CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208352
Priority or Standard	Standard
Submit Date(s)	June 30, 2016
Received Date(s)	July 2, 2016
PDUFA Goal Date	May 2, 2016
Reviewer Name(s)	Regina Zopf, MD, MPH
Review Completion Date	April 26, 2016
Established Name	Lactic acid, Citric acid, Potassium bitartrate Vaginal Gel
(Proposed) Trade Name	Amphora Gel
Therapeutic Class	Contraceptive gel
Applicant	Evofem, Inc.
Formulation(s)	Lactic acid 1.76%, Citric acid 1.00%, Potassium bitartrate 0.40%
Dosing Regimen	A single applicator of AMPHORA™ gel (5 g) applied within one hour of vaginal intercourse; repeat before each episode intercourse.
Indication(s)	Prevention of pregnancy
Intended Population(s)	Sexually active, reproductive age women

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AE	Adverse Event
BV	Bacterial Vaginosis
CDRH	Center for Devices and Radiological Health
CI	Confidence Interval
CRO	Contract Research Organization
CSR	Clinical Study Report
DBRUP	Division of Reproductive, Bone and Urologic Products
DRUP	Division of Reproductive and Urologic Products (former name of DBRUP)
DSMB	Data Safety Monitoring Board
EC	Emergency Contraception
eCRF	Electronic Case Report Form
EOP2	End-of-phase 2
FDA	Food and Drug Administration
GRAS	Generally Regarded as Safe
HIV	Human Immunodeficiency Virus
IND	Investigational New Drug
IR	Information Request
KM	Kaplan-Meier
LMP	Last menstrual period
N-9	Nonoxynol-9
NDA	New Drug Application
PCT	Post Coital Test
PI	Pearl Index
SAE	Serious adverse event
UTI	Urinary Tract Infection

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This product is not recommended for approval. A complete response (CR) with a path forward should be provided to the Applicant. Reasons for a CR include but are not limited to the following:

- Did not meet non-inferiority criteria for primary efficacy endpoint (US Data).
- Insufficient cycles for efficacy analysis due to
    - high variability in cycle length with a large number of non-evaluable cycles (based on the reported cycle length, they are likely to be non-ovulatory cycles in which the woman was not at risk for pregnancy)
    - discrepancies between the US and Russian data, such that the Russian efficacy and safety data are not considered generalizable to the US population. For this reason, we have not relied upon the Russian data in the approvability decision.
- Poor study conduct due to
    - high rate of discontinuation due to reasons other than pregnancy.
    - the statistical analyses of primary and secondary efficacy endpoints that included compressed data beyond 7 and 13 cycles.
    - inadequate collection of adverse events. Adverse events that occurred within the first hour of product use were not collected or recorded, which limits the safety conclusions that can be made.

For a path forward, we recommend a double-blind, non-inferiority trial to evaluate the pregnancy rate in women using Amphora versus nonoxynyl-9 gel. The majority of the data should come from the US population and any foreign data submitted should be generalizable to the US population. The statistical analysis plan should be pre-specified and submitted for review and comment prior to locking the database. Ovulatory cycles should be well defined based on physiologic evidence and cycles that fall outside of this range should be excluded from data analysis for efficacy evaluations. The Applicant should make every effort to minimize loss-to-follow up and to obtain data through the trial period despite discontinuation from the study.

1.2 Risk Benefit Assessment

In this application, Amphora Gel was inferior to nonoxynol-9 (N-9) gel for prevention of pregnancy. The benefit/risk profile is poor due to lack of efficacy and does not support approval of Amphora Gel.

1.3 Recommendations for Postmarket Risk Management Activities

This is deferred to the next review cycle.

1.4 Recommendations for Postmarket Studies/Clinical Trial

This is deferred to the next review cycle.

2 Introduction and Regulatory Background

2.1 Product Information

A spermicidal gel is a contraceptive method that inhibits the motility of and/or destroys sperm when the gel is inserted vaginally prior to sexual intercourse. There are many commercially available spermicides in the United States; however, this is the first New Drug Application for a topical spermicidal gel received by the FDA. The Program for Topical Prevention of Contraception and Disease (TOPCAD) originally developed the gel for its contraceptive and antimicrobial activity. CONRAD developed this gel as a bioadhesive vehicle for microbicides under Investigation New Drug (IND) Application number 64,623, where it was noted to have acid-buffering properties that enabled its use as a spermicidal gel.[1] CONRAD licensed the gel (then known as Acidform gel) to Evofem, Inc. in 2010. CONRAD authorized Evofem to cross-reference IND 64623 for preclinical, manufacturing, and clinical data. Evofem submitted IND 109300 on July 15, 2010 to develop the gel as a spermicide for prevention of pregnancy. Evofem has continued the development of this product and submitted this New Drug Application under the 505 (b)(2) pathway.

The established name of this gel is Lactic Acid, Citric Acid, and Potassium Bitartrate Vaginal Gel, 1.76 %/1 %/0.4%. In June 2004, Center for Devices and Radiological Health (CDRH) approved the gel under the 510(k) approval pathway, trade name “Instead Personal Lubricant” (application number K033776) –for use as a personal lubricant. In 2010, the 510K was licensed to Evofem, Inc. for commercialization under the trade name Amphora.

The conditionally-approved proprietary name this contraceptive gel is Amphora. It will be referred to throughout the review as Amphora, except for historical references in which “Acidform” was used. The proposed indication of this product is prevention of pregnancy.

The active ingredients, lactic acid (88 mg), citric acid (50 mg), and potassium bitartrate (20 mg), are “generally regarded as safe” (GRAS) chemicals by the FDA. Lactic acid and citric acid occur naturally in the human body and potassium bitartrate is the potassium salt that occurs naturally in fruits and is a byproduct of wine-making.

2.2 Currently Available Treatments for Proposed Indications

Historically, spermicidal gels have been developed and marketed in the US under the over-the-counter monograph process. This is the first spermicidal gel product evaluated under the NDA pathway and the first application for a prescription spermicidal product. There are no recently FDA-approved spermicidal gels on the US drug market; however, there are many commercially available over-the-counter (OTC) spermicides. The most common active ingredient in spermicide products is Nonoxonyl-9 (N-9), which acts as a surfactant attacking the acrosomal membranes of the sperm and subsequently immobilizing them. Two other OTC products evaluated for safety and efficacy by the FDA include the Today® N-9 Sponge (NDA 018683) and Delfen® N-9 vaginal aerosol (NDA 014349).

The Spermicide Trial Group evaluated N-9 in a large five-arm trial sponsored by the National Institutes of Health.[2] The N-9 arms included in the study were 52.5 mg gel, 100 mg gel, 150 mg gel, film (100 mg N-9), and suppository (100 mg N-9). The pregnancy rates after 6 months of typical use in each arm were as follows (**Error! Reference source not found.**):

Table 1: Pregnancy Rate by Treatment Arm at 6 Months of Typical Use

Nonoxyl-9 Arm	N-9 Gel 52.5 mg	N-9 Gel 100 mg	N-9 Gel 150 mg	Film (100 mg N-9)	Suppository (100 mg N-9)
Pregnancy rate (Confidence limits)	22% (16%, 18%)	16% (10%, 21%)	14% (9%, 19%)	12% (7%, 17%)	10% (6%, 15%)

Source: Table 4. Estimated Probability of Pregnancy by Spermicide Group.
Note: p-value for difference among 3 gel groups, 0.03; between Gel A and Gel B, 0.03*; between Gel A and Gel C, 0.02*; between Gel B and Gel C, 0.86; between three 100-mg product groups, 0.35.*
** Indicates significant difference between groups.*

A randomized controlled trial evaluated safety, efficacy and acceptability of N-9 (n=633) versus a spermicide mixture of two surfactants (C31 G, n=932) and revealed that over 6 months of use, the probability of pregnancy was 12% in both arms. Over 12 months of use, the pregnancy probability was 13.8% for C31G and 19.8% for N-9. There was a 40% discontinuation rate in this study for reasons other than pregnancy. There were similar safety outcomes in each group, with no significant differences found in frequency of urinary tract infection (UTI), bacterial vaginosis (BV), yeast, or genital discomfort in women (**Table 2**). The acceptability was equivalent in both arms with approximately 75% of women reporting they liked the gel and approximately 10% of women reporting that they did not like the gel.[3]

Table 2: Adverse Event by Treatment Arm

Outcome	C31G (% of women)	N-9 (% of women)	p-value
Urinary tract infection	8	8	0.55
Bacterial Vaginosis	15	15	0.78
Yeast	10	11	0.97
Genital discomfort	21	19	0.46

Reviewer's Comment:
There are more effective options for the prevention of pregnancy than spermicides, including hormonal contraception, and long-acting reversible contraception (LARC) options. Spermicides are not comparable to these methods in terms of efficacy; however, the safety profile of spermicides in the general population is favorable. The method is a choice for women who prefer a short-acting reversible contraceptive option, and who may not want to use continuous contraception.

2.3 Availability of Proposed Active Ingredients in the United States

The proposed active ingredients in Amphora gel, lactic acid, citric acid, and potassium bitartrate are all Generally Regarded as Safe (GRAS) by the FDA and have received a Type 1 conclusion from the Select Committee on GRAS Substances (SCOGS). A Type 1 conclusion means the following:

There is no evidence in the available information on [substance] that demonstrates or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or might reasonably be expected in the future.

All three are readily available in the United States. All three are used in food and marketed drug products with no limitation other than current good manufacturing principles.

2.4 Important Safety Issues with Consideration to Related Drugs

The main consideration in the assessment of efficacy and safety of vaginal spermicides is to maintain contraceptive effectiveness while limiting disruption of the vaginal mucosa. A phase 1 study evaluating frequent use of N-9 150 mg gel (4 times per day for 14 days) showed that 43% of users developed epithelial disruption of the cervix and vagina.[4] A subsequent randomized double-blind trial evaluating the safety of once-daily use of 52.5 mg of N-9 gel vs. placebo gel vs. no gel found the most common adverse event was vaginal discharge. The incidence of vaginal epithelial disruption in this trial was low (<2%) and did not differ significantly between the groups.[5] N-9 was studied in sex workers for its ability to prevent male-to-female

transmission of Human Immunodeficiency Virus (HIV). The women using N-9 with high frequency (3-5 applications daily) were twice as likely to acquire HIV compared to placebo groups.[6] They were using the spermicide with high frequency compared to that of a typical user; however, the concern for increased HIV transmission with use of any spermicide that can disrupt the vaginal microbiome is important to consider.

Other adverse events associated with spermicide use include UTI, BV, yeast and genital discomfort. Please see Section 2.2 **Error! Reference source not found.** for more detail.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Evofem, Inc. submitted NDA 208352 on July 2, 2015 pursuant to section 505(b)2 of the Federal Food, Drug, and Cosmetic Act (FDCA).

The FDA Division of Bone, Reproductive and Urologic Products (DBRUP) held a Type B Pre-IND meeting with Evofem on October 18, 2010 to discuss the 505(b)2 regulatory and drug development program of the gel for the indication of prevention of pregnancy. At this time, DBRUP agreed that a single pivotal study would be acceptable, with reference to IND 64623 and the literature for preclinical, manufacturing and additional clinical data.

DBRUP recommended and/or agreed to the following:

- A single pivotal randomized, non-inferiority trial with comparator arm Conceptrol 100 mg gel will be acceptable.
- Only colposcopy specialists would be blinded, as safety and efficacy endpoints of the trial were objective.
- Total product exposure of at least 5,000 cycles, with at least 200 subjects completing one year of Amphora gel use.
- Study population should be defined as follows:
    - Postmenarcheal females aged ≤ 35 years
    - No use of other methods of contraception, including emergency contraception
- Evofem must specify the proportion of efficacy that would be retained with a given non-inferiority margin and include justification of their non-inferiority margin.
- Additional male tolerability information should be obtained, for example through a small subset of male partners.
- Condom and diaphragm studies for integrity are required.
- Provide a Statistical Analysis Plan (SAP) stating if an interim analysis is planned
- Provide Kaplan Meier (KM) time-to-event analysis and Pearl Index calculations at 6 and 12 months.
- At least half of the cycles evaluated must be from US research sites.

The Applicant was amenable to conducting a non-inferiority trial as requested by DBRUP. They agreed to power the study to accomplish two objectives:

• Demonstrate an acceptable non-inferiority margin
• Provide 5,000 cycles of exposure data to Amphora, with 200 subjects completing a full year of treatment.

At the Applicant's request, a pre-NDA meeting was held on December 9, 2014 following completion of the pivotal trial (AMP 001). At this meeting, the DBRUP recommended the following:

- Clarify how many women in each of the analysis populations were from the US
- Address why a relatively large segment of the population was not included in the analysis.
- Provide a clear flow-chart of subject disposition from screening, through enrollment, through study completion and inclusion in efficacy populations.
- Define on-treatment pregnancy as any conceptions that occur within 7 days after the last use of the gel.
- Clarify why the efficacy analysis will consider day of ovulation.
- Provide data on ALL pregnancies occurring in the trial, regardless of whether they are determined to have been conceived on treatment or not.
- Provide justification for the non-inferiority margin selected.
- Address the large discrepancy between the Kaplan-Meier (KM) pregnancy rate and the Pearl Index
- Justify the Kaplan-Meier (KM) methodology that "compressed" cycles following a cycle in which back-up or emergency contraception was used, in order to provide contiguous cycles
- Provide data on the timing of gel application relative to intercourse, and perform a sensitivity analysis stratified by time of application. Also provide data on use of gel application with repeated acts of intercourse.
- Identify whether line-listings and data sets for studies cited as literature references in the meeting package will be provided, or whether the NDA will include only published literature
- Address concomitant use of other vaginal products, such as antimicrobials, on the performance of the vaginal gel
- Provide reasons for this high dropout rate, and provide a rationale as to why this does not adversely impact the generalizability of the data.
- Submit FDA-requested studies of safety in male partners.
- Submit concomitant use studies with condoms and diaphragms.
- Discuss the contribution of each API to the safety and/or effectiveness of the drug product

Reviewer's Comments:

- ***The Applicant has complied with most DBRUP requests from the Type B pre-IND and pre-NDA meetings; however, they have not adequately addressed how the***

high dropout rate from the AMP001 study does not adversely impact the generalizability or validity of the data from this trial. Additionally, they did not include women under the ages of 18 as per DBRUP recommendations.

- ***The Statistical Analysis Plan was never submitted for review prior to the NDA submission, despite written requests from DBRUP to the Applicant.***

2.6 Other Relevant Background Information

Amphora gel is a combination drug product that has three active ingredients that contribute to the efficacy of the product. Amphora gel will be distributed with a generic multi-use applicator and a prefilled single-use applicator. In order to be in compliance with 21 CFR 300.50, the Combination Drug Rule, the Applicant needs to provide a scientific rationale to support the contribution to efficacy of each active component.

During the pre-NDA stage, DBRUP consulted with the Center for Device and Radiological Health (CDRH) regarding the combination product and applicator. CDRH made the following recommendations:

- Perform additional testing on two recently-approved polyisoprene condoms (510K).
- Provide evidence for compatibility of use with diaphragms
- Include information in the patient instructions for use on how to load the gel into the inserter when the gel is supplied in a tube.
- Specify whether the applicator is intended for single-use or whether it can be used multiple times.
- Note that if the applicator can be used more than once, then validated cleaning instructions will be necessary.
- Identify details of the device design that aid the user in determining the proper amount for a single application.
- A risk analysis of the consequences of not including the proper amount should be included in the NDA.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The high discontinuation rate due to loss to follow-up, protocol violations and voluntary withdrawal in the US population and data discrepancies in US versus Russian data contribute to the poor quality of this NDA submission.

A small sampling of study sites were selected in for inspection in collaboration with the Office of Scientific Investigations (OSI). Three sites in the US and two sites in Russia were identified for

audit of the Applicant's data and/or analyses. The following centers were proposed for audit based on:

1. The largest number of subjects
2. Pregnancy rates that favored the non-inferiority of Amphora gel
3. Subject discontinuations
4. Protocol violations
5. Lack of recent Inspections

a.) Jesus Hernandez
1211 W. La Palma Ave.,
Suite 306
Anaheim, CA 92801

b.) Yue Chang Yang
3100 Wyman Park Drive
Baltimore, MD 21211

c.) Eugene Andruczyk
9501 Roosevelt Blvd.,
Suite 404
Philadelphia, PA 19114

d.) Svetlana Prokofyeva
Sredniy pr. V.O.,
48, housing 20H, Lit. A
St. Petersburg, Russia
991787

e.) Marina Tarasova
Mendeleyevskaya line, 3
St. Petersburg, Russia
199034

The sites of Drs. Hernandez, Yang, Prokofyeva and Tarasova had no violation and no action was indicated. Although regulatory violations were noted at the site of Dr. Andruczyk, the findings overall do not appear to affect subject safety or data quality as noted by the OSI reviewer. Roy Blay of the OSI summarized the investigations as follows:

> "The clinical sites of Drs. Andruczyk, Yang, Hernandez, Prokofyeva, and Tarasova were inspected in support of this NDA. Dr. Andruczyk's site was issued a Form FDA 483 for observations related to inadequate drug accountability and failure to adhere to protocol. The isolated findings at this site would not appear to have adversely affected subject safety or data quality. The final classification of this inspection was VAI. The final classification of the inspections for Drs. Yang, Hernandez, Prokofyeva, and Tarasova was

NAI. The study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication."

3.2 Compliance with Good Clinical Practices

As evidenced by the documentation provided by Evofem and individual research sites, good clinical practices were followed in the conduct of this research. The principles of informed consent were implemented according to the 1996 revision of the Declaration of Helsinki, ICH Consolidated Good Clinical Practice (E6), and current FDA regulations.

3.3 Financial Disclosures

The Applicant filed the FDA Certification of Financial Interests and Arrangements of Clinical Investigators (Form FDA 3454) in accordance with current financial disclosure requirements (21 CFR § 54.4). There were no reportable financial disclosures among investigators in this application; therefore, disclosed financial interests should not affect approvability of this product.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

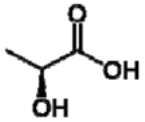
4.1 Chemistry Manufacturing and Controls

See CMC reviewer's report for full detail.

