randomized 1:1 (865 subjects per treatment arm) to either EVO100 Gel, 5g or HEC placebo 5 g supplied in a pre-filled, single-dose applicator. A baseline vaginal pH and a full gynecologic examination (including bimanual and speculum) will be obtained at enrollment.

Subjects are instructed to apply EVO100 or placebo gel immediately before or up to one hour prior to coitus for the duration of the 16-week intervention period. EVO100 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 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 β-human chorionic gonadotrophin [uHCG]) testing, eDiary review, and return of unused investigational product. At Visits 2 to 4, subjects will be re-supplied with EVO100 or placebo gel. At Visit 5, subjects will return unused investigational product and continue to use their eDiaries but will not be resupplied with EVO100 or placebo gel.

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

Figure 1 Schematic Flow of Study Design



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

(1)In the event a subject has CT or GC infection diagnosed at a local healthcare facility during the period between visits, the infection and treatment will be documented and every effort to obtain a medical record will be made.

Screening and Eligibility

Subjects who consent may be screened if they have a known case of CT or GC within 17 weeks of enrollment, or suspicion of current CT or GC infection (subsequently confirmed with NAAT test at Screening Visit). Subjects randomized within 35 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 will be one follow-up visit (Visit 6), 4 weeks after the last intervention visit or last dose of study product. These periods are outlined in the schedule of assessments (Table 2). The protocol-defined period of observation is 20 weeks. In the event a subject has CT or GC infection diagnosed at a local healthcare facility during the period between visits, the infection and treatment will be documented and every effort to obtain a medical record will be made. These subjects will be considered as failures.

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 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.

Study Conduct Strategies due to Coronavirus Disease -2019

Based on the US Food and Drug Administration (FDA) guidance, Coronavirus disease 2019 (COVID-19) strategies are planned for this study to ensure adherence to best practices for study conduct.

3.2 Randomization and Blinding

This is a Phase 3 placebo-controlled randomized study with 865 subjects per intervention arm, for a total of 1730 subjects. The 1730 subjects will be randomized using an Interactive Web Response System (IWRS) in a 1:1 fashion across the two intervention groups, EVO100 or placebo. Randomization will be stratified by prior infection documentation status (available/present versus unavailable/not present), 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.

Investigators and subjects in both intervention groups will remain blinded to their intervention assignment (EVO100 or placebo) over the entire duration of the study (double-blind). The Sponsor, Evofem, 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 dispensed to study subjects must be approved by the medical monitor.

If the code must be broken in the case of an emergency for 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.

3.3 Study Treatments and Assessments

Following screening, enrollment, and randomization, subjects will be issued a 4-week supply of investigational product based on the individual subject's projected usage. After a screening period of up to 35 days, women will be randomized to receive either EVO100 or placebo:

EVO100 vaginal gel 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.

Subjects will be asked how many pre-filled applicators they need, based on their anticipated number of sexual encounters per 4 weeks. Up to 3 boxes may be dispensed to meet their anticipated need. Additional boxes may be dispensed between visits, if needed.

At visits 2 through 4, during the intervention period, subjects will return all unused product and will be issued a new 4-week supply of investigational product based on projected usage.

Unopened kits may be re-dispensed to the same subject, provided the subject follows specified storage instructions. The staff may also re-dispense to the same subject individually wrapped product from an open kit provided specified storage instructions have been followed and the staff completes product accountability reconciliation activity. 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.

Table 1 shows the study dosing for each intervention group.

Table 1: Investigational Product Dosing

Intervention Group	**EVO100 vaginal gel**	**Placebo**
Group A	865 subjects, 5 g dose applied up to 1 hour prior to coitus	N/A
Group B	N/A	865 subjects, 5 g dose applied up to 1 hour prior to coitus

Table 2: Schedule of Study Assessments

		Intervention Period[1]					
Study Visit (V)	Screening Visit 0[2]	Enrollment/ Visit 1[3]	Visit 2[3]	Visit 3[3]	Visit 4[3]	Visit 5[3][5]	Post-Intervention Follow-up/Visit 6
Study Week	-5.0 to 0 weeks (-35 to 0 days)	0	4[4]	8[4]	12[4]	16[4]	20
Investigational Product Dispensed		X	X	X	X		
Informed Consent/HIPAA	X						
Demographic Information	X						
Inclusion/Exclusion	X	X					
Confirm Eligibility Criteria		X					
Concomitant Medications	X	X	X	X	X	X	X
AE Assessment	X	X	X	X	X	X	X
Medical/Sexual History	X	X	X	X	X	X	X
Last Menstrual Period	X	X	X	X	X	X	X
Physical Exam		X					
Targeted Physical Exam[6]			X	X	X	X	X
Body Weight/Height		X					
Vital Signs		X					
Gynecologic Exam		X				X[7]	X[7]
Urine HCG	X	X	X	X	X	X	X
Vaginal pH		X					
Self-collected CT/GC NAAT			X	X	X	X	X
Clinician-collected CT/GC NAAT	X	X					
eDiary Setup		X					
eDiary Review			X	X	X	X	X
Female Sexual Function Index (FSFI)	X	X	X	X	X	X	X
PROMIS Sexual FS (PROMIS® Brief Profile Sexual Function and Satisfaction)	X	X				X	X
Subject Sexual Impact Questionnaire			X	X	X	X	X
Product Satisfaction Questionnaire			X	X	X	X	X

Patient Global Impression of Change (PGIC)		X				X	X
Return Unused Study Product			X	X	X	X	

Abbreviations: AE = adverse event, CT = *Chlamydia trachomatis*, eDiary = electronic diary, GC = *Neisseria gonorrhoeae*, HCG = human chorionic gonadotropin, HIPAA = Health Insurance Portability and Accountability Act, NAAT = nucleic acid amplification test; V = study visit.

