STATISTICAL ANALYSIS PLAN AMP002

Title:	**AMPOWER** **A SINGLE-ARM, PHASE III, OPEN-LABEL, MULTICENTER, STUDY IN WOMEN AGED 18 TO 35 YEARS OF THE CONTRACEPTIVE EFFICACY AND SAFETY OF AMPHORA® CONTRACEPTIVE VAGINAL GEL**
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Statistical Analysis Plan Version:	Version 5 – 24 October 2018

Title:	**AMPOWER** **A** SINGLE-AR**M**, **P**HASE III, **O**PEN-LABEL, MULTICENTER, STUDY IN **W**OMEN AGED 18 TO 35 YEARS OF THE CONTRACEPTIVE **E**FFICACY AND SAFETY OF AMPHORA® CONT**R**ACEPTIVE VAGINAL GEL
Protocol Number:	**AMP002**
IND Number:	**109300**
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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE 3
1 INTRODUCTION 9
2 STUDY OBJECTIVES 9
2.1 Primary Objective 9
2.2 Secondary Objective 9
2.3 Exploratory Objectives 9
2.4 Primary Endpoint 9
2.5 Secondary Endpoints 9
2.6 Exploratory Endpoints 9
3 INVESTIGATIONAL PLAN 10
3.1 Overall Study Design and Plan 10
3.2 Schedule of Assessments 11
4 STATISTICAL METHODS 14
4.1 Data Quality Assurance 14
4.2 General Presentation Considerations 14
4.3 Analysis Populations 15
4.4 Study Subjects 16
4.4.1 Disposition of Subjects 16
4.4.2 Study Protocol Deviations 16
4.5 Demographic and Pre-Treatment Characteristics 16
4.5.1 Demographic 16
4.5.2 Gynecological History 16
4.5.3 Contraception Use History 17
4.5.4 Obstetric History 17
4.5.5 Medical History 17
4.5.6 Pre-Treatment Signs and Symptoms 17
4.5.7 Prior and Concomitant Medications 18
4.6 Treatment Compliance and Study Instruction Departures 18
4.7 Efficacy Evaluation 20
4.7.1 Analysis and Data Conventions 20
4.7.1.1 Definition of Baseline 20
4.7.1.2 Definition of Cycle 20
4.7.1.3 Multiple Comparisons/Multiplicity 21

4.7.1.4 Interim Analyses 21
4.7.2 Primary Efficacy Analysis 21
4.7.2.1 Derivation of the Primary Endpoint 21
4.7.3 Secondary Efficacy Analyses 23
4.7.3.1 Sensitivity Analysis with Respect to the Cycle Range 23
4.7.3.2 Sensitivity Analysis with Respect to the Dosing Time with Respect to Sexual Intercourse 23
4.7.3.3 Perfect-Use 7-Cycle Pregnancy Probabilities 23
4.7.3.4 Pearl Rates from 7-Cycle Data 23
4.7.3.5 Summary of Number of Diary Cycles and Cycles Excluded from EE Population 24
4.8 Safety Evaluation 24
4.8.1 Treatment Exposure 24
4.8.2 Adverse Events 25
4.8.3 Genitourinary Side Effects 25
4.8.4 Gynecological Infections 26
4.8.5 Dipstick Urinalysis and Urine Culture 26
4.8.6 Gynecological Examination 27
4.8.7 Sexually Transmitted Infection Tests 27
4.8.8 Clinical Laboratory Evaluation 27
4.8.9 Vital Signs 27
4.8.10 Pregnancy Outcome 27
4.9 Subject Satisfaction 28
4.9.1 Subject Satisfaction Questionnaires 28
4.9.2 Sexual Function Questionnaire 30
4.9.3 Sexual Satisfaction and Lubrication 30
4.10 Missing Data Handling 31
4.10.1 Imputing partial AE and prior/concomitant medication start dates 31
4.10.2 Imputing partial AE and prior/concomitant medication stop dates 32
4.11 Pregnancy Intendedness 32
4.11.1 Determination of Sample Size 32
5 Appendix 33
5.1 Grading for Vulvar, Vaginal, or Cervical Findings 33
6 PROPOSED TABLES, FIGURES AND LISTINGS 34
6.1 Proposed Tables and Figures 34
6.2 Proposed Data Listings 37
7 REFERENCES 39

LIST OF TABLES

Table 1: Study Assessment and Procedures.....11
Table 2: Handling Rules of the Analysis Populations for Special Situations.....15
Table 3: Sexual Function Questionnaire Outcomes and Coding.....30

LIST OF FIGURES

Figure 1: Study Visit Timing Based on Menstrual Cycle at Enrollment.....13

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
BV	Bacterial Vaginosis
CBC	Complete Blood Count
CI	Confidence Interval
EC	Emergency Contraception
eCRF	Electronic Case Report Form
EE	Efficacy Evaluable
FDA	The U.S. Food and Drug Administration
FSD	Female Sexual Dysfunction
FSFI	Female Sexual Function Index
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
in	Inch
ITT	Intent-To-Treat
IUD	Intrauterine Device
kg	Kilogram
KM	Kaplan-Meier
lb	Pound
m	meter
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MITT	Modified Intent-to-Treat
mL	Milliliter
N-9	Nonoxynol-9
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation

Abbreviation	Definition
SE	Standard Error
STI	Sexually Transmitted Infection
SOC	System-Organ Class
US	United States
UTI	Urinary Tract Infection
VCAS	Virtual Clinical Adjudication System
WBC	While Blood Cell
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) for AMP002, Version FINAL describes the statistical methods to be used during the analyses and reporting of data collected under Phase 3 AMP002 Protocol, dated 01 November 2017. The planned analyses identified in this SAP may be included in the clinical study report (CSR), any regulatory submissions, or future manuscripts. Post-hoc exploratory analyses not identified in this SAP may also be performed to further examine study data and will be clearly identified as such in the final CSR.

This SAP is based upon the following study documents:

- AMP002-231564_Protocol SN0051_Version 4.0_dated 01-NOV-2017

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the U.S. Food and Drug Administration (FDA) and International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH).