Chemical Name:	2-Hydroxypropanoic acid
Other Names:	L-lactic acid
Chem. Abs. Service (Registry No.):	79-33-4

Chemical Structure, Molecular Formula and Molecular Weight:

Structural Formula:



Molecular Formula: $C_3H_6O_3$

Molecular Weight: 90.08 g/mol

General Properties:

Lactic acid contributes to the acidity of the gel (b) (4) The lactic acid used in the manufacture of Amphora Gel is (b) (4)

(b) (4)

A joint review by ONDP was performed on April 11, 2016 and concluded that

> "The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance and drug product. While efficacy (prevention of pregnancy) of the product has not been unequivocally demonstrated, the product quality attributes (pH, buffering capacity, and viscosity) requisite for spermicidal activity are adequately controlled. On the other hand, in their review of the device components (pre-filled applicator and disposable applicator) of this Combination Product, CDRH-ODE identified deficiencies related to the characterization of these components (e.g., mechanical function and stability; biocompatibility). Until the device quality attributes are fully characterized, there is no assurance that the applicators will perform safely and effectively throughout the shelf-life. A final recommendation regarding manufacturing facility CGMP status from the Facilities review team within the Office of Process and Facility is pending as of this review. A review addendum will be filed when a final recommendation regarding facility acceptability is issued. On March 23, 2016, DBRUP issued a "Deficiencies Preclude Discussion" letter notifying the applicant that deficiencies had been identified that preclude discussion of labeling and PMC/PMRs at this time. These deficiencies are related to conduct of the clinical trials and analysis of the clinical study results (see 02/26/16 Memorandum to File). Therefore labeling (package insert, container/carton labels) issues have not been resolved. From the OPQ perspective, this NDA is therefore not ready for approval in its present form per 21 CFR 314.125(b)(1), 21 CFR 314.125(b)(8) and 21 CFR 314(b)(13)."

The preliminary recommendation cited in the Assessment of Facilities on April 20, 2016 was as follows:

> *"Based on the review of compliance history and risk assessments, significant risks were only identified for the API manufacturer* (b) (4) *the remaining facilities listed are adequate for the operations proposed in this submission.*
>
> (b) (4) *does not have acceptable compliance status and CDER is recommending WH for this submission."*

During the NDA, a consult was obtained from CDRH for their input on the applicator and compliance for use with condoms and diaphragms. They found that the product was compliant for use with diaphragms, polyisoprene condoms, polyurethane, and natural rubber latex condoms.

CDRH provided a full review on March 21, 2016 indicating several concerns with the application related to the pre-filled and disposable applicators. The following concerns need to be addressed prior to approval of this combination drug product:

Device Description

1. The materials of the pre-filled applicator need to be consistently stated throughout the submission.

Biocompatibility

2. Biocompatibility testing needs to be performed on the final, finished device.
3. The material supplier for the (b) (4) differs when compared to the NDA and requires correction. The Applicant must provide sufficient information to demonstrate the biocompatibility of the disposable applicator to the Amphora gel.

Bench Testing

4. Identify the minimum force that is necessary to ensure proper and accurate filling of the disposable applicator and incorporate it as a design specification. Address the maximum acceptable force for the delivery of the gel for the disposable applicator and the pre-filled applicator.
5. Repeat the testing of polyisoprene condoms using samples that have been conditioned at (b) (4) °C for 60 minutes prior to testing.

Stability/Shelf Life

6. Provide the results of testing that demonstrates that the performance of the pre-filled applicator is not adversely affected by aging.
7. Provide the results of testing that demonstrate that the performance of the disposable applicator is not adversely affected by aging.

For complete details of this report, please refer to the full CDRH consult dated March 20, 2016.

A consult from the CDRH Office of Compliance (OC) was performed. Their recommendation was for approval based on the Quality System Requirements for combination drug products. For full details, please refer to the CDRH OC consult dated March 31, 2016.

4.2 Clinical Microbiology

The product was devoid of *Candida albicans*, *Pseudomonas aeruginosa* and *Staphylococcus aureus. Burkholderia cepacia complex* (BCC) testing was not required, as the product has a pH of 3.3-3.9, making the growth of BCC highly unlikely. There were no deficiencies identified in the Microbiology portion of the application.

4.3 Preclinical Pharmacology/Toxicology

There were no nonclinical studies submitted for review. Evofem, Inc. is not relying on a listed drug, but rather, on Evofem-conducted clinical and nonclinical studies, and upon published literature, employing a 505(b)(2) approach for this application. Bridging nonclinical toxicology studies to evaluate local tolerance were completed in rats and rabbits under IND 64623.

The Applicant has obtained the right of reference to IND 64623 for nonclinical information in support of Amphora Gel.

Bridging nonclinical studies conducted under IND 64623 evaluating local tolerance with Amphora Gel did not reveal any relevant issues. General toxicology issues are limited to the mild irritation in the 10-day vaginal study in rabbits. There did not appear to be any other significant histological changes in the vaginal epithelium.

> ***Reviewer's Comment:***
> ***From a nonclinical perspective, Amphora Gel appears to be reasonably safe for approval. The pharmacology toxicology reviewer concluded that "Based on the long history of use, common nature of the active ingredients, the lack any novel excipients, and lack of significant adverse events in bridging nonclinical studies, Amphora Gel appears to be reasonably safe for approval." (Deepa Rao, DVM, PhD, Pharm Tox review dated (April 12, 2016).***

4.4 Clinical Pharmacology

In a single/double-blind cross-over post-coital test (PCT), sperm counts and motility in cervical mucus and vaginal pool samples were analyzed in women who had sex following application of placebo, N-9 or Acidform gel. Post-coital tests are performed following intercourse to evaluate the sperm found in the cervical mucus and the vaginal pool. Samples from women who received placebo, N-9 and Acidform were analyzed at 0 to 30 minutes after sex in a double-blind fashion. Acidform analysis 8 to 10 hours after coitus was blinded only to the investigators. Participants in the 8 to 10 hour post-coital testing part of the study only received Amphora gel; therefore, they were unblinded to treatment for this portion of the study. There were 56 women screened for the study and 43 women enrolled; however, 23 were excluded for various reasons.

Cervical mucus samples were obtained from 20 participants (see

Table 3) in each arm, and vaginal pool samples (see **Table 4**) were obtained from 17 women who received placebo control gel and from 19 women who received each of the active treatments. Samples were evaluated by the investigator for mid-cycle characteristics, the presence of sperm and the quantity and motility of the sperm in the cul-de-sac and endocervix

no later than 30 min after collection. Slides were reviewed in two stages: first, the entire slide was reviewed to detect the presence of any sperm (100X), and second, nine high-power fields (400X), evenly distributed, were reviewed. Non-progressively motile sperm is identified as sperm that has movement but is not moving in a forward direction. Progressively motile sperm are sperm that move in a forward direction in a mostly straight line or in a large circle. Progressive motility is required for the sperm to move through the reproductive tract towards the ovum.

The mean number of progressively motile sperm in cervical mucus was reduced in each treatment arm compared to placebo and numbers of immotile sperm and total spermatozoa were decreased in the PCT cervical mucus in the N-9 and Acidform groups (p-value <0.05 compared to placebo).[7]

Table 3: Cervical Mucus: Spermatozoa Analysis Findings by Treatment Arm

Mean Spermatozoa/HPF	Placebo Control Mean (SD)	N-9 0-30 min Mean (SD)	Acidform 0-30 min Mean (SD)	Acidform 8-10 h Mean (SD)
Progressively motile	17.94 (19.91)	0.07 (0.23), p<0.05	0.19 (0.52), p<0.05	0.75 (1.37), p<.01
Nonprogressive motile	5.36 (5.56)	0.10 (0.28), NS	0.10 (0.36), NS	0.25 (0.52), NS
Immotile	15.68 (17.40)	8.95 (13.49), p<.05	1.02 (7.21) , p<.05	6.45 (6.51) , p<.05
Total Spermatozoa	38.96 (37.19)	9.10 (13.51) , p<.01	7.30 (7.28) , p<.01	7.45 (6.42) , p<.01
(n)	(20)	(20)	(20)	(20)

HPF=High Powered Field

In the vaginal pool samples, both active treatment arms showed no progressively motile spermatozoa per HPF at 0-30 minutes; the number of progressively motile spermatozoa per high power field (HPF) was 0 in 19 out of 19 slides all treatment arms except for one slide that had 1-5 spermatozoa per HPF in the Acidform 8 to 10 hour PCT (**Error! Reference source not found.**).[7]

Table 4: Vaginal pool: Spermatozoa count per High Powered Field by Treatment Arm

Sperm/HPF	Placebo Control Cycle	N-9 0-30 min Mean (SD)	Acidform 0-30 min Mean (SD)	Acidform 8-10 h Mean (SD)
0	10/17	19/19	19/19	18/19
1-5	3/17			1/19
6-25	2/17			
>25	2/17			

HPF=High Powered Field

Reviewer's Comment:
The spermatozoa count 8-10 hours after Acidform application was 1/19 high powered fields. While there is some fertilization potential if forwardly progressive sperm are present, this is well outside of the recommended dosing time range.

4.4.1 Mechanism of Action

In contrast to spermicides that act as surfactants, Amphora gel creates an acidic pH environment (pH=3.5-4.5) in the vagina that buffers the alkaline pH of semen, especially at high concentrations relative to semen (1:2 or greater).[8] The primary mechanism of action is inhibition of sperm motility. The mean volume of semen following ejaculation is 3.7 mL, according to a study of 4500 males completed by the World Health Organization.[9] Therefore, the desired level of acidification is achieved with a topical vaginal dose of 3-5 mL of Amphora gel.[8]

Preclinical data generated in the CONRAD program showed that Amphora gel impaired sperm motility and cervical mucus penetration at high concentrations (1:2 and 1:4, gel to semen proportion). However, motility of spermatozoa recovered following dilution in an isotonic, iso-osmotic medium and incubation for 30 minutes.[10]

Reviewer's Comments:

- ***The Clinical Pharmacology reviewer, Myong-Jin Kim, stated the following in her review of Amphora gel (dated April 22, 2014):***
  "No Clinical Pharmacology studies were conducted during the development of Amphora gel. Therefore, no such studies were submitted for review. Additionally, labeling review was not conducted in this review cycle."
- ***The preclinical data may have clinical implications related to douching following product use. Please refer to Section 6.1.10 for further discussion.***

4.4.2 Pharmacodynamics

The pharmacodynamics of Amphora gel were not evaluated with this application, as the three active components are GRAS and even with maximal transvaginal absorption of the active ingredients, serum blood levels would remain within safe limits.

4.4.3 Pharmacokinetics

The pharmacokinetics of Amphora gel were not evaluated with this application. This is a locally active product and should maximal transvaginal absorption of the active ingredients occur, serum blood levels would remain within safe limits.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The pivotal study for NDA 208352, AMP001, was a single, large phase 3 double-blind, open-label, non-inferiority trial performed in the United States and Russia. AMP001 consisted of two phases:

- a 7-cycle efficacy active control phase
  - and -
- a 13-cycle extension single arm safety phase offered to Amphora subjects.

Trial data from AMP001 were used for the determination of efficacy and safety of Amphora gel as summarized in **Error! Reference source not found.** and

Table 6 below.

Table 5: Summary of Clinical Trial AMP001 for Efficacy Determination

Study Number (No. of Sites / Country) Dates of Study Conduct	Subject Population	Treatment Arms	Enrolled	Duration of Treatment	Outcomes
AMP001 (49 / U.S. & 13 / Russia) 05-19-11 to 04-23-14	Healthy, sexually active women at risk of pregnancy who desired contraception, aged 18 to 35 years with regular, normal, cyclic menses with a usual length of 21 to 40 days	Amphora Gel	Total: 1,695 US 1,371 Russia 324	up to 7 cycles of use with a subset evaluated for 13 cycles of use	**Primary** -Cumulative pregnancy percentage 6 month (183 days) **Secondary** -12 month cumulative pregnancy percentage
		Conceptrol	1,694 US 1,376 Russia 318		

Source: NDA 208352 CSR and FDA statistician Kate Dwyer, NDA 208352 Review

Table 6: Summary of Safety Subsets by Treatment Group

Study population	Safety Subset	Number of women by treatment group (and country)	Outcomes
Healthy women, ages 18-35 years who received at least one dose of study medication	All Treated 7-cycle comparative phase	Amphora gel 1,459 (US 1,135, Russia 324) N-9 gel 90 (US 1,160, Russia 316)	-Incidence of AEs -Safety -Acceptability -Rate of UTI, BV and Yeast Infection
	13 cycle extension phase	Amphora Only Treatment Arm 345 (241 US, 104 Russia)	-Adverse Events -Safety -Acceptability -Rate of UTI, BV and Yeast Infection
	Colposcopy subset (US only)	Amphora gel 74 N-9 gel 70	-Incidence of lesions detected by colposcopy
	Vaginal culture subset (US only)	Amphora gel 73 N-9 gel 79	-Changes in microflora of vagina

Source: NDA 208352 CSR, JMP extracted data from demo.xpt.

5.2 Review Strategy

The primary phase 3 clinical study, AMP001, was reviewed to assess safety and efficacy of Amphora gel. Contraceptive efficacy was assessed based on AMP001 7-cycle placebo-controlled study data for the Modified Intent to Treat (MITT) population, with a planned secondary efficacy analysis of the 13-cycle data. Safety was assessed using data from AMP001 through the 13-cycle extension; however, only the initial 7-cycle portion of the study provided controlled data.

Early in the analysis phase of the NDA, the pregnancy rates of the Russian and US populations were noted to differ dramatically with respect to pregnancy rate (US Amphora 7-cycle Kaplan Meyer (KM) Cumulative Pregnancy Rate 15.7% vs. Russian 7-cycle KM Cumulative Pregnancy Rate 1.3%), completion rates (US Completion rate 38.5% vs. Russian completion rate 96.5%) and reporting of adverse events (more frequently reported in the US). Inclusion of the Russian data drives the overall results toward non-inferiority of Amphora and the Russian pregnancy rates were not consistent with those typically observed in US spermicide trials. This review issue was brought to the attention of the Applicant in the 74-day letter. The Applicant was asked to justify the generalizability of the Russian data to the US population.

The Applicant provided a response to this review issue; however, they did not provide an adequate explanation for the differences or justify how the data were generalizable to the US population. Therefore, DBRUP made the decision that the approvability decision would be

based on the US data alone. The Russian data are presented throughout the review for informational purposes only. Section 6.3.1.4 contains a full discussion of the Applicant's justification for inclusion of the Russian data.

In the primary efficacy analysis, the Applicant defined on-treatment pregnancies as those that "occurred during the time the subject considered the study method her primary method of contraception." For the final analysis, all pregnancies that occurred 7 days after last date of product use are defined or pregnancies that occurred during a cycle in which the subject considered the gel to be her primary method of contraception as on-treatment pregnancies. Section 6.1.4 contains a full discussion of the categorization of on-treatment pregnancies.

During the review process, a high proportion of cycles of such aberrant length that they were highly likely to be non-ovulatory cycles were identified in the efficacy dataset. This led to definition of a new analysis population, referred to as the Modified Intent to Treat FDA (MITT FDA). Cycles with cycle length outside the acceptable range of 21-42 days were considered non-evaluable cycles for this analysis population. The MITT FDA is the primary efficacy analysis population for this NDA.

The Applicant had included uncontrolled data from beyond 7 and 13 cycles for their primary analysis to "back-fill" for non-evaluable cycles in the "compressed cycle" analysis. The final analysis was limited to data that were collected during the 7-cycle phase (196 days) of the study. Data from the extension study that were collected beyond 13 cycles (365 days) were not included in the safety analysis for this NDA.

The primary safety analysis population for this NDA is the all-treated (ATD) population. This includes all participants who have received at least one dose of study medication for the 7-cycle and 13-cycle extension phases.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Primary Clinical Trial AMP001

5.3.1.1 Study Title

The title of pivotal trial AMP001 is "A Multicenter, Open-Label, Randomized Study of the Contraceptive Efficacy and Safety of Amphora Gel Compared to Conceptrol Vaginal Gel."

5.3.1.2 Study Objectives

Primary Objective: To determine the contraceptive efficacy of Amphora gel 5 mL compared to N-9 100 mg vaginal gel.

Secondary Objectives: The secondary objectives of AMP001 were:

- To determine the acceptability of Amphora gel 5 mL compared to N-9 100 mg vaginal gel.
- To determine the safety of Amphora gel 5 mL over 7 cycles of use with a subset of subjects evaluated for 13 cycles of use.
- To determine the incidence of Urinary Tract Infection (UTI), Bacterial Vaginosis (BV), and yeast vaginitis following the use of Amphora gel 5 mL compared to N-9 100 mg gel.
- To evaluate the incidence of lesions detected by colposcopy in a subset of subjects using Amphora gel 5 mL compared to N-9 100 mg gel.
- To measure changes in vaginal microflora in a subset of subjects using Amphora gel 5 mL compared to N-9 100 mg gel.

Reviewer's Comment:
The primary and secondary objectives were agreed to during the meetings held between the DBRUP and the Applicant.

5.3.1.3 Clinical Trial Design

This trial was a multicenter, randomized, open-label non-inferiority study comparing the contraceptive efficacy and safety of vaginally applied Amphora gel to N-9 gel over 7 cycles of use among sexually active women from 18 to 45 years of age. In addition, for the subjects randomized to Amphora gel, there was an optional extension phase for up to a total of 13 cycles of treatment upon completion of the first 7 cycles of treatment for further safety evaluation.

Reviewer's Comments:

- ***Evofem initially planned to perform a single pivotal study to evaluate the safety and efficacy of Amphora using a historical N-9 control group. In a Type B Pre-IND meeting, DBRUP recommended a non-inferiority design with an active comparator arm (N-9 gel) for evaluation of efficacy and safety of Amphora gel. Non-inferiority trials are recommended when it is unethical to have a placebo control. Putting study participants at risk of pregnancy would be unethical for the evaluation of a pregnancy prevention product. Furthermore, the non-inferiority trial design provides a more rigorous evaluation of safety and efficacy compared to a historical control. Evofem agreed to this recommendation.***
- ***In the Type B end-of-phase 2 (EOP2) meeting held on October 13, 2013, DBRUP advised Evofem that a total Amphora exposure of 5,000 evaluable cycles would be required for safety and efficacy evaluation, with over 50% of the data from US sites. DBRUP also recommended that a minimum of 200 women complete***

the 12 month trial for additional safety evaluation. DBRUP agreed with an open-label study design given the objective endpoint of pregnancy. DBRUP recommended that the efficacy population include reproductive age women up through the age of 35 at enrollment, encouraging enrollment of women less than 18.

5.3.1.4 Clinical Trial Sites

The study was conducted at 49 study sites in the US and 13 study sites in Russia. The principal investigator at each center was responsible for the conduct of the study. Investigators were required to be qualified by training and experience to supervise clinical trials. The number of women enrolled at the different centers ranged from 289 (Axis Clinical Trials in Los Angeles, CA) to 1 (Planned Parenthood of NE Ohio, Rocky River Health Center).