(1) The intervention period is defined as Visits 1 to 5. In the event a subject has CT or GC infection diagnosed at a local healthcare facility during the period between visits, the infection and treatment will be documented and every effort to obtain a medical record will be made.

(2) Screening period may be up to 35 days. 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 35 days, subjects will not be enrolled and will need to be rescreened.

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

(4) Subjects will be asked to return ±7 days within each visit window.

(5) The procedures for Visit 5 should be followed for the Early Termination Visit.

(6) For unscheduled visits: includes provision to contact subjects or allow unscheduled visits for managing AEs.

(7) The gynecologic examination will be conducted during unscheduled visits, as necessary and during end of study and end of treatment visits. The gynecologic examination will not be conducted if the end of study/end of treatment visit is remote due to COVID-19.

4 STUDY ENDPOINTS

4.1 Primary Endpoint

- The primary efficacy endpoint is the proportion of subjects who are defined as study successes versus study failures among the intervention groups (EVO100 or placebo). Estimand Framework
    - FDA Submission
        - Success is defined as subjects completing the trial to Visit 5 without any of the following: CT/GC infection, usage of prohibited antibiotics during the study, an invalid CT/GC test at Visit 5.
        - The mITT population will be used, and the Chi-Square test will be used to compare the failure rates in EVO100 and placebo.
    - EMA Submission
        - The parallel primary efficacy endpoints define success through Visit 5 as:
            - CT Infection Endpoint:
                - The proportion of subjects without a CT infection, CT prohibited antibiotics, or invalid Visit 5 CT test.
            - GC Infection Endpoint
                - The proportion of subjects without a GC infection, GC prohibited antibiotics, or invalid Visit 5 GC test.
        - The mITT population will be used and the Chi-Square test will be used to compare the failure rates in EVO100 and placebo.

      Note: These two parallel primary endpoints enable efficacy to be assessed separately for CT and GC. In this way, if the study is successful for either CT or GC but not for both, an indication for prevention of just one of the two pathogens could still be granted. Both primary endpoints will be tested at the 0.05 significance level (with no adjustments for multiplicity of statistical testing).

4.2 Secondary Endpoint

The secondary outcome for this study will be assessing the incidence of AEs (descriptive analysis).

Secondary outcomes for the FDA submission will include the separate CT and GC infection endpoints used in the EMA primary endpoint.

4.3 Exploratory Endpoints

Exploratory assessments include:

- Comparison of the 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.
- Comparison of the proportion of subjects with overall sexual satisfaction using the FSFI overall sexual satisfaction question at Visit 5.
- Comparison of the proportion of subjects reporting overall product satisfaction at Visit 5.

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

5 SAMPLE SIZE AND POWER

The primary analysis is a comparison between proportion of subjects who are defined study successes versus study failures (success defined as subjects completing the trial to Visit 5 without any CT or GC infection and no use of prohibited antibiotics; failures defined as subjects with CT infection, GC infection, use of prohibited antibiotics, or loss to follow-up) among the intervention groups (EVO100 or placebo).

It is assumed that the proportion of subjects who will have CT infection, GC infection, use of prohibited antibiotics, or loss to follow-up will be 30.5% for active treatment versus 37.5% for placebo group based on the Phase 2B/3 study (EVO003) with equal lost to follow-ups assumed in both intervention groups. Using a Chi-Square test for the primary endpoint, 821 analyzable subjects per treatment group (1642 subjects total) will yield approximately 85% power to detect a rate difference of 7% with a 2-sided 5% type I error rate. Given the assumption that 5% of subjects are found to be positive at enrollment, the total sample size planned for this study is 1730 subjects. With an assumed screen failure rate of approximately 27.8%, 2397 subjects are estimated to be needed for screening.

6 ANALYSIS POPULATIONS

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

6.1 Intention-To-Treat Population (ITT)

The ITT population is defined as all randomized subjects. Analyses with this population will be performed based on the treatment randomized.

6.2 Modified Intention-To-Treat Population (mITT)

The mITT population is defined as all randomized subjects who are negative for chlamydia and gonorrhoeae at enrollment and are provided with study product. Analyses with this population will be performed based on the treatment randomized.

6.3 Safety Population (Safety)

Safety population will be based on subjects documented to have been distributed any study product. Subjects with proof that no study product was taken (e.g., all study drug returned) will not be included in the Safety population. Analysis with this population will be performed based on the treatment actually received.

6.4 Protocol Deviations/Violations and Exclusions from Analysis Sets

A cumulative list of protocol deviations will be reported in the Clinical Study Report.

6.5 Duplicate Patients

Patients found to have been enrolled more than once during the study (either at same site or different sites) will only have screenings/visits associated with their first enrollment counted in the study population. Any additional screenings/enrollments/visits attached to a subsequent enrollment (or attempted enrollment) will be excluded from all analyses and analysis populations.

7 STATISTICAL CONSIDERATIONS AND ANALYSIS

7.1 Derived Variables

The below table provides a list of derived variables for demographic and baseline characteristics.