2 STUDY OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objective

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

2.3 Exploratory Objectives

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

2.4 Primary Endpoint

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

2.5 Secondary Endpoints

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

2.6 Exploratory Endpoints

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

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

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

Through assessments including medical and gynecological history, pelvic examination, and laboratory procedures, subjects will be screened for eligibility in order to enroll approximately 1350 subjects into the study. After a screening period of up to 60 days, enrolled women will receive study drug. Each woman will participate in the study until she has completed seven study cycles. Women who have individual cycles that do not meet the criteria for an evaluable cycle will not have those cycles replaced by subsequent cycles in order to provide a total of seven evaluable cycles.

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

Table 1 presents an overview of the study assessments and procedures.

3.2 Schedule of Assessments

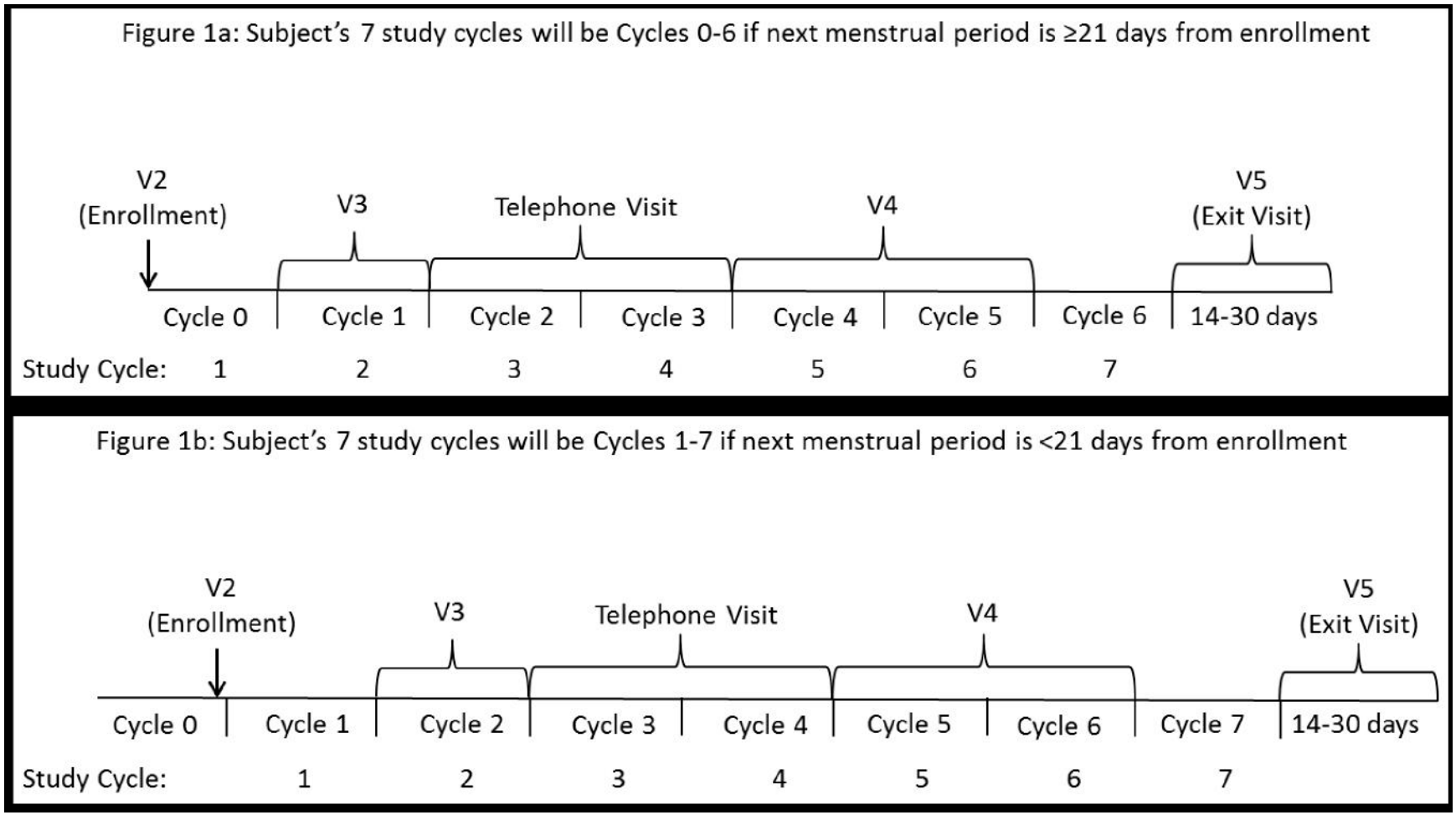
Table 1: Study Assessment and Procedures

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

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

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

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



V=clinical site visit

Visit 5/Exit visit is to take place 14-30 days after the seventh study cycle or from last use of study product for early termination (unless being followed for pregnancy)

Telephone Visit is to take place between V3 and V4

Notes: Duration of Cycle 0 is number of days from enrollment to start of first on-study menstrual period.

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures, and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Health Decisions procedures.

4.2 General Presentation Considerations

This section details general policies to be used for the statistical analyses. Deviations from these general policies may be given in the specific detailed sections of this statistical analysis plan. When this situation occurs, the rules set forth in the specific section take precedence over the general policies. The following policies will be applied to all data presentations and analyses:

- All statistical tests will use a 2-sided significance level of $a = 0.05$.
- Summary statistics will consist of the number and percentage of responses in each category for discrete variables, and N, mean, median, standard deviation (SD), minimum, and maximum for continuous variables.
- All mean and median values will be formatted to one more decimal place than the measured value. SD will be formatted to two more decimal places than the measured value.
- All percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form XX (XX.X), where the percentage is in the parentheses. The decimal of the percentage may be dropped due to space constraints when creating a table. The denominator for percentage calculations will be the number of non-missing observations.
- All listings will be sorted for presentation in order of site number, subject number, and date of procedure or event.
- When necessary for analysis purposes, partial dates will be completed (i.e., turned into complete dates) using the most conservative approach.
- All analysis and summary tables will have the population sample size in the column heading.
- Baseline is defined as the last non-missing measurement taken on (prior to treatment) or before enrollment.
- Calculating change from baseline to a visit will be done as follows: Change = Visit - Baseline
- Version 9.4 of SAS or higher will be the statistical software package used to produce all summaries, listings, statistical analyses, and graphs.