5.3.1.5 Inclusion Criteria

For entry into the study, it was required that participants:

1. Be healthy women, who are sexually active, at risk for pregnancy, and desiring contraception.
2. Be within the age range of 18 through 35 (inclusive) at enrollment if not in the subset of women aged 36-45 at enrollment (age subset at select sites).
3. Be at low-risk for both human immunodeficiency virus (HIV) and sexually transmitted disease (STD) infection and currently have a single male sex partner (for at least 4 months) who is also at low-risk for both HIV and STD infection.
4. Have a negative urine pregnancy test prior to enrollment.
5. Have regular, normal, cyclic menses with a usual length of 21 to 40 days over the last two cycles or at least one spontaneous, normal menstrual cycle (consisting of two menses 21 to 40 days apart) since delivery, abortion (spontaneous or induced), or after discontinuing hormonal contraception or hormonal therapy.
6. Be willing to accept a risk of pregnancy.
7. Be willing to engage in at least two acts of heterosexual vaginal intercourse per cycle.
8. Be willing to be randomized to either study treatment.
9. Be willing to use the study product as the only method of contraception over the course of the study (with the exception of emergency contraception (EC), when indicated).
10. Be capable of using the study product properly and agree to comply with all study directions and requirements.
11. Be willing to keep a daily diary to record coital information, product use information, information about the use of other vaginal products, and sign and symptom data for both the subject and her partner.

12. Agree not to participate in any other clinical trials during the course of the study.
13. Be capable and willing to give written informed consent to participate in the trial.

In addition, in order to be eligible to participate in the trial, potential subjects must have stated that, to her best knowledge, her male sexual partner met the following criteria:

1. Is not infertile.
2. Has had untreated chlamydia or gonorrhea in the past six months.
3. Has not had more than one sexual partner in the past four months.
4. Has no history of allergy or sensitivity to spermicides or products containing N-9.
5. Has not been previously diagnosed with or suspected of HIV infection unless he has subsequently had a negative HIV test.
6. Has not been known to have engaged in homosexual intercourse in the past five years unless he has had documented negative HIV test results since then.
7. Has not shared injection drug needles in the past unless he has documentation of a negative HIV test at least six weeks since last use.

5.3.1.6 Exclusion Criteria

To enroll in the clinical trial, potential subjects could not:

1. Have a history of allergy or sensitivity to spermicides or products containing N-9.
2. Have had three or more urinary tract infections (UTIs) in the past year.
3. Have a UTI by urine culture, symptomatic yeast vaginitis, or symptomatic bacterial vaginosis diagnosed by wet mount unless treated and proof of cure is documented.
4. Have a history of any recurrent vaginal infections/disorders (either ≥ four times in the past year or ≥ three times in the previous six months).
5. Be pregnant, have a suspected pregnancy, or desire to become pregnant during the course of the study.
6. Have a history of infertility or of conditions that may lead to infertility, without subsequent intrauterine pregnancy.
7. Have any contraindications to pregnancy (medical condition) or chronic use of medications for which significant evidence of fetal risk exists.
8. Have had more than one sexual partner in the last four months.
9. Have shared injection drug needles in the past unless has a negative HIV test at least six weeks since last use.
10. Have or have been suspected to have HIV infection.
11. Have been diagnosed with genital herpes simplex virus (HSV), with the first occurrence (initial episode) within three months prior to randomization.
12. Have three or more outbreaks of HSV within the last year.

13. Have evidence of *Chlamydia trachomatis* or *Neisseria gonorrhoeae* unless she and her partner complete treatment and proof of cure is documented.

14. Have been diagnosed with any STDs in the six months prior to the Randomization Visit other than trichomonas, gonorrhea, Chlamydia, or human papilloma virus (HPV)).

15. Be lactating or breastfeeding.

16. Have any clinically significant abnormal vaginal bleeding or spotting within the month prior to randomization.

17. Have any clinically significant abnormal finding on pelvic examination or baseline labs which in the view of the investigator, precludes her from participating in the trial.

18. Have clinically significant signs of vaginal or cervical irritation on pelvic examination.

19. Have had vaginal or cervical biopsy or vaginal surgery within three months prior to screening (with the exception of cervical biopsies performed for eligibility determination).

20. Have used vaginal or systemic antibiotics or antifungals within 14 days prior to screening or enrollment/randomization, with the exception of systemic antibiotics taken for a UTI and trichomonas diagnosed at screening. Subjects should not have used systemic antibiotics prescribed at the Screening Visit for a UTI within seven days of the enrollment/randomization visit.

21. Have had a Depo-Provera® (depot medroxyprogesterone acetate) injection in the ten months prior to enrollment.

22. Have an abnormal Pap test based on the following criteria:

a. Pap test in the past 15 months with atypical squamous cells of undetermined significance (ASC-US) unless:

i. less than 21 years of age;

ii. or a repeat Pap test at least six months later was normal;

iii. or reflex HPV testing was performed and was negative for high-risk HPV;

iv. or a colposcopy (with or without biopsy) found no evidence of dysplasia requiring treatment or treatment was performed and follow- up at least six months after the treatment showed no evidence of disease;

b. Pap test in the past 15 months with low grade squamous intraepithelial lesion (LSIL) unless:

i. less than 21 years of age;

ii. or a colposcopy (with or without biopsy) found no evidence of dysplasia requiring treatment or treatment was performed and follow- up at least six months after the treatment showed no evidence of disease;

c. Pap test in the past 15 months with atypical squamous cells in which high grade squamous intraepithelial lesion cannot be excluded (ASC-H), atypical glandular cells, or high grade squamous intraepithelial lesion (HSIL) unless

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

d. Pap test in the past 15 months with malignant cells.

23. Consume (on average) more than 3 alcoholic beverages per day.

24. Have a past history (within 12 months) or current history which, in the Principal Investigator (PI)'s judgment, constitutes drug abuse (recreational, prescription, or over-the-counter (OTC)).

25. Have taken an investigational drug or used an investigational device within the past 30 days.

26. Have issues or concerns (in the judgment of the investigator) that may compromise the safety of the subject, impact the subject's compliance with the protocol requirements, or confound the reliability of the data acquired in this study.

Reviewer's Comments:

- ***The above inclusion/exclusion criteria are acceptable as written to define the study population for the evaluation of efficacy of this spermicidal gel.***
- ***There were two versions of the study protocol between February 2011 and July 2013 with minor changes in the inclusion and exclusion criteria. The changes did not affect the ability to evaluate for efficacy in any appreciable way. The inclusion and exclusion criteria changes to the protocol are addressed in Section 5.3.1.12.***

5.3.1.7 Concomitant Therapy

Concomitant therapy was defined as all medications taken by subjects 30 days prior to the study and during the course of the study. Subjects were also asked to report use of cranberry juice or tablets. Vaginal antibiotics, antifungals and antivirals were allowed only if investigators prescribed them.

Excluded Concomitant Therapy:
Subjects were instructed to abstain from any vaginal application of self-medication, including additional lubricants or massage oils.

Reviewer's Comments:

- ***All concomitant medications were recorded on the source document and on the electronic Case Report Form (eCRF). While contraception was not explicitly excluded in the study protocol, exclusion of contraception was implied in the inclusion and exclusion criteria and in the instructions provided to study participants. Use of douche following use of Amphora gel was not listed as an excluded therapy; however, study participants were encouraged not to douche***

during the study. Subjects were instructed to record the use of douche as a concomitant medication in the coital diary in AMP001.

- ***Sperm viability and motility following the use of douche were not studied for this product in clinical or preclinical studies. In preclinical studies, sperm motility was recovered following washing with an isotonic isosmotic medium after sperm exposure to Amphora gel. Sperm can live for up to 24 hours. Therefore, without further data evaluating the use of postcoital douche on sperm motility after using Amphora gel, users should be cautioned against use of postcoital douche for at least 24 hours after intercourse.***

5.3.1.8 Study Procedures

Informed consent was obtained prior to any study-specific procedure. Subjects who met and complied with eligibility criteria were enrolled in the trial and randomized to either Amphora vaginal gel or N-9 vaginal gel. Subjects were randomized in a 1:1 ratio stratified by site. Subjects had to meet eligibility criteria prior to assignment of a randomization number via the web randomization application.

Following randomization, study participants received either:

- Amphora gel, delivered in single-use applicators with 5 ml doses

  - OR -

- Conceptrol Vaginal Gel containing 100 mg (4% concentration) of N-9 in 2.5 mL volume, delivered in single-use applicators

Participants were instructed to apply the product immediately before intercourse, reapply the product if one hour went by prior to intercourse, and/or prior to each additional act of intercourse. Participants were also instructed to keep a coital diary recording each episode of intercourse, whether or not the product was used, use of other back-up method such as condoms or emergency contraception and use of other concomitant medications, tolerance of gel, and more. See **Figure 3** for a copy of the coital diary that was provided to subjects.

Study Visits

For a detailed table of scheduled visits and procedures, see Appendix **Error! Reference source not found.** at the end of this review. There were seven scheduled study visits: screening (Visit 1), admission (Visit 2), interim visits (Visits 3, 4) after Cycle 1 and Cycle 3, and exit visit (Visit 5) after Cycle 7. For participants in the extension phase, there were two additional interim visits (Visit 5 and 6) and an exit visit (Visit 7), which occurred after Cycle 13. Between-visit contact (by telephone) occurred between Cycles 3 and 7 approximately two months after the Cycle 3 visit.

A urine pregnancy test was obtained at screening, admission, interim and exit visits. Home pregnancy tests were dispensed at admission. Participants were instructed to perform a home pregnancy test 2 weeks after admission and anytime they suspected pregnancy. Gynecologic exam with wet mount for yeast and BV was performed at the screening, interim, and exit visits. Pap test and urine culture was obtained at screening and exit visits. Urinalysis with dipstick was evaluated at each interim study visit when there were symptoms associated with UTI. If UTI was diagnosed prior to admission of the study, admission into the study was not permitted until a negative urine culture for test of cure was obtained. For future urinary symptoms, participants were instructed to contact the study site for symptoms of UTI. The study site would provide evaluation for UTI, treatment when indicated and possible discontinuation of study treatment.

Reviewer's Comments:

- ***The frequency of visits is acceptable.***
- ***The most commonly encountered side effects associated with use of vaginal spermicidal gel include genitourinary infections and discomfort.11 The monitoring and management of these commonly encountered infections is appropriate for safety evaluation of a spermicidal gel.***
- ***Pregnancy testing prior to entry and following admission reduces the chance that a participant is admitted to the study with an undiagnosed pregnancy, maintaining integrity of the study population and measures of efficacy.***

Screening Visit:
Women presenting to study sites for gynecologic care were invited to participate in the study. It was required that women not be menstruating in order to perform required screening assessments. Informed consent was obtained prior to any study-specific procedures. Screening Visit procedures could be completed over more than one visit if necessary. The following events occurred at the Screening Visit:

- Obtained signed informed consent and provided a copy to potential subject
- Collected demographic information, medical, gynecological and pregnancy history
- Vital signs (height, weight, and blood pressure only)
- Recorded history of contraceptive use in the six months prior to screening
- Gynecological exam with wet mount for monilia
- Performed Pap test (unless same-method test results performed ≤ 6 months prior to the Screening Visit were obtained)
- Endocervical swab, vaginal swab, and urine samples were taken; if positive for chlamydia and/or gonorrhea, the subject was allowed to enter study after proof of cure was documented
- BV assessment following Amsel's criteria

- CBC and chemistry panels were sent to the central laboratory for analysis
- Urine pregnancy test (if positive, a serum sample was collected to be sent to central laboratory for a β-hCG and quantitative hCG analysis)
- Dipstick urinalysis (performed only if the subject presented to the site with urinary symptoms)
- Urine culture (if a UTI was diagnosed, the subject was allowed to enter the study after proof of cure was documented)
- Recorded pre-trial medications (inquired about subject self-medication for suspected UTIs, including cranberry juice or cranberry tablets)
- Dispensed pre-admission coital diaries and instructed the subject how to complete the pre-admission coital diary

If the subject was diagnosed with genitourinary infection (UTI, symptomatic BV, symptomatic yeast vaginitis, chlamydia, or gonorrhea) at the Screening Visit and all other eligibility criteria were met; she was treated and allowed to enter the study after proof of cure was documented. Symptomatic BV was treated with oral medication. Subjects who were asymptomatic but had BV or yeast forms on wet mount (in the absence of symptoms or inflammation on pelvic exam) were enrolled but treated for those conditions at the discretion of the Principal Investigator.

Subjects diagnosed with a UTI at the Screening Visit were prescribed appropriate UTI treatment and scheduled for admission after verification of all other eligibility criteria. Dipstick urinalysis was repeated at the Admission Visit, which was seven or more days after the subject completed the antibiotic regimen prescribed for the UTI.

Admission Visit:
Upon receipt of all screening assessments, if the subject met all eligibility criteria she was scheduled for an Admission Visit (to occur within six weeks of the Screening Visit). At the Admission Visit, the following occurred:

- Verify all eligibility criteria were met
- Record pre-treatment signs and symptoms and update pre-trial medications (inquired about subject self-medication for suspected UTIs, including cranberry juice or cranberry tablets)
- Vital signs (weight and blood pressure only)
- Urine pregnancy test (if positive, serum sample was collected and sent to the central laboratory for a β-hCG and quantitative hCG analysis)
- Dipstick urinalysis (performed only if the subject presented to the site with urinary symptoms; if 1+ or greater for any analyte of blood, leukocyte esterase, protein, or nitrite results was positive, urine was sent for urine culture and microscopic urinalysis; if a UTI was diagnosed, the subject was not enrolled until proof of cure was documented)

- Provided the subject with two home urine pregnancy test kits (one to use two weeks after admission and the other to use anytime pregnancy was suspected)
- Provided instructions on how to use the test product
- Randomized the subject to either Amphora Gel or Conceptrol Vaginal Gel using the web-based randomization system
- Dispensed test product to subject (enough to last until next scheduled visit)
- Dispensed coital diaries and reminded subject how to complete coital diary
- Collected and reviewed pre-admission coital diaries
- Recorded pre-trial medications (including cranberry juice or cranberry tablets) and AEs
- Provided emergency contact information to study participant
- Reminded subject to call site with home pregnancy test results that subject was to administer two weeks after the Admission Visit.
- Reminded subjects of the right to use emergency contraception (EC) during the study
- Reminded subjects not to have intercourse, use the test product, or place anything in the vagina within 24 hours of the next scheduled visit
- Scheduled the next study visit after the subject completed Cycle 1

For subjects in the respective subset populations, the following occurred at the Admission Visit:

- Colposcopy (10x) was performed on subjects participating in the colposcopy sub-study. The colposcopy procedure was performed before any other vaginal assessments, including the gynecological exam, except for subjects who were also participating in the vaginal culture sub-study. The swabs for quantitative and semi-quantitative analyses were obtained prior to the colposcopy for subjects participating in both sub-studies. Photographs were obtained for all colposcopy sub-study subjects regardless of presence or absence of suspicious lesions.
- Quantitative vaginal cultures were obtained from subjects participating in the vaginal culture sub-study. Two vaginal swabs were taken from the vaginal pool and sent for quantitative vaginal cultures of *Staphylococcus aureus, E coli, Enterococcus species, Candida albicans, anaerobic Gram-negative rods, Gardnerella vaginali*s, and H_2O_2- positive and -negative *Lactobacillus*.

At the Admission Visit, all subjects were instructed to contact the study site as soon as possible if any of the following occurred:

- She was about to run out of study product, home pregnancy tests, or if she needed new diary cards

- Her period was late by one week or more, a home pregnancy test was positive, or she suspected she might be pregnant for any reason
- She suspected she might have a UTI or had sought care at another facility for a UTI or other vaginal infection
- She experienced any medical problem, whether or not she deemed it related to the test product
- She had any questions about using the study products or about the study
- She wished to stop using the study product as her method of contraception or to discontinue from the study
- She wished to obtain Emergency Contraception (EC)
- She missed or expected to miss a scheduled visit

Interim Visits:
Subjects returned to the study site for interim visits after their first and third menstrual cycles after enrollment; Amphora-treated subjects who participated in the extension phase returned to the site after Cycle 10. The following events occurred during these interim visits:

- Vital signs (weight and blood pressure only)
- Gynecological exam with wet mount for monilia
- BV assessment following Amsel's criteria
- Urine pregnancy test (if positive, a serum sample was collected sent to the central laboratory for a β-hCG and quantitative hCG analysis)
- Dipstick urinalysis (if analytes were 1+ positive or greater for blood, leukocyte esterase, or protein, or nitrite results were positive, urine was sent for urine culture and microscopic analysis)
- Administered the Acceptability Questionnaire (after Cycle 1 only); if the product was not used, then the acceptability questionnaire was not required
- Administered the Discomfort Questionnaire
- Investigators collected and reviewed coital diary for completeness and accuracy
- Investigators collected unused test product and completed drug accountability
- Re-supplied test product and coital diaries, as necessary
- Recorded concomitant medications (including cranberry juice or cranberry tablets) and AEs
- Reminded subjects of the right to use EC during the study
- Reminded subjects not to have intercourse, use the test product, or place anything in the vagina within 24 hours of the next scheduled visit
- Scheduled the next study visit

For subjects in the subset populations, the following occurred at interim visits:

- Colposcopy (10x) was performed on subjects participating in the colposcopy sub-study. The colposcopy procedure was performed before any other vaginal assessments including the gynecological exam, except for subjects who also participated in the vaginal culture sub-study. Swabs for quantitative and semi-quantitative analyses were obtained prior to colposcopy for subjects participating in both sub-studies. Photographs were obtained for all colposcopy sub-study subjects regardless of presence or absence of suspicious lesions.
- At Visit 3 only, quantitative vaginal cultures were obtained from subjects who participated in the vaginal culture sub-study. Two vaginal swabs were taken from the vaginal pool and sent for quantitative vaginal cultures of *Staphylococcus aureus*, *E coli*, *Enterococcus* species, *Candida albicans*, anaerobic Gram-negative rods, *Gardnerella vaginalis*, and H_2O_2-positive and -negative *Lactobacillus*.
- Yeast and E. coli cultures were obtained from subjects participating in the vaginal culture sub-study only at Visits 4 and 6.

Reviewer's Comment:
Vaginal Culture results for all quantitative and non-quantitative species were ultimately reported for "After Cycle 1", "After Cycle 7" and "After Cycle 13". This indicates that there were more collection points than were originally planned. The reason for this change was not delineated in the CSR. This research question is exploratory however, so the change should not affect the integrity or clinical interpretation of the results.

During the diary review, if site staff detected any pattern of incorrect or inconsistent product usage, the subject was reminded of proper usage instructions for the test product. In addition, diaries were reviewed to ensure that neither the study subject nor the subject's partner had experienced any signs or symptoms related to product use that required further evaluation. If a sign or symptom was reported in the subject diary that warranted follow-up, the subject was asked to return to the study site for evaluation and/or treatment. If the subject's partner experienced a sign or symptom that warranted further evaluation, he was to report to the study site for initial evaluation and referred for appropriate treatment.