Variables	Formula
Demographic and Baseline characteristics	
Age at informed consent (in years)	integer ((date of informed consent – date of birth + 1)/ 365.25)
Body mass index (BMI) (kg/m2)	weight (kg)/[height (m)]^2
Patient-Reported Outcome Scoring	
PROMIS SexFS Pain Subscale (vaginal discomfort)	In the last 30 days Question SFSCR202: Did you have any type of sexual activity? 1=No 2=Yes Question SFVAG202: When you have had sexual activity, how much discomfort have you felt inside your vagina? 1=None 2=A little bit 3=Some 4=Quite a bit 5=A lot Question SFVAG206: When you have had sexual activity, how much pain have you felt inside your vagina? 1=None 2=A little bit 3=Some 4=Quite a bit 5=A lot Scoring conversion table Conditional on 2=yes for SFSCR202

	Vaginal Discomfort for Sexual Activity Short Form Conversion Table **SFVAG202** / **SFVAG206** / **T-Score** / **SE[1]** 1 / 1 / 43.3 / 6.6 1 / 2 / 52.8 / 2.6 1 / 3 / 55.6 / 3.4 1 / 4 / 56.8 / 4.3 1 / 5 / 57.3 / 4.8 2 / 1 / 53.3 / 2.6 2 / 2 / 56.9 / 2.5 2 / 3 / 60.4 / 2.5 2 / 4 / 62.5 / 3.1 2 / 5 / 63.6 / 3.9 3 / 1 / 57.3 / 3.2 3 / 2 / 60.9 / 2.4 3 / 3 / 63.8 / 2.2 3 / 4 / 66.4 / 2.4 3 / 5 / 68.3 / 3.1 4 / 1 / 59.8 / 4.4 4 / 2 / 63.7 / 3.0 4 / 3 / 66.8 / 2.3 4 / 4 / 69.9 / 2.4 4 / 5 / 73.0 / 2.5 5 / 1 / 61.9 / 5.7 5 / 2 / 66.2 / 4.2 5 / 3 / 69.9 / 3.1 5 / 4 / 73.6 / 2.5 5 / 5 / 78.1 / 3.4 [1]SE: Standard Error
PROMIS SexFS Lubrication Subscale	In the last 30 days Question SFSCR202: Did you have any type of sexual activity? 1=No 2=Yes Question SFLUB001: How often did you become lubricated (“wet”) during sexual activity or intercourse? 5=Almost always or always 4=Most of the time (more than half the time) 3=Sometime (about half the time) 2=A few time (less than half the time) 1=Almost never or never Question SFLUB004: How difficult was it to maintain your lubrication (“wetness”) until completion of sexual activity or intercourse? 1=Extremely difficult or impossible 2=Very difficult 3=Difficult 4=Slightly difficult 5=Not difficult Scoring conversion table Conditional on 2=yes for SFSCR202

	Vaginal Lubrication for Sexual Activity Short Form Conversion Table **SFLUB004** / **SFLUB001** / **T-Score** / **SE[1]** 1 / 1 / 27.6 / 4.5 1 / 2 / 32.0 / 3.8 1 / 3 / 34.2 / 4.2 1 / 4 / 35.8 / 4.9 1 / 5 / 37.7 / 5.9 2 / 1 / 33.1 / 3.3 2 / 2 / 35.4 / 3.1 2 / 3 / 37.2 / 3.4 2 / 4 / 38.8 / 3.9 2 / 5 / 40.7 / 4.9 3 / 1 / 36.2 / 3.3 3 / 2 / 38.0 / 3.0 3 / 3 / 39.5 / 3.0 3 / 4 / 41.1 / 3.4 3 / 5 / 43.1 / 4.3 4 / 1 / 40.3 / 4.0 4 / 2 / 41.8 / 3.5 4 / 3 / 43.4 / 3.3 4 / 4 / 45.4 / 3.4 4 / 5 / 48.1 / 3.8 5 / 1 / 47.4 / 4.9 5 / 2 / 48.1 / 4.5 5 / 3 / 49.2 / 4.2 5 / 4 / 51.2 / 4.0 5 / 5 / 58.4 / 6.5 [1]SE: Standard Error
FSFI Pain Subscale	FSFI Q17: Over the past 4 weeks, how often did you experience pain during vaginal penetration? 0=Did not attempt intercourse 1=Almost always or always 2=Most times (more than half the time) 3=Sometimes (about half the time) 4=A few times (less than half the time) 5=Almost never or never FSFI Q18: Over the past 4 weeks, how often did you experience pain following vaginal penetration? 0=Did not attempt intercourse 1=Almost always or always 2=Most times (more than half the time) 3=Sometimes (about half the time) 4=A few times (less than half the time) 5=Almost never or never

	FSFI Q19: Over the past 4 weeks, how would you rate your level (degree) of discomfort or during or following vaginal penetration? 0=Did not attempt intercourse 1=Very high 2=High 3=Moderate 4=Low 5=Very low or none at all Pain Score = (FSFIQ17+ FSFIQ18+ FSFIQ19)*0.4
FSFI SexFS Lubrication Subscale	FSFI Q7: Over the past 4 weeks, how often did you become lubricated ("wet") during sexual activity or intercourse? 0=No sexual activity 1=Almost always or always 2=Most times (more than half the time) 3=Sometimes (about half the time) 4=A few times (less than half the time) 5=Almost never or never FSFI Q8: Over the past 4 weeks, how difficult was it to become lubricated ("wet") during sexual activity or intercourse? 0=No sexual activity 1=Extremely difficult or impossible 2=Very difficult 3=Difficult 4=Slightly difficult 5=Not difficult FSFI Q9: Over the past 4 weeks, how often did you maintain your lubrication ("wetness") until completion of sexual activity or intercourse? 0=No sexual activity 1=Almost always or always 2=Most times (more than half the time) 3=Sometimes (about half the time) 4=A few times (less than half the time) 5=Almost never or never FSFI Q10: Over the past 4 weeks, how difficult was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse? 0=No sexual activity

	1=Extremely difficult or impossible 2=Very difficult 3=Difficult 4=Slightly difficult 5=Not difficult Lubrication Score = (FSFIQ7+FSFIQ8+FSFIQ9+ FSFIQ10)*0.3

7.2 Handling of Missing Data and Outliers

7.2.1 Missing Data Analysis Methods

For the primary and exploratory endpoint analyses using CT/GC infection, any subject that does not have a known infection status through Visit 5 (eg, is deemed lost to follow-up) will be considered a failure. Likewise, any subject that uses prohibited antibiotics during the treatment period of the study (through Visit 5) regardless of CT/GC infection status will be considered a primary endpoint failure. Lastly, any patient who receives an invalid CT/GC test result at Visit 5 will be considered a failure. All other analyses will be conducted using data as observed in the study with no imputation.