4.3 Analysis Populations

Intent-To-Treat (ITT): all subjects enrolled into the study.

Safety Population: ITT subjects who use at least one application of the study product.

Modified Intent-To-Treat (MITT): Subjects must meet requirements 1, 2, and 3 simultaneously and at least one of 4 or 5 to be included in MITT:

1. between 18 to 35 years of age (inclusive) at enrollment
2. at least one report of pregnancy after being enrolled (subjects with a positive serum pregnancy test at enrollment will not be included in the MITT population).
3. ITT subjects whose diaries indicate they had at least one episode of coitus while using the assigned study product (also referred as "Typical-Use")
4. have at least 1 cycle without any backup contraception or emergency contraception (EC) recorded in the eDiary product use questionnaire
5. became pregnant and the pregnancy had a conception date that occurred after enrollment and within 7 days of the date of last dose of study product.

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

The Table 2 provides the handling rules of the analysis populations for special situations.

Table 2: Handling Rules of the Analysis Populations for Special Situations

Situation	Rule for ITT Population	Rule for all Other Populations
Screen failures	Excluded	Excluded
Not receiving treatment	Included	Excluded
Subject enrolled into the study more than once	Only include first enrollment	Only include first enrollment
Subject enrolled in another interventional contraceptive study	Included	Excluded

Screen failures and the 2nd enrollment for a subject will be excluded from all tables and listings except for the data listing which is specifically designed to list these subjects. However, rescreening will be allowed for this study.

4.4 Study Subjects

4.4.1 Disposition of Subjects

Subject disposition will be summarized for the ITT population. The following data will be presented:

- The number and percentage of subjects who completed or discontinued prematurely from the study. The number and percentage of subjects who discontinued for each reason will be presented. Data will be summarized for all subjects.
- A listing of subjects that discontinued prematurely from the study. The listing will include information about study center, subject number, age, date of enrollment, last study product use date, number of cycles completed, and reason for discontinuation.
- The number and percentage of all subjects at each scheduled visit.
- The number of subjects who were enrolled at each study center and the number and percentage of subjects who completed or discontinued at each study center will be summarized for all subjects.

The End of Study eCRF will be used to determine who discontinued prematurely from the study.

4.4.2 Study Protocol Deviations

The number and percentage of subjects with each violation from protocol inclusion and exclusion criteria will be summarized for all subjects in the ITT population.

4.5 Demographic and Pre-Treatment Characteristics

4.5.1 Demographic

Subject demographics will be summarized for the ITT, Safety Population, MITT, and EE populations. The summary of demographics will include age, race, ethnicity, height (in), and weight (lb) at baseline, and body mass index (kg/m^2).

A sensitivity analysis will also be performed for the ITT population to detect the differences between completers and non-completers with respect to the following characteristics: age, race, ethnicity, and body mass index ($kg/m^{2)}$.

4.5.2 Gynecological History

The following gynecological history data will be summarized for ITT population:

- The number and percentages of subjects with urinary tract infection (UTI) history (never, not in the past year, once in the past year, twice in the past year, more than twice in the past year, don't know/uncertain);
- The number and percentages of subjects with yeast infection history (never, not in the past year, once in the past year, twice in the past year, more than twice in the past year, don't know/uncertain);

- The number and percentages of subjects with bacterial vaginosis history (never, not in the past year, once in the past year, twice in the past year, more than twice in the past year, don't know/uncertain);
- Summary statistics (sample size, mean, median, SD, minimum, and maximum) for age at menarche;
- Summary statistics (sample size, mean, median, SD, minimum, and maximum) for typical length of menstrual cycle length (in days);
- Summary statistics (sample size, mean, median, SD, minimum, and maximum) for typical duration of menses (in days).

4.5.3 Contraception Use History

The number and percentage of current users, recent users (used within last 6 months), prior users (used greater than 6 months ago), and never users of the following contraceptive methods reported within the past 1 year from the time of screening will be summarized: male condom, female condom, diaphragm/cervical cap/sponge, oral contraceptive, spermicide, vaginal ring, contraceptive patch, rhythm method (fertility awareness), withdrawal method, progestin or non-hormonal intrauterine device (IUD), injectable contraceptive, contraceptive implant), abstinence, emergency contraception, and other.

This summary will be conducted on the ITT population.

4.5.4 Obstetric History

Number of pregnancies, number of full-term liveborn deliveries, number of preterm liveborn deliveries, number of living children, number of stillbirth/intrauterine demise > 20 weeks deliveries, number of ectopic pregnancies, number of spontaneous abortions, and number of elective abortions will be summarized descriptively. This summary will be conducted on the ITT population.

4.5.5 Medical History

Medical history will be coded using MedDRA. The number and percentage of subjects reporting each medical condition will be summarized by body system and preferred term for the ITT population. The number and percentage of subjects reporting any medical history will also be reported.

If subject reports the same medical condition more than once, then that subject is only counted once for the summary of that medical condition.

All medical history will be coded with MedDRA 21.0.

4.5.6 Pre-Treatment Signs and Symptoms

Pre-treatment signs and symptoms will be coded using MedDRA. The number and percentage of subjects reporting each pre-treatment sign and symptom will be summarized by body system and preferred term for the Safety population. The number and percentage of subjects reporting any pre-treatment signs and symptoms will also be reported.

If subject reports the same pre-treatment sign or symptom more than once, then that subject is only counted once for the summary of that pre-treatment sign or symptom.

All pre-treatment signs and symptoms will be coded with MedDRA 21.0.

4.5.7 Prior and Concomitant Medications

Summaries for prior and concomitant medications will be done for the Safety Population. The following summaries will be performed:

- Prior Medications – Prior medications are considered to be any medication that was stopped prior to the date of enrollment.
- Concomitant Medications – Concomitant medications are considered to be any medication that was taken on or after the date of enrollment.

All medications will be coded to the therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug classifications. The WHO Drug dictionary version used for this study will be March 2018.