At each interim visit, subjects were reminded to contact the study site as soon as possible if any of the following occurred:

- She was about to run out of study product, home pregnancy tests, or if she needed new diary cards
- Her period was late by one week or more, a home pregnancy test was positive, or she suspected she might be pregnant for any reason
- She suspected she might have a UTI or had sought care at another facility for a UTI or other vaginal infection

- She experienced any medical problem, whether or not related to the test product
- She had questions about using the study products or about the study
- She wished to stop using the study product as her method of contraception or to discontinue from the study
- She wished to obtain EC
- She missed or expected to miss a scheduled visit

Visit After Cycle 7/Treatment Exit (Visit 5):
Subjects returned to the study site after seven cycles of treatment for exit from the efficacy comparison portion of the trial. At the After Cycle 7 visit (Visit 5), Amphora-treated subjects were given the opportunity to continue treatment for an additional six months, for a total treatment exposure of up to 13 cycles. The following study activities occurred at the After Cycle 7 visit (these procedures were to be performed any time a subject discontinued the study prematurely, unless the subject entered the extension portion of the study):

- Vital signs (weight and blood pressure only)
- Gynecological exam with wet mount for monilia
- Pap test
- Endocervical swab, vaginal swab or urine sample taken for chlamydia and gonorrhea
- BV assessment using Amsel's criteria
- CBC and chemistry panels were sent to central laboratory for analysis
- Urine pregnancy test (if positive, a serum sample was collected and sent to the central laboratory for a β-hCG and quantitative hCG analysis)
- Dipstick urinalysis (only performed if the subject presented to the center with urinary symptoms)
- Urine culture
- Administered the Acceptability Questionnaire; if the product was not used, the acceptability questionnaire was not required
- Administered the Discomfort Questionnaire
- Collected and reviewed coital diary for completeness and accuracy
- Collected unused test product and completed drug accountability forms for subjects not continuing in the treatment extension phase of the study
- Recorded concomitant medications (including cranberry juice or cranberry tablets) and AEs
- Re-supplied test product and coital diaries to Amphora-treated subjects who participated in the treatment extension portion of the study

- Reminded subjects who continued treatment of their right to use EC during the study
- Reminded Amphora-treated subjects who continued treatment not to have intercourse, use the test product, or place anything in the vagina within 24 hours of the next scheduled visit
- For Amphora-treated subjects who continue treatment, schedule the next visit

Data and Safety Monitoring Board:

Routine safety monitoring adverse event (AE) assessments and vital signs) was conducted for all subjects. An independent, autonomous Data and Safety Monitoring Board (DSMB) was established to conduct periodic reviews of subject safety and to investigate pregnancy findings by treatment arm. The DSMB met four times during the course of the study. There were 4 planned meetings that were held approximately 3 months after enrollment of 500, 1000, 1500, and 2000 participants respectively. Details of the operation (including any criteria to stop the study) of the DSMB were developed in conjunction with the members of the DSMB prior to the first meeting and modified, as required, before the second meeting and any subsequent meetings. Stopping criterion included a 25% six-month cumulative pregnancy rate in either arm. This stopping criterion was never reached.

Reviewer's Comments:

- ***The frequency of clinic visits and phone calls between visits is adequate and all subjects were encouraged to call for an urgent study visit if they had:***
  - ***Pregnancy***
  - ***Symptoms of urinary tract infection or vulvovaginal infection***
  - ***Sexual partners who were experiencing discomfort***
  - ***Other worrisome symptoms***
- ***Amsel's criteria for diagnosis of BV are well-established among medical professionals for the diagnosis of BV. However, when measured against the Nugent score, the sensitivity and specificity of Amsel's criteria are 67% and 95% respectively. Low sensitivity of this test could lead to false negative diagnoses of BV, with a potential underreporting of the incidence of BV with use of spermicide gel.[12]***
- ***Use of emergency contraception by participants was allowed and provided by study sites in this trial in the event that the participant believed she did not use the study medication properly or if she felt she was at risk of pregnancy. EC was recorded as a concomitant medication on the case report form any time it was dispensed. Additionally, participants were asked to record use of EC in the coital diary.***

5.3.1.9 Primary Efficacy Variables

The primary endpoint defined by the Applicant was the evaluation of contraceptive effectiveness over six months (183 days) of Amphora gel use when compared to N-9 vaginal gel. Kaplan-Meier (KM) life-table analyses were used to estimate the six-month cumulative pregnancy probability of women in the Modified Intent-To-Treat (MITT) population (defined below) by treatment group. Pregnancies were not included if they were found to have occurred before a subject was randomized or after she had discontinued the study treatment as her method of contraception. Greenwood's method for calculating variance was used to construct 95% confidence intervals.

The non-inferiority hypothesis was tested by calculating a 95% confidence interval for the difference between treatments in the six-month cumulative pregnancy probabilities using normal distribution assumptions (asymptotically) with variance calculated from Greenwood's variance estimates. If the upper bound for the confidence interval of the difference was ≤ 5.5, then the null hypothesis (that Amphora is inferior to N-9) would be rejected.

The pre-specified analysis population for the primary analysis was the MITT population.

The analysis populations were defined as follows:

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

All Treated (ATD): ITT subjects who used at least one application of the study drug.

Modified Intent-To-Treat (MITT)**:**
Subjects must meet requirements 1, 2, and 3 to be in the MITT population. Subjects must also either meet requirement 4 **or** requirement 5 to be in the MITT population.

1. between 18 to 35 years of age (inclusive) at enrollment
2. at least one report of pregnancy status after being enrolled
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 of diary without any backup contraception or EC
5. became pregnant and the pregnancy occurred during the time the subject considered the study method her primary method of contraception (i.e., was an on-study pregnancy, regardless of whether or not she had used another method of contraception in that cycle).

Per agreement with the Division, cycles in which backup contraception or EC was used would be considered non-evaluable (unless the subject became pregnant in that cycle) and the remaining cycles would be compressed to provide contiguous cycles for KM analysis.

MITT 7: a subset of the MITT population that counts as on-treatment pregnancies any conceptions that occur during a cycle in which the participant considered the gel to be her primary method of contraception, or within 7 days after her last use of gel in the trial.

MITT FDA: a subset of the MITT7 population in which cycles with cycle length outside the acceptable range of 21-40 days were considered non-evaluable cycles.

Reviewer's Comments:

- ***The Division had advised the Applicant during protocol development that pregnancies conceived within seven days after last use of study drug should be considered on-treatment pregnancies, but the Applicant did not utilize this definition in its primary accounting for on-treatment pregnancies. Although the Applicant considered the MITT its primary analysis population, based on the Division's request at the pre-NDA meeting, the Applicant also performed and reported an efficacy analysis using the MITT7 population in the original NDA submission.***
- ***The MITT FDA population was defined during the review of the NDA when the review issues related to variable cycle length were identified. The Applicant complied with information requests related to data analyses of the MITT FDA population. (Refer to Section 6.1.4 Reviewer's Comments for more detail).***

The following populations were defined for safety analyses as discussed in more detail in Section 7.4.

Colposcopy Subset (CS): a subset of the ATD population who agreed to undergo colposcopy evaluations during the study.

Yeast Vaginal Culture Subset (YVCS): a subset of the ATD population who agreed to have swabs for quantitative vaginal microflora cultures and swabs for semi-quantitative *E. coli* and yeast vaginal cultures taken during the study

Table 7: Overview of Analyses Performed for each Analysis Population

Analysis Popula-tion	Demographics and Subject Characteristics	Exposure	Typical Use Pregnancy	Perfect Use Pregnancy	Acceptability	AEs	Colposcopy Results	Semi-Quantitative Vaginal Cultures	Quantitative Vaginal Cultures
ITT	√								
ATD	√	√				√			
MITT	√	√	√		√				
CS	√					√	√		
YS	√							√	
VCS	√								√

Reviewer's Comments

- ***From the pre-IND stage and again at the pre-NDA meeting, DBRUP recommended that the primary efficacy analysis be performed including in "on-treatment pregnancies" women who became pregnant within 7 days after last product use (MITT7). This is a standard definition of "on-treatment pregnancy" for the efficacy analysis of contraceptive methods. Instead, the Applicant defined the primary analysis population (MITT) as "became pregnant and the pregnancy occurred during the time the subject considered the study method her primary method of contraception." This led the Division, at the preNDA meeting, to request the Applicant to submit an analysis of the primary outcome using the MITT7 population. Furthermore, it was identified that a large proportion of the MITT7 data contained highly variable cycle lengths. During the NDA review, the Applicant was asked to further restrict the evaluable cycles only to cycles with lengths between 21 and 42 days (similar to the length specified in the study's entry criteria listed in section 5.3.1.5). This population was defined as the MITT-FDA population. For further discussion on this issue, refer to Section 6.1.4.***
- ***The Statistical Analysis Plan (SAP) for AMP001 was not submitted for review and comment as requested. The SAP was requested when the Division in initially reviewed the protocol. Unfortunately, the Applicant never submitted the SAP for review. Such a review might well have identified some of the statistical concerns with this application prior to the NDA submission.***
- ***Efficacy of contraceptive methods can be evaluated using KM time-to-event analysis or Pearl Index (PI). In published randomized controlled trials evaluating efficacy of spermicides, the most common primary analysis used is KM time-to-event analysis providing 6 and 12 month pregnancy rates.***
    - ***During the NDA review process, DBRUP agreed to evaluate efficacy using the KM time-to-event analyses proposed in the statistical analysis plan (SAP) by Evofem as the primary efficacy analysis.***

- ***EC was allowed and provided to participants of this clinical trial. While it was listed in the concomitant medications for 60 study participants, only 7 Amphora participants and 9 N-9 gel participants reported use of EC in the coital diaries during the trial.***
- ***At the pre-NDA meeting held on December 9, 2014, DBRUP first noted and became aware of the "compressed cycle" analysis the Applicant had performed. DBRUP agreed to the Applicant's proposal to do a sensitivity analysis using <u>all cycles</u> in the analysis, including those in which back-up contraception was used.***

5.3.1.10 Secondary Efficacy Variables

The KM analysis of pregnancy rates with 95% confidence intervals was calculated for each treatment at 12 months. The primary analysis of typical use pregnancies included on-treatment pregnancies detected both pre-clinically (using pregnancy test) and clinically.

5.3.1.11 Safety Data

The following safety parameters were monitored during the clinical trial:

- Incidence of adverse events
- Safety of Amphora gel over 13 cycles of use
- Acceptability of Amphora gel compared to N-9 gel
- Incidence of lesions detected by colposcopy in a subset of Amphora gel and N-9 gel subjects
- Incidence of urinary tract infections (UTIs), bacterial vaginosis (BV), and yeast vaginitis
- Asymptomatic vaginal yeast colonization and vaginal *E. coli* colonization as assessed by pre- and post-treatment laboratory tests in a subset of subjects

<u>Reviewer's Comments:</u>

- ***These safety endpoints are adequate for the safety analysis of a topical spermicidal gel. As discussed in Section Error! Reference source not found., the most common adverse events with spermicidal gels are genitourinary infections (UTI, BV, and yeast vaginitis). The occurrence of vaginal lesions is dose-related.***
- ***Systemic pharmacokinetic studies were not performed as part of this application, as the absorption of this topically-applied product is expected to be minimal. Furthermore, if the amount absorbed into the serum were 100% (which is unlikely), the amount of lactic acid in amphora gel would increase the serum concentration of lactic acid by 35.2 µg/mL of serum and citric acid would***

be raised by 20 µg/mL of serum. These levels would not raise the naturally occurring serum concentrations to a concentration above the ULN.

The Colposcopy Subset:

Colposcopic findings:

A subset of the study population underwent colposcopic examination to further assess the impact of the test spermicide on the subject. The evaluator was blinded regarding the subjects' treatment group. This examination followed the procedures outlined in the Manual for the Standardization of Colposcopy Findings for the Evaluation of Vaginal Products Update 2004.[13] Colposcopic photographs were obtained regardless of presence or absence of suspicious lesions, and an assessment of each area was provided. If a lesion or suspicious area was present, the assessment included observations about lesion size, lesion location, appearance of epithelium, and diagnoses of the lesion. Any lesion that developed during the study was examined with a colposcope and findings recorded on the colposcopy form of the eCRF. The subject was re-examined until resolution of clinically significant signs and symptoms, as determined by the Investigator.

Reviewer's Comment:

The methods for evaluation of colposcopic findings were acceptable. The Manual for the Standardization of Colposcopy Findings for the Evaluation of Vaginal Products Update 2004 provides clear procedures, photographs, and terminology for the colposcopic examination of the cervix and vagina. The manual was developed by CONRAD and the World Health Organization for evaluation of the cervico-vaginal epithelium in microbicide development. These standardized procedures include specific steps and terminology the vagina and cervix for epithelial disruptions. Standardized procedures in the examination include the following:

1. ***Participant positioning***
2. ***Naked eye and colposcopic examinations of external genitalia***
3. ***Insertion of speculum***
4. ***Naked eye examination of visible epithelium***
5. ***Auxiliary vaginal tests***
6. ***Lavage***
7. ***Colposcopic examination of cervix***
8. ***Auxiliary cervical tests***
9. ***Colposcopic examination of fornices***
10. ***Colposcopic examination of vagina***

5.3.1.12 Protocol Amendments

The original protocol for study AMP001 (submitted with IND 109300, February 17, 2011), was amended twice. Clinically significant amendments are listed below. Amendments were reviewed and no further comments were conveyed to the Sponsor.

Amendment 1
Amendment 1 had the following changes:

- **Study Sites**: Revised to include an updated estimate of approximately 60 sites within and outside of the United States.
- **Inclusion Criteria**: Revised one criterion to increase upper limit of the average cycle length from 35 to 40 days.
- **Exclusion Criteria**: Revised to update criteria for condylomata and STDs. Updated three criteria to use Randomization visit as a reference point instead of Screening visit.
- **4.0 Study Design**: Revised to include measurement of vaginal lesions as a secondary area of evaluation in the colposcopy subset.
- **4.3 Randomization Procedures**: Revised to reflect updated packaging and handling of the investigational product.
- **5.1.1 Screening Visit (Visit 1)**: Revised to clarify that results of a previous Pap test may be used under specified conditions.
- **Sub-Study Procedures**: Revised to clarify different sub-studies and the procedures and timing of procedures required for each.
- **Chlamydia and gonorrhea testing**: Revised to clarify all included testing methods throughout the protocol.
- **5.5 Serious Adverse Events**: Revised to clarify the proper reporting procedures and timeframes.
- **6.1 Deviation from the Protocol**: Revised to clarify study waiver/deviation approach.

Amendment 2
Amendment 2 had the following changes:

- **Exclusion Criteria**: Revised to add specific criteria for participants or partners diagnosed with gonorrhea or chlamydia. Revised to clarify procedures for cervical biopsy performed during screening. Revised to add specific criteria for participants who have used systemic antibiotics for trichomonas diagnosed during screening. Revised to highlight PI judgment in determination of drug abuse.
- **Schedule of Assessments**: Revised to clarify procedures for quantitative and semi-quantitative vaginal culture. Revised to note that acceptability

questionnaire is not required if product is not used. Revised collection expectations of adverse events and concomitant medications. Revised to note that data are collected on medications taken within 30 days prior to enrollment.

- **Drug Accountability**: Revised to clarify that it is the investigative site's responsibility for maintaining adequate investigational product supply at the site.
- **Laboratory Procedures**: Revised to clarify assessment of the urinary tract infection (UTI) diagnosis and classification.
- **Study Visits**: Revised to add procedures for proof of cure documentation with positive chlamydia or gonorrhea test. Revised to clarify procedures for proof of cure documentation for subjects diagnosed with UTI, symptomatic BV and symptomatic yeast vaginitis during screening. Revised to note collection of pregnancy history during screening. Revised to add procedure for serum sample collection with positive urine pregnancy test.
- **Discontinuing subjects**: Revised to clarify Lost-to-Follow-Up determination procedure. Revised to note discontinuation criteria for subjects diagnosed with trichomonas.
- **Pregnancy Reporting**: Revised to clarify SAE determination procedure in pregnancy outcome.

Reviewer's Comment:
The Applicant did not provide any rationale regarding the revision of the inclusion criterion increasing the upper limit of the average cycle length from 35 to 40 days.

5.3.1.13 Protocol Deviations

The Complete Study Report (CSR) for Study AMP001 had the following statements:
"Roughly a third (36.5%) of all subjects had at least one protocol deviation due to a protocol defined procedure not being performed, with similar incidence across the two treatment groups (37.2% Amphora and 35.8% Conceptrol). Significant protocol deviations, such as improper consent and subject being enrolled without meeting eligibility criteria, were very uncommon, occurring in 2% or less of the study population (2.6% and 1.3%, respectively)." Protocol violations by country and arm are presented in Table 8 below.

"There was one subject who did not receive the assigned study treatment at randomization; Subject (b) (6) was randomized to receive Amphora but was instead treated with Conceptrol. This deviation is documented in the trial master file, in the site's study file and was reported to the site's IRB per the IRB's local reporting requirements." This participant was analyzed according to actual treatment for efficacy and safety analyses. She experienced three mild drug-related AEs and completed the study. She did not experience pregnancy.

"There was an Amphora™-treated subject (b) (6)) who was diagnosed with and treated for gonorrhea at an unscheduled visit prior to Visit 3 who was mistakenly left in the study; however, by Visit 4, the gonorrheal infection was resolved and the subject remained in the study."

Table 8: Protocol Violations by Arm

Protocol Violation	Amphora		N-9 gel	
	US N=1371	Russia N=324	US N=1376	Russia N=318
	n (%)	n (%)	n (%)	n (%)
Subject not consented properly	42 (3.1)	0	41 (3.0)	0
Subject did not meet eligibility criteria	29 (2.1)	2 (0.6)	40 (2.9)	2 (0.6)
Scheduled visit occurred out of window	55 (4.0)	0	55 (4.0)	0
Deviation from protocol-defined procedure	665 (48.5)	1 (0.3)	639 (46.4)	2 (0.6)
Clinical assessment not done	220 (16.0)	4 (1.2)	216 (15.7)	4 (1.3)
Other	299 (21.8)	15 (4.6)	412 (29.9)	13 (4.1)

Source: pdev.xpt data set, JMP analysis 04/20/2016, summary by SUBJID.

The protocol deviations identified that would affect the efficacy and/or safety evaluation included the following:

- <2 sexual episodes recorded during one cycle
- Missing pregnancy test
- Missing diary data

These deviations were found in more than one of the above-listed categories; therefore, an information request was submitted to the Applicant on November 9, 2015 to request the number of subjects with these protocol deviations, listed by subject ID. The Applicant submitted the requested information in
Table **9** below.