For the EMA parallel primary endpoints and the FDA secondary endpoint analyses of separate CT and GC infections, any subject that does not have a known infection status through Visit 5 (eg, is deemed lost to follow-up or discontinued but was not lost to follow-up) will be assumed to have not had a CT/GC infection. Any subject that uses prohibited medications for CT or GC will be considered failures in those respective endpoints. Lastly, any patient who received an invalid CT/GC test result at Visit 5 will be considered a failure. All other analyses will be conducted using data as observed in the study with no imputation.

7.2.2 Handling of Missing or Incomplete Dates

Imputation rules for missing or partial AE start date are defined below:

If only Day of AE start date is missing:

If the AE start year and month are the same as that for the first dose date, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date; otherwise, impute the AE start day as 1.
- If the full (or partial) AE end date IS before the first dose date, the AE will be classified as a pre-treatment AE.

Compare the imputed AE start date with TE period to determine whether the AE is pre-treatment AE, TEAE or post-treatment AE.

If Day and Month of AE start date are missing:

If AE start year = first dose year, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start Month and Day as the Month and Day of first dose

date; otherwise, impute the AE start Month as January and the Day as 1.

- If the full (or partial) AE end date IS before the first dose date, the AE will be classified as a pre-treatment AE.

Compare the imputed AE start date with TE period to determine whether the AE is pre-treatment AE, TEAE or post-treatment AE.

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing, then query site with no imputation. Also compare the full (or partial) AE end date to the first dose date. If the AE end date is before the first dose date, then the AE should be considered as a pre-treatment AE. Otherwise, the AE will be considered as TEAE.

Imputation rules for missing or partial medication start/stop dates are defined below:

Missing or partial medication start date:

- If only DAY is missing, use the first day of the month.
- If DAY and Month are both missing, use the first day of the year.
- If DAY, Month and Year are all missing, use a date before the first dose date.

Missing or partial medication stop date:

- If only DAY is missing, use the last day of the month.
- If DAY and Month are both missing, use the last day of the year.
- If DAY, Month and year are all missing, assign 'continuing' status to stop date.

8 STATISTICAL METHODS

8.1 General Statistical Conventions

All statistical procedures will be completed using SAS version 9.4 or higher.

Unless otherwise stated, all statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05. Two-sided 95% confidence intervals (CIs) will be provided when relevant.

For continuous variables, descriptive statistics will include the number of non-missing values (n), mean, standard deviation, median, minimum, and maximum. For categorical variables, descriptive statistics will include counts and percentages per category. All summaries will be presented by treatment group and overall, unless otherwise specified.

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

All subject data will be presented in individual subject data listings. Unless otherwise stated, unscheduled visit results will be included in date/time chronological order, within subject listings only. All listings will be sorted by investigational site, subject number, and visit. The treatment group (EVO100, Placebo) as well as subject's age and sex (if available) will be stated on each listing. With respect to study tables, the mITT population will be used for efficacy analyses; safety population will be used for safety analyses.

8.2 Subject Disposition

Subject disposition information will be summarized by treatment group and overall. The number and percent of subjects who are randomized, who complete the study treatment, who complete the study and who withdraw early from the treatment and study will be presented.

The primary reason for early withdrawal from treatment and/or the study will also be tabulated.

The number of subjects randomized will be used as the denominator for the percentage calculation.

The number and percent of subjects in each analysis set will also be tabulated.

Subject disposition including primary reason to indicate why subject was not randomized will be listed.

The number of subjects excluded from ITT, mITT, Safety analyses sets and reasons for exclusion will be summarized by treatment group and overall. Listings will also be provided for subjects excluded from the analysis set with reasons for exclusion.

8.3 Protocol Deviations

All key protocol deviations identified will be summarized by treatment group and overall based on ITT population.

A listing will include the inclusion/exclusion criteria violated at screening and enrollment visits as well as other key protocol deviations.

To explore potential changes in study conduct due to COVID-19 (e.g., flexibility regarding

Screening window, visit time-frames, and follow-up were allowed in order to capture more touchpoints within a patient's timeline during the study), an additional analysis will be performed to recognize and indicate the impact of participation of subjects by COVID-19. The impact of COVID-19 will be summarized by treatment group and overall by visit for all subjects in ITT population. This table will present the subjects affected by COVID-19 in all aspects (e.g., missed visit and/or assessment due to COVID-19, remote visit due to COVID-19, modified assessment due COVID-19). In addition, key protocol deviations related to COVID-19 will also be summarized using ITT population.

A by-subject listing will also be provided for all subjects that have their participation impacted by COVID-19.

8.4 Demographics and Baseline Characteristics

8.4.1 Demographics

Demographic variables include age, race, ethnicity, height, weight, BMI and will be summarized and listed using ITT population. Continuous measures will be summarized treatment group and overall using descriptive statistics (n, mean median, standard deviation, minimum, and maximum). Categorical variables will be summarized by treatment group and overall using frequency counts and percentages. All demographic information will be presented in a subject-level listing.

8.4.2 Baseline and Disease Characteristics

The baseline characteristics includes CT/GC infection history, gynecological exam details, current contraceptive methods used, vaginal pH, CT/GC NAAT sample result, risk factors and vital signs. Categorical variables summarized using frequency counts and continuous variables will be summarised by descriptive statistics using ITT population. Baseline characteristics will be listed.

8.4.3 Medical History

A summary of medical/surgical/gynecologic/sexual health history will be presented by system organ class and preferred term (PT) using Medical Dictionary for Regulatory Affairs® (MedDRA) version 23 or higher based on ITT population. Medical history will be listed.