Each summary will give the number and percentage of subjects who took medications that were coded to each generic drug name and therapeutic drug class, as well as the number and percentage of subjects that took any medication at all.

4.6 Treatment Compliance and Study Instruction Departures

Treatment compliance in the Safety Population will be calculated using 5 indices. These 5 indices are the proportion of following acts among all acts of intercourse:

A. study product only and was used as directed
B. study product only but product not used as directed
C. study product and other birth control were used
D. other birth control only was used
E. no study drug or birth control was used (i.e. unprotected intercourse)
F.

For individual subjects, each index will be calculated as:

$$\frac{\text{Total number of acts of intercourse for this index in all cycles}}{\text{Total number of acts of intercourse in all cycles}} \times 100$$

Descriptive statistics will be presented for each index.

Based on the index value, each subject will be in one, and only one, of the following categories for study method only and proper use:

- 0% - 49%
- 50% - 69%
- 70% - 89%
- > = 90%

Based on the index value, each subject will be in one, and only one, of the following categories for study product only but product not used as directed, study product and other birth control, other birth control only, and no birth control was used:

- 0% - 9%
- 10% - 19%
- 20% - 29%
- 30% - 39%
- 40% - 49%
- ≥50%

The number and percentage of subjects in each of the above categories will be presented for all subjects.

Various departures from study instructions are as follows:

- Intercourse occurred more than 1 hour but less than or equal to 1.5 hours after application
- Intercourse occurred more than 1.5 hours but less than or equal to 2 hours after application
- Intercourse occurred more than 2 hours but less than or equal to 2.5 hours after application
- Intercourse occurred more than 2.5 hours after application

The departures from study instructions summary will include the number and percent of subjects who report at least one departure from study instructions. The table will also summarize the percentage of acts with departure and categorize them in the following categories:

- 0% - 5%
- 6% - 10%
- 11% - 25%
- 26% - 49%
- ≥ 50%

4.7 Efficacy Evaluation

Typical-use 7-cycle pregnancy analyses will be done for the MITT populations, and perfect-use 7-cycle pregnancy analyses will be done for the EE population.

4.7.1 Analysis and Data Conventions

4.7.1.1 Definition of Baseline

Baseline is defined as the last non-missing measurement on (prior to treatment) or before enrollment.

4.7.1.2 Definition of Cycle

The cycle number will be derived from the eCRF menses start dates as follows:

Cycle 0 = date of enrollment through date before 1st menses started after enrollment (Note: this cycle includes cases where menses started on the day of enrollment)

Cycle 1 = date 1st menses started after enrollment through date before 2nd menses started after enrollment

Cycle 2 = date 2nd menses started after enrollment through date before 3rd menses started after enrollment

Cycle 3 = date 3rd menses started after enrollment through date before 4th menses started after enrollment

Cycle 4 = date 4th menses started after enrollment through date before 5th menses started after enrollment

Cycle 5 = date 5th menses started after enrollment through date before 6th menses started after enrollment

Cycle 6 = date 6th menses started after enrollment through date before 7th menses started after enrollment

Cycle 7 = date 7th menses started after enrollment through date before 8th menses started after enrollment

Cycle 8 = date 8th menses started after enrollment through date before 9th menses started after enrollment

If the subject became pregnant and the pregnancy adjudication committee estimated the date of conception, but the subject has no diary for the cycle that contains the estimated date of conception, then the pregnancy will be assigned to day 14 of the cycle. If partial start/end dates occur, then it will be assumed that the cycles were equal length to determine the imputed start/end dates of the cycle. If estimated date of conception could not be provided by the pregnancy adjudication committee due to insufficient information, then pregnancy will be assigned day 14 of the first potentially evaluable cycle after enrollment unless there is documentation to show the pregnancy occurred in a later cycle.

4.7.1.3 Multiple Comparisons/Multiplicity

This study has only one primary endpoint, no multiplicity adjustment is necessary.

4.7.1.4 Interim Analyses

No formal statistical interim analyses for efficacy are planned for this study.

4.7.2 Primary Efficacy Analysis

The primary efficacy endpoint is the cumulative percentage of typical-use 7-cycle pregnancy. The primary hypothesis to be tested is whether subjects using Amphora vaginal gel have a 7-cycle cumulative pregnancy percentage less than or equal to 21%, that is,

$$H_{O:}\ \pi_A > 21\%\ \ vs.\ \ H_{A:}\ \pi_A \leq 21\%$$

where π_A represents the 7-cycle cumulative pregnancy percentage for Amphora. The Kaplan-Meier (KM) estimate and its 95% CI (based on Greenwood's method) of the 7-cycle cumulative pregnancy percentage of women in the MITT population will be calculated. If the upper bound of the 95% CI is $\leq 21\%$, then the null hypothesis will be rejected and the conclusion will be that the 7-cycle cumulative pregnancy percentage is $\leq 21\%$.

4.7.2.1 Derivation of the Primary Endpoint

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

- Determining the evaluable cycles: Cycles must meet all conditions given below to be considered evaluable cycles:
    - Cycles 0-6 for subjects who are enrolled for at least 21 days prior to the start of her next menses (includes subjects who start menses on the day of enrollment), or Cycles 1-7 for subjects who are enrolled in less than 21 days prior to the start of her next menses;
    - Cycles that are indicated by the eDiary product use questionnaire that no backup contraception or EC are used or in which subjects become pregnant;
    - Cycles with length within the range of 21 days to 35 days or in which subjects have an on-treatment pregnancy.
    - Cycles where at least one entry of diary is recorded or in which subjects are pregnant.
    - Cycles must have at least one act of intercourse.
    - Cycles must start on or before date of last study product use + 7 days
    - For EE analyses, cycles in which the eDiaries indicate that study drug was used correctly for every act of intercourse during that cycle.

- Compressing the evaluable cycles: Evaluable cycles will be compressed to form contiguous evaluable cycles for each subject sequentially.