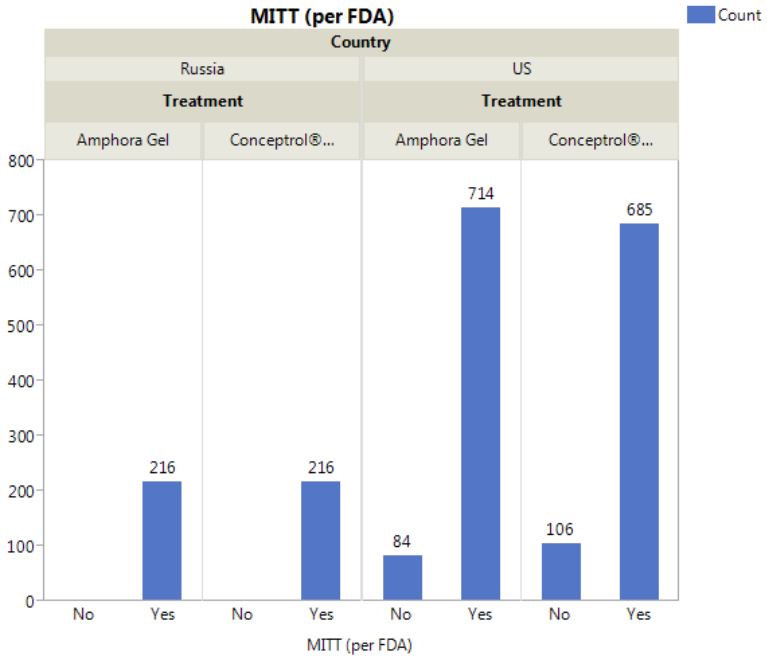
Table 9: Specific Protocol Deviations by Treatment Arm

	Amphora gel		N-9 gel		All Subjects	
	Subjects	Events	Subjects	Events	Subjects	Events
Missing Pregnancy Tests	199	290	199	276	398	566
Missing/Incomplete Diary Cycles	476	698	433	607	909	1305
Diary Cycles with 0 or 1 Intercourse Acts	736	1,017	736	1,007	1,472	2,024

Source: Evofem submission to NDA 208352, November 18, 2015 eCTD sequence number 0013.

There were roughly equal proportions of cycles with fewer than two episodes of intercourse per cycle by treatment arm. However, the US subjects were more likely to have fewer than two episodes of intercourse per cycle than Russian subjects.

Figure 1: Number of Cycles with Fewer than 2 Episodes of Intercourse Included in the MITT-FDA Population by Country and Treatment Arm



Source: jmp analysis NDA dataset pdev.xpt, joined with demo.xpt

Reviewer's Comments:

- ***Intercourse occurred less than twice per cycle in approximately 17% of cycles in both treatment arms in the US and 10% of cycles in Russia. Cycles in which***

participants reported no intercourse were censored from analysis for the MITT (FDA) population.

- ***Consistent with other aspects of this application, there were large differences in the numbers of US protocol deviations in the US population compared to the Russian population.***

6 Review of Efficacy

Efficacy Summary

Amphora gel did not demonstrate non-inferiority to Conceptrol for the primary efficacy endpoint among the US population and is therefore non-approvable. The upper confidence interval of the treatment difference of Amphora versus N-9 gel in the US data was above the Applicant-designated non-inferiority margin of 5.5.

Early in the review process of this NDA, marked differences between the US and Russian pregnancy and completion rates were identified. The Division advised the Applicant of these concerns in the 74-day filing review and asked the Applicant to discuss the reasons for these discrepancies, and provide a strong justification as to why data from Russian sites would be generalizable to the US population. The Applicant provided a response to the concern; however, they did not provide adequate explanation for the differences or justify how the data were generalizable to the US population. The large data discrepancies preclude consideration of the Russian data in the Division's decision about approvability due to non-generalizability to the US population.

During the review process, a high proportion of aberrant cycle lengths was identified (cycle lengths outside 21-42 days). These cycle lengths are inconsistent with ovulatory cycles; therefore, DBRUP requested that the Applicant limit evaluable cycles to include only those with cycle lengths between 21 and 42 days. This restriction, combined with a low completion rate led to poor quality data and insufficient cycles for the efficacy analysis. The reliability and conclusions that may be drawn from the efficacy data of this study are limited. The number of evaluable cycles (3,228 cycles) was ultimately far lower than requested (5,000 cycles) by DBRUP for the efficacy evaluation of the 7-cycle study.

In the primary efficacy analyses, the Applicant defined on-treatment pregnancies as those that "occurred during the time the subject considered the study method her primary method of contraception;" the Division had commented previously that this definition did not conform to the definition upon which the Division relies in contraceptive trials. For the final efficacy analyses, pregnancies were recategorized to include all pregnancies that occurred within 7 days after last date of product use as on-treatment pregnancies.

The initial analysis included a "compressed cycle" KM analysis that included unmatched data from beyond the 7-Cycle phase (196 days) and beyond the 13-cycle phase (365 days) for the primary and secondary efficacy endpoints, respectively. The final analysis accepted by the Division was limited to data that were collected during the 7-cycle phase (196 days) of the study.

6.1 Indication

Amphora gel is indicated for the prevention of pregnancy in women who elect to use a spermicidal gel for contraception.

6.1.1 Methods

AMP001 was the pivotal phase 3 trial designed and performed to evaluate efficacy for this NDA. The trial design was an open-label, randomized, comparator, non-inferiority, international, multi-center trial.

The target sample size for enrollment in this study was 2,800 healthy, sexually active women, with 2,600 women between the ages of 18 and 35 and 200 women 36 through 45 years of age. Treatment assignments were stratified by site and age in a 1:1 randomization ratio to Amphora and N-9 arms. Randomization was performed using a web randomization application. Enrollment at target levels would provide 80-89% power and approximately 7,000 cycles of Amphora gel use. It was assumed that approximately 40-55% (209-289 women) of the Amphora gel group would continue use of the gel into the extension phase for up to 13 cycles.

Recruitment was planned in approximately 60 research centers located within and outside of the US. Women were enrolled from 49 research sites in the US and 13 sites in Russia. Participants were required to meet the following inclusion and exclusion criteria:

See

Figure **2** for a detailed outline of the study visits and procedures. Refer to section 5 for a detailed discussion of study design.

Figure 2: Schedule of Assessments

Procedure	Visit 1 Screening	Visit 2 Admission	Visit 3 After Cycle 1	Visit 4 After Cycle 3	Between Cycles 3 and 7	Visit 5 [A] After Cycle 7/ Exit Visit	Visit 6 [B] After Cycle 10	Visit 7 [B] After Cycle 13/ Extension Exit
Informed Consent	X							
Medical/Gyn History/Demo	X							
Contraceptive History	X							
Eligibility Assessment	X	X						
Pre-Trial Medications	X	X						
Randomization		X						
Vital Signs [C]	X	X	X	X		X	X	X
CBC and Chemistry [D]	X					X		X
Gynecological Exam [E]	X		X	X		X	X	X
Colposcopy (10x) [F]		X	X	X		X	X	X
Pap Test	X [G]					X		X
Chlamydia/Gonorrhea Test [H]	X					X		X
BV Assessments [I]	X		X	X		X	X	X
Quantitative and Semi-quantitative Vaginal Culture [J]		X	X	X [K]		X	X [K]	X
Urine Culture [L]	X					X		X
Dipstick Urinalysis [M,N]			X	X			X	
Urine Pregnancy Test [O]	X	X [P]	X	X		X [P]	X	X [P]
Dispense/Review diaries	X	X	X	X		X	X	X
Dispense IP		X	X	X		X	X	X
IP Return and Accountability			X	X		X	X	X
Dispense Home Preg Test		X				X		X
Acceptability Questionnaire [Q]			X			X		X
Discomfort Questionnaire			X	X		X	X	X
Adverse Events	X	X	X	X		X	X	X
Concomitant Meds			X	X		X	X	X
Between-Visit Contact		X [R]			X [S]			

A Treatment was to end after 7 cycles for subjects who do not continue into the extension; Amphora™ subjects were given an opportunity to extend treatment to 13 cycles
B Visit 6 and 7 procedures were only performed on subjects who continued Amphora™ treatment
C Height, weight, and blood pressure were recorded at screening; only weight and blood pressure was recorded at subsequent visits
D CBC and Chemistry panels did not include a differential or electrolytes; a central lab analyzed CBC and Chemistry panels
E Gynecological Exam included wet mount for monilia; if a subject experienced any severe gynecological symptoms, she was to return to the site as soon as possible for a gynecological exam
F Only subjects included in the colposcopy subset underwent colposcopy and had colposcopic photographs taken; however, colposcopy was to be performed on any subject when the investigator deemed it necessary to evaluate the subject
G Results from a Pap performed at the study site or another center ≤6 months prior to the Screening Visit if the same methods were used
H Chlamydia and Gonorrhea assessments were performed at Visits 3, 4, and 6 only if the subject changed sexual partners
I BV assessment was performed following Amsel's Criteria
J Only subjects in the *E. coli* and Yeast semi-quantitative culture subset underwent these evaluations (analyzed by a central laboratory)
K During these visits, only the semi-quantitative culture was to be obtained; during other quantitative/semi-quantitative visits, only the quantitative cultures were obtained
L In addition to the urine culture at Screening, Cycle 7, and Cycle 13, subjects were instructed to contact the site to schedule a dipstick urinalysis and possibly a urine culture any time they suspected they may have a UTI
M If dipstick urinalysis was 1+ for analytes of blood, leukocyte esterase, protein or nitrites, the urine was to be sent for urine culture and microscopic urinalysis
N Dipstick urinalysis was to be performed at any visit where a subject presented to the center with urinary symptoms
O A urine pregnancy test was to be administered anytime a subject missed her period or suspected pregnancy
P In addition to the scheduled urine pregnancy test, a home urine pregnancy test was given to subjects to take two weeks after the visit. If an Amphora™-treated subject continued into the extension, they did not need the home urine pregnancy test at Visit 5
Q If product was not used, the acceptability questionnaire was not required
R Subjects were instructed to call the site with results of two week post admission pregnancy test results, if subject failed to call; the site was to contact the subject for test results
S If the Principal Investigator deemed it appropriate, subjects were to be contacted 2 months after the Cycle 3 visit

Study Design:

Eligibility determination and screening were performed at a screening visit. Participants were given weekly coital diaries at this visit and given instructions on how to complete the diary. Participants returned for an admission visit within six weeks of the screening visit.

At the admission visit, participants were randomized to treatment group using a computerized randomization tool. Coital diaries were reviewed to determine eligibility for enrollment. Participants were provided with two home pregnancy kits, coital diaries, and test product and given instructions on how to use them. They were also reminded of their right to use EC during the study. Participants were instructed check a pregnancy test two weeks after the admission visit. Participants were instructed to administer the gel using the pre-filled applicator immediately prior to each act of intercourse.

Participants returned for follow up visits after Cycle 1, Cycle 3 and Cycle 7 where pregnancy and adverse events were assessed, discomfort and acceptability questionnaires were administered, physical (including gynecologic) examination was performed and lab assessments were collected. Following Cycle 7, participants were invited to participate in a 13-cycle extension phase. If they chose not to participate, an exit visit was to be performed.

Participants who enrolled in the extension returned for follow up visit after Cycles 10 and 13. At the Cycle 13 visit, an exit visit was to be performed.

The coital diary was of particular importance in the determination of efficacy. Table 11 provides the variables measured in the diary along with the corresponding Case Report Form (CRF) items that subsequently constructed the NDA data set diar.xpt. Please refer to

Figure **3** to view the coital diary that was provided to participants. Participants recorded individual acts of intercourse along with product usage practices, concomitant medications and discomfort (participant and partner). All variables in the diary contained the date of the act and the corresponding use of back up or emergency contraception; however, these dates were not recorded into the CRF. Therefore, all data are available for analysis by subject-reported "cycle" only.

Figure 3: AMP001 Coital Diary

AMP001 Subject Diary

Subject Number _____ Subject Initials _____

DAY	DATE	#1 Did you have a Period or other bleeding today?	#2 Did you insert the study product today (with or without having sex)?	#3 Did you have vaginal sex today? (If No, skip to question #9)	#4 How many times today did you use ONLY the study product with ALL instructions followed?	#5 How many times today did you use ONLY the study product with instructions NOT followed? *For each act, how were instructions not followed? (see Key for Codes)*	#6 How many times today, did you use the study product AND another method?	#7 How many times today did you use another method alone? (e.g. condoms only)	#8 How many times today did you use No method at all? (un-protected)	#9 **Even if you did not have sex today**, please describe any discomforts you and/or your partner may have had in the genital area. Please list any other medical problems or medications taken on the back of this page.
SUN		Period ☐ Other Bleeding ☐ None ☐	Yes ☐ No ☐	Yes ☐ No ☐		# of acts: Code:	#: Method	#: Method		
MON		Period ☐ Other Bleeding ☐ None ☐	Yes ☐ No ☐	Yes ☐ No ☐		# of acts: Code:	#: Method	#: Method		
TUE		Period ☐ Other Bleeding ☐ None ☐	Yes ☐ No ☐	Yes ☐ No ☐		# of acts: Code:	#: Method	#: Method		
WED		Period ☐ Other Bleeding ☐ None ☐	Yes ☐ No ☐	Yes ☐ No ☐		# of acts: Code:	#: Method	#: Method		
THU		Period ☐ Other Bleeding ☐ None ☐	Yes ☐ No ☐	Yes ☐ No ☐		# of acts: Code:	#: Method	#: Method		
FRI		Period ☐ Other Bleeding ☐ None ☐	Yes ☐ No ☐	Yes ☐ No ☐		# of acts: Code:	#: Method	#: Method		
SAT		Period ☐ Other Bleeding ☐ None ☐	Yes ☐ No ☐	Yes ☐ No ☐		# of acts: Code:	#: Method	#: Method		

Codes for Box #5

Code	Description
A	Additional act of intercourse within 1 hour after application and extra study product not applied.
B	Original act delayed or additional act of intercourse more than 1 hour but less than 2 hours after application and extra study product not applied.
C	Original act delayed or additional act of intercourse more than 2 hours after application and extra study product not applied.
D	Less than one full applicator of study product used for each act of intercourse.
E	Inserted study product after intercourse started.
F	Lubricant used with study product during act of intercourse.
G	Other:

For Research ONLY: Cycle #: ____ # of Acts: _____ Date Reviewed: _____ Initials: _____

Table 10: Diary Variables with Corresponding Case Report Form Variables

Variable (Completed daily with date listed)	Diary Response	Case Report Form (CRF)
Bleeding	□Period □Other □None	Cycle number (numeric) Admission date / first day of menses (date) Last day of cycle / end of trial (date)
Insertion of study product today?	□Yes □No	
Vaginal sex today?	□Yes □No	Total number of acts of unprotected intercourse (numeric)
Number of times ONLY study product was used correctly?	Blank space (for number)	Total number of intercourse acts with proper usage (numeric)
Number of times ONLY study product was used incorrectly?	# of acts: Error code (A-G):	Total number of intercourse acts where product instructions were not followed (numeric) Total number of additional acts of intercourse within 1 hour after application and extra study product not applied (numeric) Total number of times the original act delayed or additional act of intercourse more than 1 hour but less than 2 hours after application and extra study product not applied (numeric) Total number of times the original act delayed or additional act of intercourse more than 2 hours after application and extra study product not applied (numeric) Number of other departures during this cycle (numeric) Describe other departures (character)
Number of times study product and another method were used?	#: Method:	Total number of intercourse acts with study product and another contraceptive method (numeric)
Number of times another method alone was used?	#: Method:	Total number of intercourse acts with non-study contraceptive method only (numeric) Was emergency contraception used during this cycle? □Yes □No
Number of times no method was used?	Blank space (for number)	Total number of acts of unprotected intercourse (numeric)
List discomforts for self and/or partner even if no product was used	Blank space (for characters)	Not specified in diary section of CRF, may be collected in AE section of CRF but unclear.
Concomitant medications	Instructions to list on the back of the diary	Prior and concomitant medications section

Reviewer's Comments:

- ***While the open-label study design is prone to bias with regard to safety, this design is acceptable for efficacy given that pregnancy is an objective primary endpoint. Pregnancy assessment was completed using a urine pregnancy test. Ultrasound was also used to confirm the pregnancy. These measures are extremely sensitive for detecting pregnancy and appropriate for the determination of the primary efficacy variable of pregnancy.***
- ***The subject diary used to collect information on frequency of intercourse, concomitant medications, and subject and partner discomfort. The reliability of this measure is poor as the validity of the information provided cannot be determined. Furthermore, in cases where subjects forgot to complete the diary on time, the data are subject to recall bias. Additionally, diaries were collected infrequently. If subjects did not complete a diary, the cycle without diary entries was not included in the MITT analysis. This suggests that the analysis data may be subject to selection bias, which may lead to unreliable conclusions. The Division requested that the Applicant perform sensitivity analyses including cycle lengths of 21 to 35 days.***
- ***The planned enrollment listed in the most recent study protocol (Amendment 2) was 2,600; however, in the final study report, planned enrollment was changed to 3,300. In Section 9.8.2 of the AMP001 Complete Study Report (CSR), Evofem noted that they increased enrollment to meet the goal of 5,000 cycles of Amphora gel for analysis, with 200 subjects completing one full year of treatment.***
- ***The absence of a calendar date in the CRF related to intercourse and concomitant contraception precluded the calculation of efficacy variable using a 28-day cycle approach, as is typically done for hormonal contraceptives.***
- ***Diary data were collected according to cycle number. The Applicant defined "cycle" as running from the first day of menses to the day before the first day of the next menses. The cycle number data were recorded by the investigators upon receipt of diaries, which were collected at follow-up visits (see Figure 3 Coital Diary). The extent of data reporting on cycles much shorter than 21 days and longer than 42 days (see further discussion in Section 6.1.4) raises questions as to how the investigators assigned the "cycle number.". Ultimately, the Division did not believe it would be appropriate to include these cycles with such aberrant cycle lengths, which are extremely unlikely to represent ovulatory cycles, in the calculation of pregnancy rates.***

6.1.2 Demographics for AMP001

The following tables display demographic characteristics of the efficacy population in AMP001 by country and study arm. Table **11** shows demographics of participants of the seven-cycle controlled phase of the study.

Table 11: Study demographics by country, MITT (FDA) population

Demographic and Baseline	US			Russia	
	Amphora Gel	**N-9 Gel**		**Amphora Gel**	**N-9 Gel**
	N=971	**N=999**		**N=323**	**N=316**
	n (%)	**n (%)**		**n (%)**	**n (%)**
Age (years)					
Mean years (SD)	26.9 (4.6)	26.9 (4.7)		26.8 (4.7)	26.6 (4.4)
Median years	27	27		26	26
Race					
White	507 (52)	548 (55)		323 (100)	326 (100)
Black or African American	345 (36)	338 (34)		0 (0)	0 (0)
Asian	28 (3)	33 (3)		0 (0)	0 (0)
Other	78 (9)	73 (8)		0 (0)	0 (0)
Ethnicity					
Hispanic or Latino	291 (30)	289 (29)		1 (0)	0 (0)
Not Hispanic or Latino	679 (70)	710 (71)		322 (100)	316 (100)
Weight (kg)					
Mean weight (SD)	175 (52)	171 (49)		133 (23)	132 (24)
Median weight	163	161		130	128
Weight < 175	565 (58)	595 (60)		305 (94)	300 (95)
Weight $\geq$ 175	406 (42)	401 (40)		18 (6)	16 (5)
BMI (kg/m^2)					
Mean BMI (SD)	30 (8)	29 (8)		22 (3)	22 (4)
Median BMI	28	28		21	21
BMI < 30	570 (59)	605 (61)		313 (97)	308 (97)
BMI $\geq$ 30	399 (41)	391 (39)		10 (3)	8 (3)

SD=standard deviation; BMI=body mass index
Source: FDA Statistician Kate Dwyer

Reviewer's Comments:
Trial demographics were similar by arm but differed significantly by country. Russian participants had a lower BMI, were all white and displayed less variability in age and BMI when compared to US participants. In the US, Amphora and N-9 participants were comparable with respect to race, BMI and age.