8.4.4 Concomitant Medications

Concomitant medications will be assessed and includes any medication that would be taken during the study including all over the counter medications, vitamins, and nutritional supplements.

Medications used in this study will be coded by using latest version of World Health Organization (WHO) drug dictionaries.

Concomitant medications will be summarized descriptively using frequency tables by anatomical therapeutic chemical (ATC) class level 2 and preferred name by treatment group and overall based on ITT population. Concomitant medications will be listed. Additionally, a listing of subjects taking prohibited medications for intercurrent infections other than CT or GC will be provided.

8.5 Extent of Exposure

8.5.1 Treatment Adherence

Adherence with treatment gel usage during study (rate of product use adherence) will be estimated using the eDiary data.

Adherence ratio will be calculated as = [# of times product is properly used as noted in the eDiary / # of coital events noted during the treatment phase in the eDiary].

Study product adherence (compliance) will be calculated as: 100x [adherence ratio as calculated above]. The maximum percentage of doses used will be 100%.

Study drug compliance, number of times of product use (determined via eDiary), and number of times sexual intercourse occurred will be summarized descriptively by treatment group and overall using mITT population.

Study drug compliance will be summarized in categories "0%", ">0% and <20%", "≥20% and <40%", "≥40% and <60%", "≥60% and <80%", "≥80% and <100%", "≥80% and ≤100%", and "100%" using frequency count and percentages. For the purposes of the frequency table, each compliance group will be deemed mutually exclusive (e.g., compliance rate of 41% would be in the ≥40% category only and would not be counted in the ≥20% category).

Study product distribution details and subject diary data will be listed.

8.6 Efficacy Analyses

This section addresses separately the analyses to be conducted on the primary, secondary, and exploratory efficacy endpoints.

8.6.1 Analysis Methods - Multiplicity

FDA Submission:

To control for multiple testing issues, a hierarchical testing strategy will be employed for exploratory endpoints that evaluate the efficacy of EVO100 vaginal gel in the prevention of urogenital CT and GC infection by assessing the proportions of subjects with:

- Overall sexual satisfaction using the FSFI overall sexual satisfaction question at Visit 5 and not having a CT or GC infection (Endpoint A), and
- Overall sexual satisfaction using the FSFI overall sexual satisfaction question at Visit 5 (Endpoint B).

If the primary endpoint is successful, then Endpoint A will be tested using a two-sided alpha=0.05. Endpoint B will be tested in succession if Endpoint A has a successful outcome.

EMA Submission:

For the EMA analysis, the primary endpoint can be either of the parallel primary endpoints for CT only and GC only. If either parallel primary endpoint is successful, then Endpoint A (same as above) will be tested using a two-sided alpha=0.05. Endpoint B (same as above) will be tested in succession if Endpoint A has a successful outcome.

8.6.2 Analysis of Primary Endpoints

FDA Submission

For the primary analysis, the proportion of subjects who are defined study successes (i.e., have

all of the following through Visit 5: no CT/GC infection, no use of prohibited antibiotics, not lost to follow-up/otherwise discontinued, and no invalid CT/GC test at Visit 5) will be compared between the intervention groups (EVO100 or placebo) using a Chi-Square test. The primary efficacy analysis will be completed using the subjects deemed analyzable* from the mITT population.

*All subjects in the mITT population are deemed analyzable for the purpose of the primary endpoint analysis. Those subjects who are in ITT but not in mITT will be excluded from said analysis. The primary analysis will be performed using all subjects in the mITT population.

The primary statistical hypothesis being tested is that there is no difference in the proportion of subjects deemed study success in the EVO100 intervention group versus placebo. In statistical terms:

$$H0: pEVO100 = pplacebo, HA: pEVO100 \neq pplacebo$$

where, pEVO100 and pplacebo denote the proportion of subjects deemed a study success while on EVO100 or placebo, respectively. Denominators for percentages are number of subjects in the mITT population in each intervention group. To test superiority over placebo, the percentage of study successes will be compared against placebo based using 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 (α=0.05) will be used. The Fisher's Exact test will be conducted in place of the Chi-Square test if necessary due to issues with the expected cell counts.

For the primary endpoint and exploratory analyses using CT/GC infection, any subject that does not have a known infection status through Visit 5 (i.e., at least through study day 105) (e.g., is deemed lost to follow-up) will be considered a failure. Likewise, any subject that uses prohibited antibiotics during the treatment period of the study regardless of CT/GC infection status will be considered a primary endpoint failure. Lastly, a patient having an invalid CT/GC test at Visit 5 will be considered a failure.

Secondary analyses of CT only and GC only endpoints will be performed as specified in the below EMA analysis section. See that section for more details.

In addition, a sensitivity analysis will be provided for the primary endpoint. For the sensitivity analysis, the proportion of subjects who are defined as study successes will be irrespective of the use of prohibited antibiotics. Success will be defined as no CT/GC infection through Visit 5 (i.e., at least through study day 105). The statistical analysis described for the primary endpoint will be used for the secondary and sensitivity analyses.

A listing will be provided for CT/GC NAAT sample result.

EMA Analysis

For the parallel primary analyses, the proportion of subjects who are defined study successes will be compared between intervention groups (EVO100 or placebo) using a Chi-Square test. The primary efficacy will be completed using the subjects deemed analyzable* from the mITT population.

*All subjects in the mITT population are deemed analyzable for the purpose of the primary endpoint analysis. Those subjects who are in ITT but not in mITT will be excluded from said

analysis. The primary analysis will be performed using all subjects in the mITT population.

For the CT infection endpoint, success will be defined as having no CT infection, taking no CT prohibited medications, and no invalid CT test at Visit 5. For the GC infection endpoint, successes will be defined as having no GC infection, taking no GC prohibited medications, and no invalid GC test at Visit 5.