- Determining the date of conception:

    - The Pregnancy Review Committee will review all confirmed pregnancies except for subjects who had a borderline or positive b-hCG serum at enrollment, and this information will be provided to data management in an Excel file from the VCAS database. The committee will determine if the pregnancy occurred on-treatment (defined as date of conception between enrollment to <8 days after final study product use) or not on-treatment (defined as date of conception prior to enrollment or after 7 days following final study product use), or whether there is insufficient information for adjudication. The Pregnancy Review Committee assessment of pregnancies being on-treatment or not will be used for the primary endpoint. Pregnancies that could not be adjudicated due to insufficient information will be treated as on-treatment. The medical monitor will review the VCAS file and if the committee provided their own estimated date of conception in the "If disagree, provide rationale" field then the medical monitor will create a new column in the VCAS excel file and will enter into the new column the estimated date of conception provided by the adjudication committee in the "If disagree, provide rationale" field. This re-entry of the estimated date of conception will enable the programming of the statistical analysis.

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

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

- Determining of censoring for cycles to pregnancy: Subjects will be censored from analysis at the earliest of:

    - The estimated date of conception that occurred between enrollment and <8 days after final study drug use
    - Date of last study product use + 7 days

- The conclusion of her seventh cycle on-treatment + 7 days (up to a total of 252 days [or 301 days for the sensitivity analysis, allowing a cycle length range of 21 to 42 days])

4.7.3 Secondary Efficacy Analyses

4.7.3.1 Sensitivity Analysis with Respect to the Cycle Range

The primary analysis will be repeated with the cycle length expanded from 21 – 35 days to 21 – 42 days.

4.7.3.2 Sensitivity Analysis with Respect to the Dosing Time with Respect to Sexual Intercourse

To evaluate the effect of the dosing time with respect to the time of sexual intercourse, the number and percentage of intercourse acts in the following categories will be shown:

- The number of intercourse acts where dosing time <= 1 hour before intercourse
- The number of intercourse acts where dosing time > 1.5 hours but <= 2 hours before intercourse
- The number of intercourse acts where dosing time > 2 hours but <= 2.5 hours before intercourse
- The number of intercourse acts where dosing time > 2.5 hours before intercourse

The number and percentage of subjects in the following categories will also be shown:

- The number of pregnancies that occurred in a cycle where the longest duration from dosing time to intercourse was <= 1 hour
- The number of pregnancies that occurred in a cycle where the longest duration from dosing time to intercourse was > 1 hour but <= 1.5 hours
- The number of pregnancies that occurred in a cycle where the longest duration from dosing time to intercourse was >1.5 hours but <=2 hours
- The number of pregnancies that occurred in a cycle where the longest duration from dosing time to intercourse was >2 hours but <=2.5 hours
- The number of pregnancies that occurred in a cycle where the longest duration from dosing time to intercourse was >2.5 hours

4.7.3.3 Perfect-Use 7-Cycle Pregnancy Probabilities

As a secondary evaluation of contraceptive efficacy, the 7-cycle cumulative pregnancy percentage of women in the EE population will be estimated by KM method. Each woman in the EE population is evaluated for efficacy for menstrual cycles when she has used the study product consistently and correctly as reflected in her diary recordings. Non-perfect-use and non-evaluable cycles will be removed from the analysis. The perfect-use analysis will use the same conventions and analysis rules mentioned for the typical-use analysis, except that non-perfect cycles with a pregnancy will not be included. Greenwood's method for calculating variance will be used to construct 95% confidence intervals.

4.7.3.4 Pearl Rates from 7-Cycle Data

The Pearl rate, also called the Pearl index (Higgins 1985), is defined as the number of pregnancies in 100 woman-years of method use.

Because this study will use natural women cycles and the days will vary from woman to woman, the primary method of analysis will be:

$$\frac{\text{Number of pregnancies} * 365.25 * 100}{\text{Total number of days exposed}}$$

For comparison, the Pearl rate will also be calculated using a 28-day cycle:

$$\frac{\text{Number of pregnancies} * 13 * 100}{\text{Total number of menstrual cycles}}$$

Both cycle-based and year based Pearl rates and their two-sided 95% CI will be presented, assuming a Poisson distribution. The Pearl rate will be done for the MITT and EE populations.

4.7.3.5 Summary of Number of Diary Cycles and Cycles Excluded from EE Population

The average number of diary cycles will be summarized for all MITT subjects through seven cycles. Diaries where backup contraception or EC were used will be excluded unless the subject became pregnant in that cycle. The number of cycles with incorrect use of study product which result in exclusion from the EE analysis will be calculated for each subject and summarized descriptively.

4.8 Safety Evaluation

All safety analyses will be done for the Safety Population.

All laboratory data will be presented in the conventional United States (US) units.

Final evaluation is defined to be the last evaluation performed after the date of enrollment.

4.8.1 Treatment Exposure

Treatment exposure will be summarized for the Safety Population. Treatment exposure will be summarized by the number of times the treatments are used in acts of intercourse, the length of time over which the treatments are used, the number of times study product was used per cycle, and the number of cycles in the study. The number of times the treatments are used in acts of intercourse will be calculated as the sum of total number of intercourse acts where study product used as directed, total number of intercourse acts where study product not used as directed, and total number of intercourse acts with study product and other birth control. The length of time will be calculated as: last date study product was used – date of enrollment + 1. The number of cycles in the study will be the highest numbered cycle that started on or before the date of last study product use + 1 (the +1 is to account for cycle 0 (subjects are randomized mid cycle and that cycle is cycle 0)).

4.8.2 Adverse Events

Incidence of adverse events will be summarized by SOC and PT. The number and percentage of subjects with each SOC and PT will be presented. Tables to summarize the incidence rates will be created for each of the following groups:

- Adverse events
- Serious adverse events
- Adverse events leading to premature discontinuation
- Adverse events by intensity
- Adverse events by relationship to study drug
- Adverse events by intensity and relationship to study drug (summary will present number of adverse events reported, not number of subjects)
- Adverse events presented in descending order of frequency by PT (no SOC shown)

If subject reports the same adverse event more than once, then that subject is only counted once for the summary of that adverse event, using the most severe intensity. The only exception to this will be for the summary by relationship to study drug. For that summary, if subject reports the same adverse event more than once, then that subject is only counted once for the summary of that adverse event, using the most severe relationship to study drug. The same principle will be applied at the body system level summary.