6.1.3 Subject Disposition

The subject disposition for the AMP001 MITT FDA population is shown in **Table 12** below.

Table 12: Subject Disposition AMP001, MITT FDA population

	US					Russia			
	Amphora Gel		N-9 Gel			Amphora Gel		N-9 Gel	
	n (%)		n (%)			n (%)		n (%)	
ITT	1,341		1,342			324		317	
ATD	1,135		1,160			324		316	
MITT-FDA	971	100%	999	100%		323	100%	316	100%
Completed Treatment (7-cycle phase)	355	37%	401	40%		310	96%	307	97%
Pregnancy	136	14%	119	12%		9	3%	4	1%
Discontinued Prematurely	480	49%	479	48%		4	1%	5	2%
Reasons for Discontinuation									
Lost to Follow-up	180	19%	165	17%		0	0%	0	0%
Withdrew Consent	101	10%	114	11%		1	0%	0	0%
Protocol Deviation	103	11%	112	11%		1	0%	3	1%
Not sexually active	22	2%	15	2%		2	1%	0	0%
Adverse Event	18	2%	19	2%		0	0%	0	0%
Investigator/Sponsor Decision	17	2%	19	2%		0	0%	0	0%
no longer primary method	10	1%	7	1%		0	0%	0	0%
Other	29	3%	28	2%		0	0%	2	0%
# of Subjects at Risk of Pregnancy at the Time of Enrollment	823		859			320		310	
Number of On-treatment Pregnancies	98		87			6		4	
7-Cycles Cumulative Pregnancy Rate (196 days)	18.0%		14.1%			2.1%		1.3%	
7-Cycles 95% CI	(14.0%, 22.1%)		(11.2%, 17.1%)			(0.4%, 3.7%)		(0.0%, 2.6%)	
Treatment Differences	3.9% (-1.1%, 8.9%)					0.8% (-1.3%, 2.9%)			
Number of Evaluable Cycles*	3,232		3,229			2,082		1,992	

Source: FDA Statistician Kate Dwyer

Reviewer's Comments:

- ***Completion rates reflect the number of cycles a subject was expected to complete – for all N-9 subjects, this refers to completion of 7 cycles. For Amphora subjects, if they entered the extension phase, their completion rate reflects whether they completed all 13 cycles, while for those Amphora subjects who did not enter the extension, it reflects their completion of the first seven cycles.***
- ***Subject disposition was similar by arm, but was significantly different by country. US participants had a 17-fold higher discontinuation rate compared to Russian participants. Russian sites experienced negligible discontinuations due to any reason. The US, in comparison, had a completion rate of 37% in the Amphora arm and 40% in the N-9 arm. US participants in each arm discontinued the trial at a rate of approximately 50% for reasons other than pregnancy or adverse event.***
- ***Women who entered the 13-cycle extension phase of the study were more likely to complete the study. Of the 350 women who entered the extension phase, 75% completed the study (completion rate 66% US vs. 91% Russia).***
- ***Russian participants were much more likely to complete the study and much less likely to become pregnant compared to US participants. Pregnancy rates in Russian sites were also much lower than those reported in previously published spermicide trials evaluating efficacy of spermicide gels.***
- ***In both the US and Russia, there were few participants who were discontinued early because of an adverse event. This is expected for a topical spermicidal gel with a favorable safety profile.***
- ***The low completion rate in the trial and the number of premature discontinuations is problematic as it contributes to poor quality trial data. In non-inferiority trials, poor quality data can obscure treatment differences with a bias towards treatment equality. This can lead to an incorrect conclusion of non-inferiority, in this case a Type 1 error.***

6.1.3.1 Reasons for Screen Failure- Study CL12

At US research sites, there were a total of 4,556 participants screened for AMP001 with 39.3% of these participants failing enrollment. In Russian sites, there were a total of 697 participants screened, with 7.9% failing enrollment. The reasons for screen failure are presented in **Table 12**.

Table 13: Reasons for Screen Failure by Country

Reasons for Screen Failure	US N (%)	Russia N (%)
Other	818 (46)	29 (52)
Lost to Follow Up	264 (15)	1 (2)
Abnormal Pap test	211 (12)	8 (15)
Average length of menstrual cycle	122 (7)	0
Pregnancy	96 (5)	1(2)
Diagnosed with an STD in the past 6 months (not including HPV)	78 (4)	2 (4)
Not willing to be randomized	76 (4)	4 (7)
Clinically significant abnormal finding on pelvic examination or baseline labs	58 (3)	10 (18)
More than one sexual partner in the last four months	17 (1)	0
Partner meets exclusion criterion	14 (1)	0
Subject not willing to accept risk of pregnancy	11 (<1)	0
Not willing to comply with study product instructions	9 (<1)	0
History of >= 3 UTI in past year	5 (<1)	0
Total	1,779	55

Source: NDA 208352 AMP001 SD0018 scrnfail.xpt, jmp extracted data.

Reviewer's Comments:

- ***The majority of screen failures were due to "Other" reasons. This indicates that the data were not collected into meaningful categories. The top reasons for screen failure in the other category were "Not interested," "Withdrew consent," "Screening period exceeded," "Drug use," "Depo-Provera" and "presence of IUD."***
- ***The US and Russian data are discrepant with respect to the proportion of screen vs. enrolled. Notably, the loss to follow-up rate is much lower, indicating much higher compliance of participants at Russian research sites.***

6.1.3.2 Reasons for Protocol Deviations

Please see Section 5.3.1.13 Protocol Deviationsprotocol deviations for AMP001.

6.1.3.3 Applicant's Justification of Data Discrepancies and Discontinuations

The Applicant offered the following explanation for the discrepancies found in the US and Russian data on page 11 of their Integrated Summary of Efficacy (ISE) Addendum. The ISE addendum was submitted on October 30, 2015 in response to an information request.

"When comparing rates for discontinuation across the US and Russian sites, discontinuation rates were higher at the US sites, with a broader range of reasons for discontinuation observed at the US sites mostly related to protocol deviations, and patient issues such as withdrawal of consent or loss to follow-up (see Table 6, Table 7, Table 8, and Table 9); this may be due to variations in patient compliance at Russian versus US sites. Consistent with the differences in pregnancy rates during the study (see Table 4 and Table 5), a lower percentage of subjects were discontinued from the study due to pregnancy at the Russian sites (1.7%), in comparison to the percentage of subjects who were discontinued from the study due to pregnancy at the US sites (10.3%).

Demographics at the Russian and US sites were similar. The overall age of subjects was the same at the Russian and US sites, with an overall mean age of 26.7 years at the Russian sites and 26.7 years at the US sites in the 18-35 age group. When including the 36-45 age group subset at the US sites (only the US sites allowed subject to enroll in this age subset), the mean age for the US sites was 27.8 years; 91.8% of subjects at the US sites were between 18-35 years of age. Although one hundred percent of subjects at the Russian site were white and the majority of subjects at the US sites were white (53.0%) or black/African American (34.9%), the US subjects comprise the majority of the study population (80.7% of ITT population). In addition, the majority of subjects at both the Russian and US sites were of non-Hispanic origin (99.85% Russian sites and 71.1% US sites) (see Table 10 and Table 11)."

The Applicant goes on to conclude:

"Evofem believes that data from the Russian sites are generalizable to the US population as the statistical and general conclusions from the US only population and the overall study population are the same. The inclusion or exclusion of the Russian site data does not alter the overall conclusions of the study: Amphora Gel is non-inferior to Conceptrol gel, with demonstrated contraceptive efficacy."

In response to the high number of discontinuations, Evofem stated in the ISE submitted with the NDA.

"Recent spermicide studies confirm the expectation of 60% continuation at 6 months for clinical trials of this contraceptive method. The largest two published controlled clinical trials of vaginal spermicides report similar 6-month completion rates. In addition, Trussell has estimated that 67% of women who use the combined pill as their contraceptive method will continue to do so after one year, while 42% who use spermicides as their contraceptive method will continue to do so after one year, compared to the 55.7% observed at 6 months without pregnancy in Study AMP001.

Reviewer's Comments:

- ***The Russian and US population are similar in age (as the Applicant mentions); however, contrary to the Evofem's comment about similar demographics, US and Russian demographics differ on BMI. Furthermore, there are extensive differences in discontinuations, pregnancy rate, and reporting rates of AEs among US and Russian populations, which were not addressed by the Applicant.***
- ***The Applicant did not provide adequate justification of the discrepancy in US versus Russian data. The Russian data generated in this trial are not generalizable to the US population primarily due to the large unexplained differences in pregnancy and completion rates. Therefore, the Russian trial data are not applicable to the decision-making regarding approvability and labeling of this product.***
- ***Evofem's justification of the high discontinuation rate is not adequate to minimize the data quality concerns that arise when there is a large proportion of missing data due to discontinuations. The explanations provided related to spermicide continuation rates or the discontinuation rates observed in other publicly funded spermicide trials do not provide adequate an acceptable rationale for the extremely high discontinuation rates in a trial that is seeking approvability for the US drug market. The conclusions that can be made related to efficacy and safety are limited due to high drop-out rate. It is likely that women who terminated participation prematurely differ from those who stayed in the study, including the possibility that they had higher (unreported) pregnancy and adverse event rates. As previously mentioned, this will bias the results toward non-inferiority and risk approval of a drug that may not sufficiently preserve the treatment effect of the active comparator.***

6.1.4 Analysis of Primary Endpoint(s)

Applicant's Analysis

The Applicant defined the primary efficacy endpoint for this trial as cumulative percentage of pregnancy for typical use of Amphora gel compared to N-9 gel over 6 months (183 days). Kaplan-Meier analysis was performed to estimate the 7-cycle cumulative pregnancy probability of women in the MITT population by treatment group. Pregnancies that occurred before randomization or after discontinuing the study method were not included as "on-treatment" in the Applicant's primary analysis.

In the 74-day Filing Review Issues letter dated September 11, 2015, DBRUP requested that the efficacy analysis be performed for a 7-cycle analysis period (196 days). The Applicant did comply with this request.

The non-inferiority hypothesis was tested by calculating a 95% confidence interval (CI) for the

difference between treatments in the six-month cumulative pregnancy probabilities. If the upper bound for the CI is ≤ 5.5, then the null hypothesis will be rejected.

For non-evaluable cycles, a contiguous compressed cycle analysis was performed. Additional analysis was performed that included all cycles, regardless of whether or not back-up contraception was used.

The Applicant's pre-specified primary efficacy dataset was based on the MITT population, defined as follows:

1. between 18 to 35 years of age (inclusive) at enrollment
2. at least one report of pregnancy status after being enrolled.
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")

AND EITHER:

4. have at least 1 cycle of diary without any backup contraception or EC

OR

5. became pregnant and the pregnancy occurred during the time the subject considered the study method her primary method of contraception (i.e., was an on-study pregnancy).

This population is a subset of ITT, which included all women age 18-40 from the US and Russia. The Applicant's analysis is presented stratified by country due to the dissimilarity in the data from the two countries.

FDA-Requested Analyses

In a Type B pre-NDA meeting held on December 9, 2014, DBRUP specified that the primary efficacy population should include all pregnancies that occurred within 7 days of last use of the product. The Applicant provided an additional analysis using this revised definition of on-treatment pregnancy in the original submission (MITT 7 population). In the 74-day letter, DBRUP requested that the Applicant include all pregnancies for which the estimated date of conception occurred during a cycle in which the subject considered the gel to be her primary method of contraception, or within 7 days after her last use of gel in the trial. This was the definition of "on-treatment" pregnancy in the final analysis.

During the NDA review, it was identified that a large proportion of the data contained cycle lengths that were highly variable, ranging from 1 to over 100 days in length. To address the concern that the data was inclusive of many cycles that were unlikely to be ovulatory in nature, DBRUP requested that the Applicant restrict the evaluable cycles to those with cycle lengths between 21 and 42 days (MITT FDA). The Applicant did provide this analysis as requested.

Additionally, the compressed KM analysis performed for the primary analysis included data

from the Amphora treatment arm that was generated from the extension study after the 7-cycle (196-day) study period was completed. This was done to "back-fill" for non-evaluable cycles. The final efficacy analysis that was agreed upon by DBRUP and the Applicant covered the 196-day study period beginning at enrollment, without inclusion of cycle data beyond that time period.

The major analysis populations are shown in Table 14:

Table 14: Number of Participants in Analysis Populations by Country and Treatment Arm

	US			Russia			ALL
Analysis Population	**N-9**	**Amphora**	**Total**	**N-9**	**Amphora**	**Total**	**Total**
ATD	1,161	1,134	2,295	316	324	640	2,935
MITT	998	969	1,967	316	323	639	2,606
MITT FDA	999	971	1,970	316	323	639	2,610

Source: Applicant provided NDA 208352 dataset Master.xpt, and FDA Statistician Kate Dwyer
ITT=Intent to treat, ATD=All treated, MITT=Modified intent to treat, MITT FDA=FDA defined MITT population, N-9=Nonoxonyl-9. See pg. 38-39 for definitions of populations.

Reviewer's Comments:

- ***The primary efficacy outcome (KM cumulative pregnancy percentage over 196 days, by arm) is acceptable for evaluating the efficacy of this product.***
- ***Multiple statistical concerns were identified in the primary efficacy analysis of this NDA. They are summarized as follows:***
  - ***On-treatment pregnancy was not defined according to DBRUP recommendations;***
  - ***The primary endpoint was based on a 6-month (183 days) cumulative pregnancy rate instead of a 7-cycle (196 days);***
  - ***Russian data that was non-generalizable to the US population drove the overall results in favor of Amphora Gel;***
  - ***With the use of 'compressed cycles' in the Kaplan-Meier analysis to avoid censoring a subject entirely after a non-evaluable cycle, the Applicant "back-filled" the 7-cycle analysis with cycles from the extension study window; this resulted in inclusion of Amphora data from post-Cycle 7, when there were no N-9 control data.***
  - ***A large number of cycles with cycle lengths outside of 21 to 42 days were included in the original efficacy analysis. Because cycles of this length are not likely to represent ovulatory cycles (the normal range for ovulatory cycles is between 28 and 35 days), women are not clearly at risk for pregnancy during such cycles. Therefore, the Division requested that cycles outside the range of 21-42 days be considered non-evaluable***

cycles in the final analysis to be used for DBRUP decision-making related to efficacy.

- ***Following a teleconference on February 10, 2016 to discuss the statistical and clinical concerns identified in the application, a final information request (IR) was sent to the Applicant on February 26, 2106. In this IR, the Division clearly defined the following:***
  - ***Cycles to be included in the primary analysis are Cycles 1-7, based on data obtained through a maximum of 196 days after enrollment.***
  - ***The cycle should be considered non-evaluable if:***
    - ***The subject did not enter any diary data during a given cycle***
    - ***The subject did not have any intercourse during a given cycle***
    - ***The subject used back-up or emergency contraception at any time during a given cycle***
    - ***In addition, the typical cycle length should be ≥ 21 days and ≤ 42 days. Cycles outside these limits should be considered non-evaluable and excluded from analysis.***

On-treatment pregnancies for the MITT population were originally defined by the Applicant as follows:

- Enrollment date ≤ Estimated date of conception ≤ date the product was last considered her primary method of contraception (as determined by the subject and recorded in the eCRF).
- If the estimated date of conception could not be provided by the site, then a Pregnancy Adjudication Committee decision of a pregnancy being on-treatment would include the pregnancy in the analysis.

The Applicant was asked to redefine on-treatment pregnancies for the MITT7 population as requested by DBRUP at the pre-NDA meeting:

- Enrollment date ≤ Estimated date of conception ≤ (date last product use + 7 days)

The MITT7 population definition led to 25 subjects (10 Amphora and 15 N-9 gel) with an on-treatment pregnancy classification change. For these 25 subjects, there are 15 on-treatment pregnancies in the MITT population (8 Amphora gel and 7 N-9 gel) and 10 on-treatment pregnancies in the MITT7 population (4 Amphora gel and 6 N-9 gel). In summary, there were 5 fewer pregnancies defined as on-treatment in the MITT7 population.
The specific difference in "on-treatment pregnancy" definitions between the analysis populations that caused the difference in number of on-treatment pregnancies was due to the fact that "the last day the product was considered to be the primary method of contraception" was the benchmark for the MITT population, while the "date of last product use plus 7 days" was used for the MITT7 population. The date of last use and the date the product was considered to be the primary method of contraception were not the same for all subjects.

Therefore, in a case in which a pregnancy occurred more than 7 days after last documented use of the product but while the product was still considered to be the primary means of contraception, this pregnancy would have been counted as an on-treatment pregnancy for the MITT population, but would not be considered an on-treatment pregnancy for the MITT7 population (it would be considered a post-treatment pregnancy).

In the 74 day letter, DBRUP requested the following:

- *"Provide a clear definition of on-treatment pregnancies for the MITT and MITT7 populations. Our definition of the MITT7 population would be all pregnancies for which the estimated date of conception occurs during a cycle in which the subject considered the gel to be her primary method of contraception,* ***or*** *within 7 days after her last use of gel in the trial. If your definition is at variance with this, provide an analysis using our definition, and a table of the pregnancies that are discrepant between the two definitions."*

The final definition of on-treatment pregnancy was therefore all pregnancies for which the estimated date of conception occurred during a cycle in which the subject considered the gel to be her primary method of contraception, or within 7 days after her last use of gel in the trial.

Table **15** presents the distribution of pregnancy categories by country and treatment arm.

Table 15: Pregnancy Categorization by Country and Treatment Arm, 7-Cycle Phase

	US		Russia	
	Amphora Gel	**N-9 Gel**	**Amphora Gel**	**N-9 Gel**
MITT-7	971	999	323	316
# of Subjects at Risk of Pregnancy at the Time of Enrollment	823	859	320	310
Number of On-treatment Pregnancies	98	87	6	4
Number of Pre-treatment pregnancies	6	5	0	0
Number of Post-treatment pregnancies	32	27	3	0

Source: FDA Statistician Kate Dwyer

If the investigator at the study site was unable to provide an estimated conception date, then (b) (4) (the Contract Research Organization [CRO] contracted by Evofem to run

Study AMP001) had a group of medical experts (b) (4) adjudicate pregnancies based on all available data. The Pregnancy Committee classified the pregnancy in one of the following three categories:

1. Pre-treatment pregnancy: a pregnancy with an estimated date of conception before the enrollment date
2. On-treatment pregnancy: a pregnancy with an estimated date of conception in the period from the subject's enrollment date up to and including the last date the study product was her primary means of contraception)
3. Post-treatment pregnancy: a pregnancy with an estimated date of conception after the last date the study product was considered the primary means of contraception

In addition to the above categories, the Pregnancy Committee provided their estimate of the date on which the subject became pregnant. If the pregnancy review committee could only determine the cycle in which the pregnancy occurred, the pregnancy was assigned to Day 14 of that cycle.