The primary statistical hypothesis being tested is that there is no difference in the proportion of subjects deemed study success in the EVO100 intervention group versus placebo. In statistical terms:

$$H0: pEVO100 = pplacebo, HA: pEVO100 \neq pplacebo$$

where, pEVO100 and pplacebo denote the proportion of subjects deemed a study success while on EVO100 or placebo, respectively. Denominators for percentages are number of subjects in the mITT population in each intervention group. To test superiority over placebo, the percentage of study successes will be compared against placebo based using 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 (α=0.05) will be used. The Fisher's Exact test will be conducted in place of the Chi-Square test if necessary due to issues with the expected cell counts.

For the primary endpoint, any subject that does not have a known infection status through Visit 5 (i.e., at least through study day 105) (e.g., is deemed lost to follow-up/otherwise discontinued) will be considered as having a negative CT/GC test through Visit 5.

8.6.3 Analysis of Exploratory Endpoints

The following summary and analysis will be provided for the exploratory endpoint using mITT population:

Patient-reported outcomes measures for this study are to evaluate the efficacy of EVO100 vaginal gel in the prevention of urogenital CT and GC infection by assessing the following proportions of subjects:

- With overall sexual satisfaction using the FSFI overall sexual satisfaction question at Visit 5 (i.e., at least through study day 105) and not having a CT or GC infection using FDA primary endpoint rules.
- With overall sexual satisfaction using the FSFI overall sexual satisfaction question at Visit 5 (i.e., at least through study day 105).
- Reporting overall product satisfaction at Visit 5 (i.e., at least through study day 105).
- A subset analysis of the primary endpoint (FDA rules) looking at results based on prior infection documentation will be performed.

Above endpoints will be compared against placebo based on 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 (α=0.05) will be used. The Fisher's Exact test will be conducted in place of the Chi-Square test if necessary due to issues with the expected cell counts.

From the FSFI questionnaire, question (#16) "over the past 4 weeks, how satisfied have you been with your overall sexual life?" will be considered for sexual satisfaction. The question from product satisfaction questionnaire "How satisfied are you with the study product?" will be used

to assess the overall product satisfaction. Responses will be categorized as satisfied (i.e., combined responses of very satisfied, moderately satisfied, about equally satisfied and dissatisfied) and dissatisfied (i.e., combined response of moderately & very dissatisfied) for the comparison.

Additional exploratory endpoints are:

- Compliance with EVO100 vaginal gel usage versus placebo usage during study (rate of product use adherence and placebo) will be summarised descriptively (see section 8.5 for more details).
- The proportion of subjects who are defined success versus failure (FDA primary endpoint) will be summarized using the below adherence categories by treatment groups. The estimated difference in proportions, 95% confidence interval, and p-value will be presented.
    - Subjects with 0%, >0% and <20%, ≥20% and <40%, ≥40% and <60%, ≥60% and <80%, ≥80% and <100%, ≥80% and ≤100%, and 100% product use adherence. For the purposes of the frequency table, each compliance group will be deemed mutually exclusive.
- Similar to the FDA primary endpoint analysis, failure components of the primary endpoint (i.e., CT infection, GC infection, use of prohibited antibiotics, lost to follow-up, or invalid CT/GC test at Visit 5) will be summarized using frequencies and percentages with the difference between treatment groups analysed using a Chi-Square test. The Fisher's Exact test will be conducted in place of the Chi-Square test if necessary due to issues with the expected cell counts.
- Responses to the PROMIS SexFS Satisfaction, Pain and Lubrication subscales with EVO100 vaginal gel usage and placebo at each visit will be summarized using count and percentage. Descriptive summary will also be provided using the derived subscale scores (refer section 7.1). In addition, the shifted change from baseline to post baseline response will also be summarized.
- Response to FSFI questionnaire- Lubrication and Pain subscales with EVO100 vaginal gel usage and placebo at each visit will also be summarised using count and percentage. Response to questions 7, 8, 9, 10 will be considered for lubrication subscale and questions 17, 18 and 19 will be considered for pain subscales from the FSFI questionnaire. In addition, the shifted change from baseline to post baseline response will be summarized.
- Patient Global Impression of Change (PGIC) with EVO100 vaginal gel usage versus placebo will be summarized by treatment group.

Validation related analyses for the patient-reported outcomes (FSFI, product satisfaction questionnaire, PROMIS SexFS etc.) referenced here will be outlined in a separate psychometric analysis plan.

Listings will be provided for PROMIS SexFS, FSFI, product satisfaction questionnaire and PGIC.

8.6.4 Other Analysis

Condom usage rates and their effect on study successes will be explored. The rate of condom usage will be defined as # of coital acts where male condom usage is noted in the eDiary (over the course of the treatment phase) / total # of coital acts during the treatment phase.

To assess the usage rate of condoms during the study, a summary will be presented using descriptive statistics for subjects displayed by treatment group. Additionally, a summary of study success or failure rates by treatment group and condom usage (none, low, high) will be presented. For the purposes of this display, low condom use will be defined as subjects that have a rate that is less than or equal to the 50th percentile of subjects using condoms (i.e., no condom use will not be used for the 50th percentile calculation).

8.7 Safety Analyses

All safety data will be summarized by intervention group and overall. Safety analyses will be conducted on the safety analyses set and will be performed for all safety variables specified in the below sections.

No statistical tests will be performed.

8.7.1 Adverse Events

All Adverse events (AEs) will be classified by System Organ Class (SOC) and Preferred Term (PT) according to the most current version of Medical Dictionary for Regulatory Activities (MedDRA version 23.0 or higher).

Treatment emergent AEs (TEAEs) are defined as any AE that started or worsened on or after the first dose of study drug.

GU TEAEs include: Dysuria, Genital Burning Sensation, Genital Discomfort, Genital Pain, Vaginal Discharge, Vulvovaginal Burning Sensation, Vulvovaginal Discomfort, Vulvovaginal Erythema, Vulvovaginal Pruritus.