If intensity to study drug is reported as unknown, then the adverse event will be summarized as severe. If relationship to study drug is reported as unknown, then the adverse event will be summarized as certain/definite.

Adverse events that led to premature discontinuation from the study will be listed. Serious adverse events will also be listed. These listings will contain details about the adverse event such as intensity and relationship to study drug. Other supportive data, such as the subject's age, will be given.

A sensitivity analysis will also be performed for the Safety population to detect the differences between completers and non-completers with respect to adverse events.

All adverse events will be coded with MedDRA 21.0.

4.8.3 Genitourinary Side Effects

Genitourinary side effects will include vaginal discharge, vaginal burning, vaginal itching, vaginal pain, and other vaginal symptoms as reported by the subject in her eDiary. Partner side effects (burning, itching, pain, and other side effects) will also be captured in eDiary. Number and percentage of subjects with genitourinary side effects and partner side effects will be summarized in the following stratifications:

- By the time of symptom onset after product application
    - < 5 minutes
    - 5 – 30 minutes

- 31 - 60 minutes
- > 1 hour

- By the severity of the symptom
  - Mild
  - Moderate
  - Severe
- By duration of the symptom
  - < 5 minutes
  - 5 – 30 minutes
  - 31 – 60 minutes
  - > 1 hour

4.8.4 Gynecological Infections

The number and percentage of subjects responding to the question "Subject has a Vaginitis?" will be presented for the Safety Population by visit.. The following types of vaginitis will also be summarized by visit for subjects responding Yes or No for Vaginitis:

- Yeast/Monilia
- Bacterial VaginosisTrichomoniasis
- Other

Unscheduled visits will be grouped with associated visit (e.g., visit 3.1 will be included with visit 3).

4.8.5 Dipstick Urinalysis and Urine Culture

Dipstick urinalysis analytes include blood (negative, trace, 1+, 2+, 3+), leukocyte esterase (negative, trace, 1+, 2+, 3+), protein (negative, trace, 1+), and nitrites (negative, trace, 1+, 2+, 3+,4+). Number and percent of subjects for each category will be presented by visit and final evaluation.

For urine culture and UTI results, number and percent of subjects will be presented for the Safety Population by visit and final evaluation. Urine culture result categories are as follows: ≥100,000 CFU/ml, <100,000 CFU/ml, indeterminate and negative. UTI result categories are as follows: Yes – a symptomatic UTI: compliant of urinary symptoms and 1+ for analytes of blood, leukocyte esterase, protein or nitrites and a minimum bacterial count of 10,000 colony forming units (CFU)/mL with the presence of uropathogen; Yes – a symptomatic UTI: presence of symptoms and ≥ 100,000 CFU/mL presence of uropathogen without a positive leukocyte esterase by dipstick; Yes – an asymptomatic UTI : absence of symptoms and a bacterial count of ≥ 100,000 CFU/mL with the presence of uropathogen; No – not per protocol definitions.

Wet mount assessment results are classified as normal or abnormal. The number and percentage of subjects with improved (changed from abnormal in baseline to normal), no change, and worsened (changed from normal in baseline to abnormal) results will be presented for each visit and final evaluation. Number and percent of subjects in each sub-category of abnormal wet

mount (including WBC, trichomonas, hyphae/spores, clue cells (>20%)) will also be presented. Vaginal pH will also be summarized for each visit and final evaluation.

Unscheduled visits will be grouped with the associated visit (e.g., visit 3.1 will be included with visit 3).

4.8.6 Gynecological Examination

For gynecological examinations, each body system will be categorized as normal or abnormal. Gynecological examination changes from baseline will be categorized as improved, no change, or worsened for each body system. The number and percentage of subjects in each category of change will be given at each visit and final evaluation and body system.

An adaptation of *the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, Addendum 1 – Female Genital Grading Table for Use in Microbicide Studies* will be used by the investigator to grade changes from baseline in vulvar, vaginal or cervical findings noted during the gynecologic exam and determine if they are considered significant, as defined as at least one grade increase from baseline (see appendix 5.1).

Vulvar, vaginal, and cervical findings will be summarized by visit and final evaluation. The number and percentage of subjects and events for each grade will be presented.

Unscheduled visits will be grouped with the associated visit (e.g., visit 3.1 will be included with visit 3).

4.8.7 Sexually Transmitted Infection Tests

Sexually transmitted infections (STI) tests for chlamydia and gonorrhea will be classified as positive or negative. The number and percentage of subjects in each test result will be presented by visit. Unscheduled visits will be grouped with the associated visit (e.g., visit 3.1 will be included with visit 3).

4.8.8 Clinical Laboratory Evaluation

CBC and chemistry and their change from baseline to final evaluation will be summarized.

A summary of shifts from baseline to final evaluation will be given for each parameter. The normal range for each parameter will be used to create categories of low, normal, or high. Any result that is higher (lower) than the upper (lower) limit of normal will be categorized as high (low) and any result within the lower and upper limits of normal will be categorized as normal.

CBC and chemistry data will be located in separate tables.

4.8.9 Vital Signs

Vital signs and weight and their change from baseline will be summarized by visit. Unscheduled visits will be grouped with the associated visit (e.g., visit 3.1 will be included with visit 3).

4.8.10 Pregnancy Outcome

The pregnancy outcomes will be summarized as follows:

- The number and percentages for each fetal status category (pre-term birth, full term birth, stillbirth, spontaneous termination, induced termination, ectopic pregnancy, unknown).

- The number and percentages for sex of fetus (male, female, unknown)
- The number and percentages for maternal complications
- Summary statistics (sample size, mean, median, SD, minimum, and maximum) for Apgar Scores (1 min and 5 min)
- Summary statistics (sample size, mean, median, SD, minimum, and maximum) for the gestational age (weeks)
- Summary statistics (sample size, mean, median, SD, minimum, and maximum) for the birth weight (pounds)

4.9 Subject Satisfaction

All analyses described in this section will be performed on the Safety population.