The following data were provided to the group of experts to make the above assessments:

- Narrative of the site's impression of the pregnancy details
- Listing of the following CRF data points:
    - Enrollment date
    - Last date study product was primary means of contraception
    - Dates of all subject visits
    - Diary data:
        - Any diary for the cycle?
        - Complete data for the cycle?
        - Cycle number
        - Start and end dates of the cycle
        - Number of acts unprotected intercourse in the cycle
        - Use of emergency contraception in the cycle
        - Number of acts with study method only with proper use in the cycle
        - Number of acts with study method only with non-proper use in the cycle
        - Number of acts with study method and another contraceptive method in the cycle
        - Number of acts with only another contraceptive methods in the cycle
    - Urine and Serum pregnancy tests
    - Ultrasound data
    - Date of the last menstrual period (LMP) before pregnancy

Out of 18 pregnancies that were reviewed by the pregnancy adjudication committee, 16 were determined to be on-treatment pregnancies and two were post-treatment studies. The post-

treatment pregnancies are reviewed below.

Pregnancy Narrative for Subject (b) (6)**:** This participant was a 20 year old female who enrolled in the study on February 15, 2012. The recorded date of last study method use is February 27, 2012. There were no diary data provided by the patient. Pregnancy test results were negative and screening, admission and exit visits. The exit visit was March 14, 2012. The last menstrual period was March 9, 2012. The patient reported a positive pregnancy test during a follow-up call on April 30, 2012. No follow-up information on sonograms or pregnancy outcomes was obtained as the patient was lost to follow-up.

Reviewer's Comment:
There is no way to determine the actual dating of this pregnancy based upon the data available; however, it is possible that this participant experienced an implantation bleed and became pregnant while using the study method. In a "worst-case" analysis, this subject should be considered an on-treatment pregnancy; however, in light of the high pregnancy rates already demonstrated in this study, the efficacy analysis was not redone to include her.

Pregnancy Narrative for Subject (b) (6)**:** This participant was a 32 year old female who enrolled in the study on December 28, 2011. The recorded date of last study method use is January 23, 2012. She had negative pregnancy tests at screening, admission in December, 2011 and after Cycle 1 in January, 2011. Her last menstrual period was recorded as March 5, 2012 and she reported cycle lengths of 32 days. On May 1, 2012 the site contacted the participant and she reported that she was pregnant. She was scheduled for an exit visit on May 7, 2012 but never returned to the site. No data during the cycle the subject became pregnant were provided to the site. The pregnancy outcome and date of ovulation are unknown. The participant was deemed lost to follow up on August 15, 2012.

Reviewer's Comment:

- ***A large sample of pregnancy narratives and pre-treatment, on-treatment and post-treatment status was reviewed. In all cases reviewed, pregnancy status was determined and recorded appropriately. I agree with the assessments made by the pregnancy adjudication committee, although under "worst case" assessment, Subject*** (b) (6) ***would be considered an on-treatment pregnancy.***
- ***The determination of on-treatment pregnancy in the primary efficacy analyses presented by the Applicant was based on "last date the study product was considered the subject's primary means of contraception" instead of the FDA-recommended determination using conceptions within 7 days after last use of product. This led to the request in the 74-day letter to include all pregnancies that occurred within 7 days after last product use or pregnancies that occurred during a cycle in which the subject considered the product to be her primary method of contraception.***

- ***The pregnancy adjudication committee did not have any additional information available to them as compared to the site investigators and algorithms they applied for on-treatment pregnancy determination were not made clear in this NDA.***
- ***The method for determining the "last date the study product was considered the subject's primary means of contraception" was not made clear in the protocol or the CSR. This was an item the eCRF; however, the question was not recorded in the diary. This leaves the answer subject to recall bias on the part of the participant and subject to reporting bias on the part of the investigator. The latter is of particular concern given that this was an open-label trial. However, it should be noted that the Applicant's method for determining on-treatment pregnancies actually resulted in more on-treatment pregnancies.***

The Applicant complied with the above request and final efficacy results were submitted to DBRUP on March 01, 2016, March 10, 2016, and March 17, 2106. The results are presented in Table 16 and Table 17. The six-month (183-days) results are presented in Table 18 for informational purposes.

Table 16: Seven-cycle (196 Days) Pregnancy Rate for MITT FDA Population, 21-42 Day Cycle Length, by Country and Treatment Arm

	US		Russia	
	Amphora Gel	**N-9 Gel**	**Amphora Gel**	**N-9 Gel**
MITT-FDA	971	999	323	316
# of Subjects at Risk of Pregnancy at the Time of Enrollment	823	859	320	310
Number of On-treatment Pregnancies	98	87	6	4
7-Cycles Cumulative Pregnancy Rate (196 days)	18.0%	14.1%	2.1%	1.3%
7-Cycles 95% CI	(14.0%, 22.1%)	(11.2%, 17.1%)	(0.4%, 3.7%)	(0.0%, 2.6%)
Treatment Differences	3.9% (-1.1%, **8.9%**)		0.8% (-1.3%, 2.9%)	
Number of Evaluable Cycles*	3,232	3,229	2,082	1,992

Source: Applicant NDA 208352 Table 14.2.41, (submitted 3/7/2016), confirmed by FDA: Kate Dwyer Statistician, using NDA dataset EFF7CYC.XPT, *evaluable cycles included all cycles with cycle length equal to 21-42 days, at least one episode of intercourse and completed diary data.

Table 17: Sensitivity Analysis using Cycle Length 21 to 35 days, Seven-cycle (196 Days) Pregnancy Rate for MITT FDA Population, by Country and Treatment Arm

	US		Russia	
	Amphora Gel	**N-9 Gel**	**Amphora Gel**	**N-9 Gel**
MITT-FDA	971	999	323	316
# Subjects at Risk of Pregnancy at the Time of Enrollment	813	851	320	310
Number of On-treatment Pregnancies	98	87	6	4
7-Cycles Cumulative Pregnancy Rate (196 days)	17.9%	14.4%	2.2%	1.3%
7-Cycles 95% CI	(14.0%, 21.9%)	(11.4%, 17.5%)	(0.4%, 4.0 %)	(0.0%, 2.6%)
Treatment Differences	3.5% (-1.5%, **8.5%**)		0.9% (-1.3%, 3.1%)	
# Evaluable Cycles	3,063	3,075	2,032	1,939
Number of All Cycles	4,572	4,722	2,186	2,129

Source: Applicant NDA 208352 Table 14.2.45, (submitted 03/07/2016), FDA data: Kate Dwyer Statistician, using NDA dataset EFF7CYC.XPT, *evaluable cycles included all cycles with cycle length equal to 21-35 days, at least one episode of intercourse and completed diary data.

Table 18: Six-month (183 Days) Pregnancy Rate for MITT FDA Population, 21-42 Day Cycle Length, by Country and Treatment Arm

	US		Russia	
	Amphora Gel	**Conceptrol**	**Amphora Gel**	**Conceptrol**
MITT-FDA	971	999	323	316
# Subjects at Risk of Pregnancy at the Time of Enrollment	823	859	320	310
Number of On-treatment Pregnancies	96	87	4	4
Six-Month Cumulative Pregnancy Rate 183 days)	16.6%	14.1%	1.3%	1.3%
Six-Month 95% CI	(13.0%, 20.1%)	(11.2%, 17.1%)	(0.0%, 2.5%)	(0.0%, 2.6%)
Treatment Differences	2.4% (-2.2%, **7.1%**)		-0.1% (-1.8%, 1.7%)	
Number of Evaluable Cycles*	3,232	3,229	2,082	1,992

Source: FDA Statistician Kate Dwyer, *evaluable cycles included all cycles with cycle length equal to 21-42 days, at least one episode of intercourse and completed diary data.

Reviewer's Comments:

- ***The primary efficacy endpoint was not met. The upper confidence interval in the US data was above the Applicant-designated non-inferiority margin of 5.5. As previously mentioned in this review, Russian data was not relied upon in the final primary efficacy analysis due to lack of generalizability of the Russian data to the US population.***
- ***Amphora gel also did not achieve non-inferiority when compared to Conceptrol for the primary efficacy endpoint in the US population in the sensitivity analysis or in the 6-month (183 days) analysis.***
- ***Also of note, the number of evaluable cycles (3,232 in the US Amphora arm) was well below that requested from DBRUP for efficacy analyses (5,000).***

6.1.5 Analysis of Secondary Endpoints(s)

The 13-cycle cumulative pregnancy probabilities (Amphora arm only) are presented in Table 19 below for the US and Russia, respectively.

Table 19: 13-cycle Pregnancy Rates for Amphora Gel Modified Intent to Treat (FDA) Population, 21-42 day cycle length, US Sites

	US	Russia
	(N = 971)	(N=323)
Number of Subjects at Risk of Pregnancy at the Time of Enrollment	835	321
Number of Pregnancies on or before Day 364	113	8
Twelve-Month (364 days) Cumulative Pregnancy Probability	26.8%	3.9%
Twelve-Month (364 days) 95% CI for Pregnancy Probability	(19.5%, 34.2%)	(0.8%, 7.0%)

Source: Applicant NDA 208352 Table 14.2.42, US Sites (submitted 03/07/2016)

Reviewer's Comment:
The primary efficacy endpoint did not meet non-inferiority criteria; therefore, the secondary efficacy endpoint is not relevant to this application. The US and Russian 13-cycle pregnancy rates are provided here for informational purposes only.

6.1.6 Other Endpoints

Other endpoints are not relevant to this application given that the primary non-inferiority criteria were not met.

6.1.7 Subpopulations

The data were reported by Country subgroups throughout this review due to the Russian and US data differences previously discussed. Further analyses in other subpopulations are not relevant to this application given that the primary non-inferiority criteria were not met.

The NDA included secondary safety endpoints, which are reviewed in Section 7 Review of Efficacy.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

According to the clinical pharmacology data presented with this application, the dosing recommendations are appropriate (see Section 4.4 Clinical Pharmacology for details).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Drug concentration measurements were not obtained in this NDA. This is a topical gel with local effects. The effectiveness of the product relies upon its ability to maintain a low pH in the vaginal milieu. Therefore, it is unlikely that there is any persistence of efficacy following use. It is also unlikely that a tolerance or dependence to the product can be developed.

6.1.10 Additional Efficacy Issues/Analyses

6.1.10.1 Douching

Non-clinical studies showed that when a mix of semen and the product were washed with an isotonic solution, sperm viability was regained. The impact of douching was not formally evaluated in the phase 3 study or in preclinical studies. Douching was recorded in the concomitant meds database. There were only two subjects with reported douching during the trial.

> ***Reviewer's Comment:***
> ***If this product is approved in the future, the label should reflect that, while it has not been studied, douching following use of this product is not recommended.***

7 Review of Safety

Safety Summary

The safety profile for Amphora gel is acceptable. It should be noted, however, that the high percentage of early study discontinuation and subjects lost to follow-up makes it difficult to determine the true safety profile.

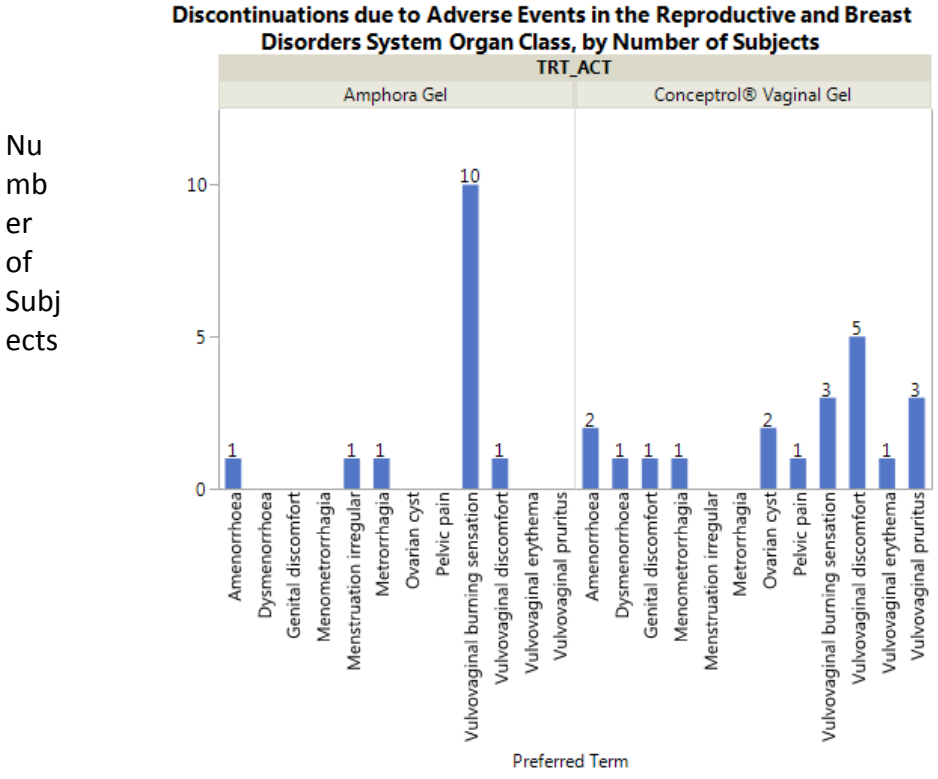
There were no deaths.

The most common non-serious AE associated with use of Amphora gel were BV, UTI and vaginal yeast infection. The frequency of these AEs was roughly equivalent in Amphora and N-9 arms, and is consistent with what has been seen in previous spermicide trials.

In the colposcopy subset (performed at baseline, after Cycles 1, 3, 7 and 10 and 13 in the extension subset), 68% of the subjects were free of vaginal and cervical lesions. When lesions were observed, it was most common to observe 1-2 lesions.

Overall, the AEs that were recorded as leading to study discontinuation were those commonly seen in spermicide studies and do not raise a safety signal. Fewer than 2% of study participants were recorded as discontinuing due to an AE. The most common AEs leading to discontinuation in the 7- and 13-cycle phases in the Amphora arm occurred in the Reproductive System and Breast Disorders MEDDRA System Organ Class (SOC), as shown in . The total number of women who discontinued due to an AE was similar across treatment arms (29 in the Amphora arm, 30 in the N-9 arm); however, participants in the Amphora arm were twice as likely to have discontinued due to vulvovaginal burning. A summary of overall safety findings from AMP001 is presented in **Table** 20 below.

Figure 4:



SOURCE: ADEX.xpt, All treated subset, generated in JMP

Table 20: Adverse Events AMP001 by Subject

	Amphora Gel		N-9 Gel	
	US N=1,135 n (%)	**Russia N=324 n (%)**	**US N=1,160 n (%)**	**Russia N=316 n (%)**
All Subjects with AEs	805 (70.9)	128 (39.5)	838 (72.2)	116 (36.7)
Subjects with severe AEs	29 (2.6)	42(1.3)	6 (0.5)	1 (0.3)
Subjects with serious AEs (SAE)	11 (1)	1 (0.3)	22 (1.9)	0
"Drug-related" AEs per investigator/Applicant All Subjects	557 (49.1)	29 (9.0)	633 (54.6)	36 (11.4)
Subjects with AEs resulting in study drug discontinuation	28 (2.5)	1 (0.3)	30 (2.6)	0
Subjects with drug-related SAEs	2 (0.2)	0	3 (0.3)	0
Subjects who died	0	0	0	0

Source: JMP ADEX.xpt analysis data set, ATD population.

7.1 Methods

Safety data for this NDA were provided by the Applicant in the Clinical Overview, Summary of Clinical Safety, Integrated Safety Summary (ISS), Clinical Study Report (CSR), and electronic datasets. The ISS includes safety information from the AMP001 trial and provides published references that the Applicant is relying on for this 505(b)(2) application. Narrative summaries and case report forms (CRFs) are provided for all subjects who experienced a serious adverse event (SAE) or discontinued from the clinical trial due to an AE.

A summary of the results of the AMP001 pivotal clinical trial is presented in the following sections. Minor differences between the Applicant's results and the FDA's results may occur due to differences in methods of conducting the analysis. The differences do not significantly alter the final conclusions.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety data obtained from the AMP001 trial constitutes the primary safety population. FDA analyses of these data were performed. The safety population included the All Treated population from the 7-cycle controlled phase and a 13-cycle extension phase. Additional safety populations in this study included a colposcopy subset and the yeast and vaginal culture subset. There are 10 published articles submitted with this NDA to provide supportive safety data. Safety information gathered through the review of available data will be used to inform product labeling and use of the final product, if eventually approved.

For a summary of supporting studies from the published literature, please refer to **Table 21** below.

Table 21: Amphora Gel Exposure in Clinical Studies

Reference	N	Age	Dose, Regimen	Duration	Location	Summary of Safety Findings
Studies in Women; Total N = 298						
Amaral, 1999 [14]	18	20–49 years	Amphora gel with N-9 0%, 2.5%, or 5%, 5 mL daily (Unblinded)	6 days	Brazil	No irritation or other symptoms were reported by users of Amphora without N-9.
Amaral, 2006 [15]	20	19–45 years	Amphora gel, 5 mL, 0–30 min or 8–10 hr before coitus versus N-9 and control (Blinded)	2 months	Brazil	4/20 women, 1/20 men with irritation (burning/pruritis) with Amphora gel Nugent scores negative No difference in IL-6 levels
Keller, 2012 [16]	17	18–50 years	Amphora gel, 5 mL, twice daily versus placebo gel (partially blinded)	14 days	New York, USA	65% of amphora experienced vaginal itching and burning All AEs mild and most following gel application 2 episodes of abdominal cramping
Williams, 2007, [17] Anderson, 2009 [18]	27	18–48 years	Amphora gel, 5 mL, 6–10 hrs/night Used with cervical diaphragm versus buffer gel or K-Y (Blinded)	14 days	Virginia and Pennsylvania, USA	Low incidence of mild AEs among Amphora users, most commonly vaginal irritation symptoms (5/20), No difference in measured cytokine levels
von Mellendorf, 2010 [19]	60	18–48 years	Amphora gel, dose N/A, prior to each vaginal sex act Used with cervical diaphragm (partially blinded)	6 months	South Africa	Most common AE among Amphora users: vaginal itching and discharge (37% and 28.6% respectively), most common colposcopic finding: erythema, superficial mucosal disruption in 3 subjects) UTI more common in Amphora group (7/60 women)
Guest, 2007 [20]	60	mean ~30 years	Amphora gel, dose N/A, prior to vaginal intercourse Used with cervical diaphragm and male condom (partially blinded)	6 months	South Africa	Qualitative with some quantitative data is presented related to acceptability and sexual practices.
Behets, 2008 [21]	96	24–37 years	Amphora gel, dose N/A, prior to each sex act Used with cervical diaphragm and male condom (un-blinded)	4 weeks	Mad-agascar	69% of Amphora users had Genitourinary AE (irritation, burning, itching, frequent urination, discharge). More inflammation, discharge, ulcers, and cervicitis in Amphora arm.
Studies in Men, Total N 24						
Schwartz, 2005 [22]	24	19–72 years	Amphora gel, 2 mL, 6-10 hr of penile exposure (blinded)	7 days	Texas, USA	8.3% experienced tingling and dryness. 1 report of small ulceration on the glans of the penis.