An overall AE summary tables will be provided, and summary include number of TEAEs and number and percentage of subject with any TEAEs, GU TEAEs, related TEAEs, TEAEs leading to discontinuation, serious adverse event (SAE), and TEAEs leading to death.

Additionally, the following summaries will also be provided.

- TEAEs by SOC and PT
- GU TEAEs by SOC and PT
- Related TEAEs by SOC and PT
- TEAEs by SOC, PT and maximum severity
- TEAEs leading to treatment discontinuation by SOC and PT
- Related TEAEs leading to treatment discontinuation by SOC and PT
- TEAEs leading to death by SOC and PT

- Serious TEAEs by SOC and PT

Where a subject has the same adverse event, based on preferred terminology, reported multiple times in the study period, the subject will only be counted once at the preferred terminology level in adverse event frequency tables.

If a subject has multiple adverse events within the same system organ class in the study period, the subject will only be counted once at the system organ class level in adverse event frequency tables.

AEs with relationship to study treatment of "certain," "probable/likely," "possible," and "missing relationship" will be considered as related AEs.

In summaries by SOC and PT, adverse events will be sorted by decreasing frequency of overall column within each SOC and PT.

All adverse events will be listed. In addition, AEs leading to discontinuation, leading to death and SAEs will also be listed.

8.7.2 Clinical Laboratory Evaluations

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

Vaginal pH, CT/GC NAAT sample result, and urine human chorionic gonadotropin (HCG) will be summarized by visit (where applicable) for each treatment group. Listings will be provided as well. Separate listings will be provided for urine pregnancy test.

8.7.3 Physical Examinations

All physical examination data will be listed using safety population.

8.8 Monthly Safety Reports

Blinded cumulative safety reports will be generated to check for potential safety issues and to ensure that there are no safety concerns noted during the course of the study. These will consist of AE summaries by SOC and PT along with other safety tables as deemed necessary.

9 CHANGES TO PLANNED ANALYSIS FROM STUDY PROTOCOL

The following changes to the analysis plan have changed since the approval of the protocol:

1) Male condom usage summary statistics.
2) Assessing the effect of male condom usage on study success rates.
3) Added sensitivity analysis for the primary endpoint to check the impact of the use of prohibited medication.
4) Patients with duplicate enrollments will have their second entries will be excluded from all analyses
5) Added secondary analyses for separate CT and GC Only analyses. These analyses will serve as parallel primary endpoints for the EMA marketing authorization application.
6) An exploratory analysis of the FDA primary endpoint by subgroups of prior infection documentation status (available, not available)
7) A subgroup analysis of the FDA primary endpoint by Age groups (18-24, 25-45, 46-64, 65+)

10 TABLE OF CONTENTS FOR DATA DISPLAYS

Table Number	Table Title	Population
14.1.1.1	Summary of Subject Disposition	All Subjects
14.1.1.2	Summary of Subjects to Be Excluded from Analysis Population	ITT
14.1.1.3	Summary of Protocol Deviations	ITT
14.1.1.4	Summary of Protocol Deviations Related to COVID-19	ITT
14.1.1.5	Summary of COVID-19 Impact	ITT
14.1.2.1	Summary of Baseline and Demographic Characteristics	ITT
14.1.2.2	Summary of Baseline Disease Characteristics	ITT
14.1.2.3	Summary of Medical/Surgical/Gynecological/Sexual Health by System Organ Class and Preferred Term	ITT
14.1.3	Summary of Concomitant Medications by Anatomic and Therapeutic Class and Preferred Term	ITT
14.1.4	Summary of Treatment Adherence	mITT
14.2.1.1	Summary of Proportion of Subjects with Success (No CT/GC Infection and No Use of Prohibited Antibiotics) and/or Failure Through Visit 5	mITT
14.2.1.2	Summary of Proportion of Subjects with Success (No CT/GC Infection) and/or Failure Through Visit 5 – Sensitivity Analysis	mITT

Table Number	Table Title	Population
14.2.1.3	Summary of Proportion of Subjects with Success (No CT Only) and/or Failure Through Visit 5 – Secondary Endpoint / EMA Primary Endpoint	mITT
14.2.1.4	Summary of Proportion of Subjects with Success (No GC Only) and/or Failure Through Visit 5 – Secondary Endpoint / EMA Primary Endpoint	mITT
14.2.1.5	Summary of Proportion of Subjects with Success (No CT/GC Infection and No Use of Prohibited Antibiotics) and/or Failure Through Visit 5 by Age	mITT
14.2.1.6	Summary of Proportion of Subjects with Success (No CT/GC Infection and No Use of Prohibited Antibiotics) and/or Failure Through Visit 5 by Prior Infection Documentation	mITT
14.2.2.1	Summary of Proportion of Subjects with Overall Sexual Satisfaction Using the Female Sexual Function Index at Visit 5 and Not Having a CT or GC Infection	mITT
14.2.2.2	Summary of Proportion of Subjects with Overall Sexual Satisfaction Using the Female Sexual Function Index at Visit 5	mITT
14.2.2.3	Summary of Proportion of Subjects with Overall Product Satisfaction at Visit 5	mITT
14.2.3.1	Summary of Proportion of Subjects with Success (No CT/GC Infection and No Use of Prohibited Antibiotic) Through Visit 5 by Adherence Categories	mITT
14.2.3.2	Summary of PROMIS® v2.0 Brief Profile Sexual Function and Satisfaction (Female) – Lubrication and Pain Subscales by Visit	mITT

Table Number	Table Title	Population
14.2.3.3	Summary of PROMIS® v2.0 Brief Profile Sexual Function and Satisfaction (Female) – All Questions by Visit	mITT