4.9.1 Subject Satisfaction Questionnaires

Four endpoints will be defined for Subject Satisfaction Questionnaires:

- Satisfaction level to study product which will be evaluated at baseline and visit 3-5 based on the answers to question "how satisfied were you with your most recent/study birth control method":
    a. Very satisfied
    b. Satisfied
    c. Somewhat satisfied
    d. Somewhat dissatisfied
    e. Dissatisfied
- Likelihood of recommendation as a vaginal contraceptive gel which will be evaluated at Visit 3-5 with outcome:
    f. Very likely
    g. Likely
    h. Somewhat likely
    i. Somewhat unlikely
    j. Unlikely
- Likelihood of recommendation as another birth control option which will be evaluated at Visit 3-5 with outcome:
    k. Very likely
    l. Likely
    m. Somewhat likely
    n. Somewhat unlikely
    o. Unlikely
- Likelihood to continue use which will be evaluated at Visit 3-5 with outcome:
    p. Very likely

q. Likely
r. Somewhat likely
s. Somewhat unlikely
t. Unlikely

All four endpoints will be summarized using frequency and percentage by visit and outcome level. Unscheduled visits will be grouped with the associated visit (e.g., visit 3.1 will be included with visit 3).

4.9.2 Sexual Function Questionnaire

The Sexual Function Questionnaire has 10 variables:

1. Vaginal dryness during sexual activity
2. Lack of sexual interest or desire
3. Vaginal tightness
4. Pain during penetration or intercourse
5. Anxiety about your sexual performance
6. Unable to orgasm
7. Vaginal bleeding or irritation from penetration or intercourse
8. Increased sensitivity of your skin to intimate touching
9. Sharp pain inside or outside your vagina
10. Other problem with sexuality

The outcomes and coding for these 10 Variables are provided in Table 3.

Table 3: Sexual Function Questionnaire Outcomes and Coding

Subject's Answer	***Code***
Not at all	1
Seldom, less than 25% of the time	2
Sometimes, about 50% of the time	3
Usually, about 75% of the time	4
Always	5
The problem stops your sexual activity	6

All variables given above will be summarized using frequency and percentage by visit and outcome categories. Unscheduled visits will be grouped with the associated visit (e.g., visit 3.1 will be included with visit 3).

4.9.3 Sexual Satisfaction and Lubrication

Sexual Satisfaction and Lubrication will be assessed with the following questions, asked at baseline and at each subsequent visit:

- Baseline: What impact did your most recent contraceptive method have on your sex life in the last 4 weeks of use?
- Visit 3-5: What impact has the study contraceptive method had on your sex life since your last study visit?

The response set for these questions is as follows:

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

The Female Sexual Function Index (FSFI), a 19-item questionnaire, provides scores on six domains of sexual function (desire, arousal, lubrication, orgasm, satisfaction, and pain) as well as a total score. Only question 10 from the FSFI will be summarized according to the following response set:

- 10. Over the past 4 weeks, how difficult was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?
    u. No sexual activity
    f. Extremely difficult or impossible
    g. Very difficult
    h. Difficult
    i. Slightly difficult
    j. Not difficult

All variables given above will be summarized using frequency and percentage by visit and outcome categories. Unscheduled visits will be grouped with the associated visit (e.g., visit 3.1 will be included with visit 3).

4.10 Missing Data Handling

4.10.1 Imputing partial AE and prior/concomitant medication start dates

a) If the year is unknown, the date will not be imputed if the stop date of the event is earlier than the first dose time; otherwise, it will be imputed as the year of the first dose time.

b) If the month is unknown, then:

11. If the year matches the first dose date, then impute to the month and day of the first dose date.
12. Otherwise, assign 'January'.

c) If the day is unknown, then:

13. If the month and year match the first dose date, then impute to the day of the first dose date.
14. Otherwise, assign '01'.

4.10.2 Imputing partial AE and prior/concomitant medication stop dates

a) If the year is unknown, the date will not be imputed if the start time of the event is after the last dose time, otherwise it will be imputed as the year of the last dose time.

b) If the month is unknown, then assign 'December'.

c) If the day is unknown, then impute to the last day of the month.

4.11 Pregnancy Intendedness

The pregnancy intendedness scale and its change from the baseline will be summarized descriptively by visit. Unscheduled visits will be grouped with the associated visit (e.g., visit 3.1 will be included with visit 3).

4.11.1 Determination of Sample Size

Simulation methods are used to evaluate the likelihood of various sample sizes providing enough information to test the primary hypothesis (one-sided Type 1 error of 0.025) and enough use cycles of Amphora gel to address other regulatory requirements. The six month (183 d) cumulative pregnancy percentage was estimated using Kaplan-Meier methods.

The sample size determination assumes the following:

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

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

5 Appendix

5.1 Grading for Vulvar, Vaginal, or Cervical Findings

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

Parameter	Grade 0	Grade 1
Bleeding	None	Present
Petechiae	None	Present
Sloughing	None	Present

6 PROPOSED TABLES, FIGURES AND LISTINGS

6.1 Proposed Tables and Figures

Number	Title	Population
14.1.1	Subject Disposition	ITT
14.1.2	Listing of Subjects that Discontinued Prematurely	ITT
14.1.3	Number of Subjects at Each Visit	ITT
14.1.4	Number of Subjects at Each Study Site	ITT
14.1.5	Summary of Protocol Deviations	Safety Population
14.1.6	Demographics	ITT
14.1.6.1	Demographics for the Safety Population	Safety Population
14.1.6.2	Demographics for the Modified Intent-to-Treat Population	MITT
14.1.6.3	Demographics for the Efficacy Evaluable Population	EE
14.1.7	Sensitivity Analysis to Dropouts with Respect to Demography	ITT
14.1.8	Gynecological History	ITT
14.1.9	Contraception Use History	ITT
14.1.10	Obstetric History	ITT
14.1.11	Medical History	ITT
14.1.12	Pre-Treatment Signs and Symptoms	ITT
14.1.13	Incidence of Prior Medications	Safety Population
14.1.14	Incidence of Concomitant Medications	Safety Population
14.1.15	Summary of Compliance as Determined by Contraceptive Method	Safety Population
14.1.16	Percent of Coital Acts as Determined by Contraceptive Method	Safety Population
14.1.17	Percent of Coital Acts with Departures from Study Instructions	Safety Population
14.1.18 (figure)	Percentage of Subjects who Completed the Study or Prematurely Discontinued	ITT