Table Number	Table Title	Population
14.2.3.4	Shift from Baseline Summary of PROMIS® v2.0 Brief Profile Sexual Function and Satisfaction by Visit	mITT
14.2.3.5	Summary of Female Sexual Function Index – Lubrication and Pain Subscales by Visit	mITT
14.2.3.6	Summary of Female Sexual Function Index – All Questions by Visit	mITT
14.2.3.7	Shift from Baseline Summary of Female Sexual Function Index – Lubrication and Pain Subscales by Visit	mITT
14.2.3.8	Summary of Patient Global Impression of Change by Visit	mITT
14.2.4.1	Summary Statistics for Subject Level Condom Usage Rate During the Study Treatment Phase	mITT
14.2.4.2	Analyses of Subject with Success Rate by Condom Usage Rates (No Condom Usage vs. Low Condom Usage vs. High Condom Use)	mITT
14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events	Safety
14.3.2.1	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety
14.3.2.2	Summary of GU Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety
14.3.2.3	Summary of Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety

Table Number	Table Title	Population
14.3.2.4	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity	Safety
14.3.2.5	Summary of Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term	Safety
14.3.2.6	Summary of Treatment-Related Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term	Safety
14.3.2.7	Summary of Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term	Safety
14.3.3.1	Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety
14.3.4.1	Summary of Observed Values for Clinical Laboratory Tests by Visit	Safety

Listing Number	Listing Title	Population
16.2.1.1	Listing of Subject Disposition	All Subjects
16.2.1.2	Listing of Protocol Deviations	ITT
16.2.1.3	Listing of Protocol Deviations Related to COVID-19	ITT
16.2.1.4	Listing of Analysis Populations and Reasons for Exclusion	ITT
16.2.4.1	Listing of Demographics	ITT
16.2.4.2.1 16.2.4.2.2 16.2.4.2.3	Listing of Baseline Characteristics	ITT
16.2.4.3	Listing of Medical/Surgical/Gynecological/Sexual Health History	ITT
16.2.4.4	Listing of Concomitant Medications	ITT
16.2.4.5	Listing of Vaginal Ring Use	ITT
16.2.4.6	Listing of Subjects with Prohibited Medications for Intercurrent Infections Other than CT and GC Infection	ITT
16.2.4.7	Listing of Treatment Adherence	mITT
16.2.6.1	Listing of CT/GC Nucleic Acid Amplification Test Sample Result	mITT
16.2.6.2	Listing of Female Sexual Function Index Questionnaire	mITT
16.2.6.3	Listing of Product Satisfaction Questionnaire	mITT
16.2.6.4	Listing of PROMIS® v2.0 Brief Profile Sexual Function and Satisfaction (Female)	mITT
16.2.6.5	Listing of Patient Global Impression of Change	mITT
16.2.7.1	Listing of Adverse Events	Safety
16.2.7.2	Listing of Adverse Events Leading to Study Drug Discontinuation	Safety
16.2.7.3	Listing of Adverse Events Leading to Deaths	Safety
16.2.7.4	Listing of Serious Adverse Events	Safety

Listing Number	Listing Title	Population
16.2.8.1	Listing of Laboratory Data	Safety
16.2.9.1	Listing of Subject Diary Entries	Safety
16.2.9.2	Listing of Physical Examination	Safety
16.2.9.3	Listing of Telephone Contact Details	Safety
16.2.9.4	Listing of Pregnancies	All Subjects

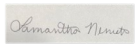
11 REFERENCES

1. ICH Topic E3: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95-adopted December 1995).
2. ICH Topic E9: Statistical Principles for Clinical Trials (CPMP/ICH/363/96 – adopted March 1998).
3. EVO100-311 Protocol Version 2.0, 14SEP2020.

Protocol Title:	**Phase 3 double-blind placebo-controlled efficacy trial of EVO100 vaginal gel for the prevention of urogenital *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infection (EVOGUARD)**
Protocol Number:	EVO100-311
Protocol Version, Date	Version 4.0, May 26, 2021
Document Version, Date:	Final 2.0, April 6, 2022

Prepared at Premier Research by:

DocuSigned by:



Signer Name: Samantha Nemeth
Signing Reason: I am the author of this document
Signing Time: 07-Apr-2022 | 10:32:58 EDT
5CD5D79B8033411F8261BB25543FBFD8

07-Apr-2022 | 10:33:08 EDT

Samantha Nemeth, Senior Statistician

Date
DD Mmm YYYY

Reviewed at Premier Research by:

DocuSigned by:

Clint Dart

Signer Name: Clint Dart
Signing Reason: I approve this document
Signing Time: 07-Apr-2022 | 11:17:49 EDT
6850FFBFFA2C4C268968DE4F2AD674FE

07-Apr-2022 | 11:17:54 EDT

Clint Dart, VP Biostatistics and Programming

Date
DD Mmm YYYY

Approved at Evofem, Inc. by:

DocuSigned by:

Catherine Maher

Signer Name: Catherine Maher
Signing Reason: I approve this document
Signing Time: 07-Apr-2022 | 08:31:38 PDT
7A8DD88F054D431699182263335F68FA

07-Apr-2022 | 08:32:02 PDT

Catherine Maher, VP Regulatory Affairs & PV

Date
DD Mmm YYYY

REVISION HISTORY

Version/Date	Version name	Section	Changes implemented
1.0/ 04Nov2020	Final 1.0	Tables & Listings	Baseline Version
2.0/ 06Apr2022	Final 2.0	Tables and Listings	GU TEAE table, COVID table, treatment-related TEAE leading to discontinuation table, safety population defined using distributed/returned product, separate CT and GC endpoints, EMA endpoint language, specifying discontinued but not lost to follow-up and invalid test at Visit 5 as failure reasons for FDA primary endpoint, subgroup analysis by documentation status, subgroup analysis by age, additional subject adherence category, pregnancy listing, vaginal ring use listing, planned treatment/actual treatment added as a column to all listings