Number	Title	Population
14.2.1	Seven-Cycle Cumulative Pregnancy Probabilities for Subjects with Typical-Use	MITT
14.2.2	Sensitivity Analysis with Respect to the Cycle Length	MITT
14.2.3	Sensitivity Analysis with Respect to the Dosing Time with Respect to Sexual Intercourse	MITT
14.2.4	Seven-Cycle Cumulative Pregnancy Probabilities for Subjects with Perfect-Use	EE
14.2.5	Typical-Use Seven-Cycle Based Pearl Rates	MITT
14.2.6	Perfect-Use Seven-Cycle Based Pearl Rates	EE
14.2.7	Summary of Number of Evaluable Cycles	MITT
14.2.8	Summary of Cycles Excluded from Efficacy Evaluable Analysis	MITT
14.2.9 (figure)	Pregnancy Percentage Curves by Kaplan-Meier Method for Subjects with Typical Use	MITT
14.2.10 (figure)	Pregnancy Percentage Curves by Kaplan-Meier Method for Subjects with Perfect-Use	EE
14.3.1.1	Incidence of Adverse Events	Safety
14.3.1.2	Incidence of Serious Adverse Events	Safety
14.3.1.3	Incidence of Adverse Events Leading to Premature Discontinuation	Safety Population
14.3.1.4	Incidence of Adverse Events by Intensity	Safety
14.3.1.5	Incidence of Adverse Events by Relationship to Treatment	Safety
14.3.1.6	Incidence of Adverse Events by Intensity and Relationship to Treatment	Safety Population
14.3.1.7	Incidence of Adverse Events by Descending Frequency	Safety
14.3.1.8	Sensitivity Analysis to Dropouts with Respect to Adverse Events	Safety
14.3.2.1	Listing of Serious Adverse Events	Safety Population
14.3.2.2	Listing of Adverse Events that Led to Premature Discontinuation	Safety Population
14.3.5.1	Treatment Exposure	Safety Population

Number	Title	Population
14.3.5.2	Incidence of Genitourinary Side Effects by the Time of Symptom Onset after Product Application	Safety Population
14.3.5.3	Incidence of Genitourinary Side Effects by Severity of the Symptom	Safety Population
14.3.5.4	Incidence of Genitourinary Side Effects by Duration of the Symptom	Safety Population
14.3.5.5	Incidence of Genitourinary Infections	Safety Population
14.3.5.6	Dipstick Urinalysis and Urine Culture Results	Safety Population
14.3.5.7	Summary of Wet Mount Assessment Results	Safety Population
14.3.5.8	Change in Gynecological Examination Findings	Safety Population
14.3.5.9	Incidence of Vulvar, Vaginal, or Cervical Findings	Safety Population
14.3.5.10	Sexually Transmitted Infection Test Results	Safety Population
14.3.5.11	Mean Change from Baseline to Final Evaluation for Hematology Analytes	Safety Population
14.3.5.12	Shift from Baseline to Final Evaluation for Hematology Analytes	Safety Population
14.3.5.13	Mean Change from Baseline to Final Evaluation for Clinical Chemistry Analytes	Safety Population
14.3.5.14	Shift from Baseline to Final Evaluation for Clinical Chemistry Analytes	Safety Population
14.3.5.15	Mean Change from Baseline to Each Visit for Vital Signs and Weight	Safety Population
14.3.5.16	Summary of Pregnancy Outcomes	Safety Population
14.3.5.17	Summary of Subject Satisfaction Questionnaires	Safety Population
14.3.5.18	Summary of Sexual Function Questionnaire	Safety Population
14.3.5.19	Summary of Sexual Satisfaction and Lubrication	Safety Population
14.3.5.20	Summary of Pregnancy Intendedness	MITT

6.2 Proposed Data Listings

Number	Title	Population
16.2.1.1	Analysis Population	ITT
16.2.1.2	Subject Disposition	ITT
16.2.1.4	End of Trial	ITT
16.2.2.1	Protocol Deviations	ITT
16.2.3.1	Subjects Excluded from MITT or EE Population	ITT
16.2.3.2	Screen Failures and Second Enrollments	ITT
16.2.4.1	Demographics	ITT
16.2.4.2	Medical History	ITT
16.2.4.3	Gynecological History	ITT
16.2.4.4	Contraceptive History	ITT
16.2.4.5	Pregnancy History	ITT
16.2.4.6	Prior and Concomitant Medications	ITT
16.2.4.7	Pre-Treatment Signs and Symptoms	ITT
16.2.5.1	Product Use Diary	ITT
16.2.5.2	Nightly Diary	ITT
16.2.5.3	Follow-up Diary	ITT
16.2.6.1	Menses Data	ITT
16.2.6.2	Pregnancy Test Results	ITT
16.2.6.3	Pregnancy Notification	ITT
16.2.6.4	Pregnancy Outcomes	ITT
16.2.6.5	Ultrasound Report	ITT
16.2.7.1	Adverse Events	ITT
16.2.8.1	Dipstick and Urine Culture Assessments	ITT
16.2.8.2	Laboratory Assessments: STI Tests	ITT

Number	Title	Population
16.2.8.3	Bacterial Vaginosis and Yeast Assessments	ITT
16.2.8.4	Hematology Tests	ITT
16.2.8.5	Clinical Chemistry Tests	ITT
16.2.9.1	Gynecological Exam	ITT
16.2.9.2	Vital Signs	ITT
16.2.9.3	Physical Exam	ITT
16.3.1	Subject Satisfaction Questionnaires	ITT
16.3.2	Sexual Function Questionnaire	ITT
16.3.3	Sexual Satisfaction and Lubrication	ITT
16.4.1	Pregnancy Intendedness	ITT

7 REFERENCES

Higgens J.E., Wilkens L.R. (1985) Statistical comparison of Pearl rates. Am J Obstet Gynecol 1985; 151:656-9.