N/A= not-applicable, N-9= Nonoxonyl-9.
Source: Applicant Integrated Safety Summary Table 5, page 14. Referenced articles

Reviewer's Comment:
The MedDRA Adverse Events Diagnostics (MAED) and JMP reviewer tools were used in the high-level analysis of the safety of Amphora gel to identify safety signals not

addressed in the Integrated Safety Summary (ISS). The Amphora gel safety data were assessed alone and in comparison to N-9 gel used in the AMP001 clinical trial. The submitted articles were also reviewed for safety findings. In general, the most common AEs that are probably due to Amphora gel tend to be mild in nature and occur in the Infections and Infestations System Organ Class (SOC). No obvious safety signals were identified using the MAED system. There were no unexpected or expected serious adverse events uncovered in the clinical trial and published data presented above that might be related to this spermicidal gel. For purposes of this review, the Applicant's analysis adex.xpt data set was used for this safety review and analysis.

7.1.2 Categorization of Adverse Events

Medical Dictionary for Regulatory Activities (MedDRA) 14.0 was used by the Applicant for AE coding. The mapping of verbatim AEs to MedDRA preferred terms is provided in the data files of this application. The All-Treated subgroup was used for all safety analyses. These were participants that received at least one application of the study drug.

Safety parameters were summarized for all data, including safety data collected for subjects who extended their treatment beyond the Cycle 7 Visit. Serious Adverse Events (SAEs) and AEs were also presented by relationship to investigational product ("drug related" is defined as possibly, probably, or highly probable related to investigational product) and intensity of AE. AEs were also summarized for the subset of subjects who were aged 36-45 at enrollment. A summary of participants who discontinued due to SAEs and AEs is also provided by the Applicant.

Reviewer's Comment:
In the AMP001 phase 3 trial, the incidence rates of treatment-emergent adverse events (TEAEs), drug-related TEAEs, severe TEAEs, TEAEs resulting in study discontinuation, SAEs, and drug-related SAEs were analyzed. Causality (related or not related to treatment) was determined primarily by the investigator at the site where the subject was enrolled. Adverse events by Body System and Preferred terms are summarized and the most common AEs are listed and appropriate mapping was performed. All adverse events are categorized by severity from mild to moderate to severe, according to standard criteria.

7.1.3 Pooling of Data Across Studies to Compare AE Incidence

There was one pivotal phase 3 trial submitted with NDA 208,352. For purposes of this analysis data from the 7-cycle and 13 cycle extension phases have been pooled. Given the low incidence of AEs and SAEs among Russian participants, this safety analysis is reported by country.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses; Study Demographics

Drug Exposure in the Clinical Trials in the safety review

The safety data are derived from the All Treated population, which consisted of 1,135 women in the US and 324 women in Russia who received at least one dose of Amphora gel during the clinical trial. There were 298 women and 24 men exposed to the study drug in supportive publications submitted with this 505(b)(2) application (see **Table 21** for additional details).

> ***Reviewer's Comment:***
> ***The majority of the women exposed in the AMP001 study were from the US. There were a total of 6,248 cycles in the global All Treated population for analysis of safety endpoints. Data from 5,000 cycles had been requested by DBRUP, with at least half from the US population. In the completed trial, there were 4,074 cycles from the US study sites. Overall, however, there were an inadequate number of cycles for the safety analysis, because the disparities in the Russian AE data compared to the US data renders it non-generalizable to the US population. Therefore, as with the efficacy analysis, evaluation of safety is based solely on the US data.***

7.2.2 Explorations for Dose Response

Amphora Gel clinical studies demonstrated that the 2-5ml dose provided acceptable tolerability (minor symptoms and minimum irritation) and inhibited sperm motility effectively by maintaining the pH of <5.0. A 1:2 ratio of undiluted Amphora/semen caused significant sperm immobilization and a pH of 4.56. It was concluded from these studies that the desired acidification of semen should also be achieved with a 3–5 mL dose because the average volume of the human ejaculate is about 3 mL. An increased dose directly correlates to increased sperm immobilization. Acceptable tolerability was demonstrated at the 5 mL dose; therefore, this was the dose selected.

7.2.3 Special Animal and/or *In Vitro* Testing

An *in vitro* study (Protocol# EFM-COOO 1-GMPOO 16.00) was conducted under IND 109,300 to assess the effect of commonly used (based on the publicly available sales information and the reported use by subjects in Study AMP001) vaginal products on the pH of Amphora gel. The pH of Amphora gel (5 g dose, equivalent to 5 mL) was determined after preparing mixtures with ~5 g Miconazole 7 (miconazole nitrate vaginal cream 2%), ~5 g Metronidazole Vaginal Gel (0.75%), 2 g RepHresh Vaginal Gel personal lubricant, and 4.6 g 1-Day Ticonazole Ointment 6.5% Vaginal Antifungal. No significant shift in the intended pH of Amphora was observed when Amphora was mixed with these commonly-used vaginal products. This testing was performed at 25°C.

Reviewer's Comment:
Amphora gel appears to be compatible for use with common over-the-counter vaginal products. Evaluation with douche was not performed. (b) (4)

7.2.4 Routine Clinical Testing

The routine clinical testing obtained in this NDA was adequate for the safety evaluation of a topical spermicide product. The three active components are GRAS and are approved for consumption in food products in the US. For clinical testing obtained at specific study visits, please refer to the Applicant's schedule of assessments provided in **Figure 2**.

7.2.5 Metabolic, Clearance, and Interaction Workup

No metabolic, or clearance studies were performed for this NDA. If approved, this will be reflected in the final labeling. For drug interactions with gels and antifungals, please see section 7.2.3.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The adverse events associated with other spermicidal gels are well known. This study was not designed to evaluate the risk of HIV transmission; however, increased transmission of HIV with use of N-9 gel among sex workers was noted in one previous study. The effect of this spermicide on male-to-female HIV transmission rates is unknown.

The schedule of assessments is provided in **Figure 2**, indicating the procedures for evaluating potential adverse events in the AMP001 study.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in subjects using Amphora gel in the AMP001 trial or in any of the supporting studies.

7.3.2 Nonfatal Serious Adverse Events (SAEs)

There were 11 SAEs among participants in the Amphora arm of the AMP001 trial. There were 19 SAEs among participants treated with Conceptrol. All SAEs occurred in the 7-cycle portion of the trial with no SAEs reported among any participants in the 13-cycle extension study. Incidence of SAEs, by country and arm is presented in Table 22.

Table 22: SAEs Occurring in the AMP011 Study Among Subjects by Arm and Country

	US		Russia	
	Amphora gel N=1,135 n (%)	**N-9 gel N=1,160 n (%)**	**Amphora gel N=324 n (%)**	**N-9 gel N=316 n (%)**
System Organ Class/PT				
Any Serious Adverse Events	10 (0.9%)	19 (1.6%)	1 (0.3%)	0
Infections and Infestation	3 (0.3)	7 (0.6)	0	0
Abdominal Abscess	0	1 (0.1)	0	0
Anal abscess*	1 (0.1)	0	0	0
Appendicitis	0	1 (0.1)	0	0
Campylobacter gastroenteritis	0	1 (0.1)	0	0
Gastroenteritis viral	1 (0.1)	0	0	0
Kidney infection	0	1 (0.1)	0	0
Post procedural sepsis	0	1 (0.1)	0	0
Pyelonephritis*	1 (0.1)	2 (0.2)	0	0
Urethral abscess	0	1 (0.1)	0	0
Gastrointestinal disorders	1 (0.1)	4 (0.3)	0	0
Abdominal Pain	1 (0.1)	1 (0.1)	0	0
Gastrointestinal hemorrhage	0	1 (0.1)	0	0
Pancreatitis	0	1 (0.1)	0	0
Pancreatitis acute	0	1 (0.1)	0	0
Cardiac disorders	0	1 (0.1)	0	0
Wolff-Parkinson White Syndrome	0	1 (0.1)	0	0
Ear and labyrinth disorders	0	1 (0.1)	0	0
Vertigo	0	1 (0.1)	0	0
General disorders and administration site conditions	0	1 (0.1)	0	0
Non-cardiac chest pain	0	1 (0.1)	0	0
Injury, poisoning and procedural complications	2 (0.2)	0	0	0
Road traffic accident	2 (0.2)	0	0	0
Investigations	0	1 (0.1)	0	0
Investigation	0	1 (0.1)	0	0
Nervous system disorders	1 (0.1)	0	0	0

	US		Russia	
	Amphora gel N=1,135 n (%)	**N-9 gel N=1,160 n (%)**	**Amphora gel N=324 n (%)**	**N-9 gel N=316 n (%)**
System Organ Class/PT				
Migraine	1 (0.1)	0	0	0
Pregnancy, puerperium and perinatal conditions	0	0	0	0
Ectopic pregnancy	1 (0.1)	3 (0.3)	0	0
Reproductive Disorders	0	0	1 (0.3)	0
Ovarian cyst rupture	0	0	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	2 (0.2)	1 (0.1)	0	0
Asthma	2 (0.2)	0	0	0
Pulmonary embolism	0	1 (0.1)	0	0
Surgical and medical procedures	0	1 (0.1)	0	0
Gastrectomy	0	1 (0.1)	0	0

Source: Applicant Tables 16 and 17 in the summary of clinical safety (addendum), page 21.
*Represent SAEs that are likely to be drug-related.

Reviewer's Comments:

- ***Overall, 11 (0.8%) of the Amphora participants experienced an SAE compared with 19 (1.3%) of the N-9 participants. Only 1 Amphora participant in Russia experienced an SAE. The most frequent SAE was ectopic pregnancy, with 3 in the N-9 arm and 1 in the Amphora arm. These were deemed unrelated to treatment. Pyelonephritis was deemed possibly related to Amphora gel treatment in 1 participant. I agree with this assessment. There were 2 Amphora participants who experienced AEs of severe asthma and both cases were deemed unrelated to treatment. There was 1 participant who experienced an anal abscess that was deemed unrelated to treatment. I did not agree with this assessment.***
- ***All of the SAE cases in the Amphora treatment arm were reviewed. The SAEs that I believe to be associated with the use of the spermicide are discussed in detail below.***

Subject ID no. (b) (6): Anal abscess The participant was a 31 year old woman, white race, with a BMI of 20.4. This participant had a past history of caffeine headaches. Her gynecologic exam was normal on study entry. She began using Amphora on September 28, 2012. She

experienced BV, which was deemed mild and possibly related to the study medication on January 1, 2013. This was reported as recovered following treatment with "Bactrim 1 tablet PO BID for 5 days, cranberry juice 8 oz TID and Diflucan 1 tablet PO once." The cycle prior to the infection, she had used the gel for a total of 14 applications. She continued to use the gel after treatment for the BV (7 to 16 applications per cycle). The subject experienced an anal abscess on (b) (6), for which she was hospitalized for incision and drainage and treated with Zosyn, Vancomycin, Bactrim DS and docusate. She subsequently developed a yeast infection on (b) (6) and was treated with "diflucan 100 mg PO once, diflucan 150 mg PO once, repeat in 3 days." She recovered from the anal abscess and the yeast infection on (b) (6)

Reviewer's Comment:
The Applicant deemed this SAE as unrelated to the drug product. I disagree with this assessment and believe that this was a drug-related SAE. The anal abscess experienced by this participant could possibly have been related to the study drug. The application of a gel that alters the pH of the vagina can lead to a shift in the microbiome of the vagina. The microbiome of the vagina, perineum and anal areas are closely related. Furthermore, transmission of vaginal organisms could have occurred with vaginal followed by anal intercourse. It is also possible that the participant self-inoculated through a scratch around her anus. It is not clear why the original episode of BV was treated with a UTI treatment regimen.

Subject ID no. (b) (4): Pyelonephritis This participant was a 40 year old women, black race with a BMI of 34.2. She was hospitalized for 6 days due to pyelonephritis on (b) (6) She was treated with cefepime, bacitracin, danocrine, and dilaudid for the treatment of pyelonephritis. This was deemed as possibly related to the study medication.

Reviewer's Comment:
I agree with the Applicant's assessment that this was a drug-related SAE. As in the previously discussed case, Amphora gel can lead to a shift in the microbiome of the vagina. This can lead to an increased risk of UTIs (which is the most common AE in this trial). When left untreated, UTIs can progress to pyelonephritis. It is not reported whether or not there were symptoms of UTI prior to the onset of pyelonephritis.

7.3.3 Dropouts and/or Discontinuations

See Section 6.1.3 of this review for the analysis and comments on the data for subjects who did not complete the study. There were a total of 54 participants over the 13 cycles of the AMP001 trial (26 on the Amphora arm and 28 on the N-9 arm) identified in the JMP analysis of the Applicant's safety dataset who discontinued the study due to an AE. There were an additional 5 participants identified among subjects who discontinued due to "withdrew consent" that were associated with AEs (3 on the Amphora arm and 2 on the N-9 arm) that were identified by this reviewer in a systematic review of reasons for withdrawn consent. These included Subjects

(b) (6). Almost all discontinuations due to AEs occurred in the US subgroup. In summary, when all discontinuations due to AEs are properly accounted for, there were 29 participants on the Amphora arm and 30 on the N-9 arm who discontinued due to AEs. **Table 23** shows a summary of discontinuations due to AEs by MedDRA System Organ Class (SOC) and Preferred Term (PT) name.

Table 23: AMP001 Subjects with AEs Leading to Discontinuation

System Organ Class	Preferred Term	Amphora Gel N =1,459 n (%)	N-9 Gel N =1,476 n (%)
All		29 (2.0)	30 (2.0)
Reproductive system and breast disorders	Vulvovaginal burning sensation	8 (0.5)	3 (0.2)
	Vulvovaginal discomfort	1 (<0.1)	4*(0.3)
	Amenorrhea	1 (<0.1	2 (0.1)
	Vulvovaginal pruritus	0	3*(0.2)
	Ovarian cyst	0	2 (0.1)
	Dysmenorrhea	0	1 (<0.1)
	Genital discomfort	2*(0.1)	3 (0.2)
	Menometrorrhagia	0	1 (<0.1)
	Menstruation irregular	1 (<0.1)	0
	Metrorrhagia	1 (<0.1)	0
	Pelvic pain	0	1 (<0.1)
	Vulvovaginal erythema	0	1 (<0.1)
	All	**15 (1.0)**	**19 (1.3)**
Infections and infestations	Gynecological chlamydia infection	4 (0.3)	0
	Gonorrhea	1 (<0.1)	1 (<0.1)
	Vulvovaginitis trichomonal	1 (<0.1)	1 (<0.1)
	Cystitis	0	1 (<0.1)
	Genitourinary chlamydia infection	1 (<0.1)	0
	Ovarian infection	1 (<0.1)	0
	Vulvitis	1 (<0.1)	0
	Vulvovaginal mycotic infection	1* (<0.1)	1 (<0.1)
	All	**10 (0.7)**	**4 (0.3)**
General disorders and administration site conditions	Administration site reaction	1 (<0.1)	0
	Non-cardiac chest pain	0	1 (<0.1)
	All	**1 (<0.1)**	**1 (<0.1)**
Pregnancy, puerperium and	Abortion spontaneous	0	1 (<0.1)
	Ectopic pregnancy	0	1 (<0.1)

	All	**0**	**2 (0.1)**
Immune system disorders	Drug hypersensitivity	1 (<0.1)	0
	All	**1 (<0.1)**	**0**
Injury, poisoning and procedural complications	Lower limb fracture	1 (<0.1)	0
	All	**1 (<0.1)**	**0**
Investigations	Simplex virus test positive	1 (<0.1)	0
	All	1 (<0.1)	**0**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uterine leiomyoma	0	1 (<0.1)
	All	**0**	1 (<0.1)
Renal and urinary disorders	Dysuria	0	1 (<0.1)
	All	**0**	1 (<0.1)
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	0	1 (<0.1)
	All	**0**	1 (<0.1)

Source: Generated in JMP on 12/9/2015 from NDA 208352 analysis data file adex.xpt, *includes subject(s) who withdrew consent due to AEs, Subject IDs (b) (6)

Reviewer's Comments:

- ***Discontinuations occurring due to AEs were rare in the AMP001 trial. Discontinuations due to AEs in the reproductive system and breast disorders SOC were the most common, followed by the infections and infestations SOC.***
- ***Discontinuations due to AEs may be underreported given that there was a high rate of loss of follow-up in this trial. There is no way to ascertain whether or not these participants stopped the study due to AEs.***
- ***In a review of the participants in the Amphora arm who withdrew consent, reasons for withdraw from the trial included "partner dislikes" the method (N=7), the product was "too messy" (N=4), or participants "did not like the product" (N=7 Amphora). There were also 7 discontinuations in the N-9 arm due to partner dislike.***

7.3.4 Significant Adverse Events

There were no additional significant adverse events related to the use of Amphora gel.

7.3.5 Submission-Specific Primary Safety Concerns

Symptoms of genitourinary discomfort were reported at lower rates in this trial compared to the majority of the supportive literature. In the submitted literature, the most common side effect was vulvovaginal irritation (itching and/or burning). This occurred more commonly in studies that included the use of a diaphragm (up to 69% of participants) and in a study with twice daily application of Amphora gel (65% of participants).[21,20,19,23] When the gel was used only around the time of coitus, as in the AMP001 trial, the incidence of vulvovaginal irritation was reported in up to 20% of participants17. In this study, vulvovaginal burning or pruritus was reported in just under 7% of subjects, and 11% of subjects when the term "vulvovaginal discomfort" is included.

> ***Reviewer's Comment:***
> ***The difference in reporting of vulvovaginal discomfort symptoms could possibly be attributed to a difference in the study population or lower frequency of use of Amphora gel in the AMP001 trial compared to the supportive safety trials. However, it is more likely that the study design contributed to this difference. In the AMP001 protocol submitted by the Applicant under IND 109,300 on August 16, 2012, it was noted that***
>
> > ***"The mild genitourinary symptoms that last no more than one hour and are associated with the use of the study method do not need to be reported as AEs. Those symptoms include irritation, itching burning, rash, abnormal discharge (not including gel), and pain or difficulty in urination."***
>
> ***The exclusion of AEs based on temporal occurrence is not common and may have led to a gross underreporting of these symptoms among users. The occurrence rate of these symptoms as expressed in the supportive trials is likely closer to the truth.***

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Amphora gel has a favorable safety profile and did not differ significantly from the active control arm. AEs were common, but mild in nature. Russian subjects reported fewer AEs than US participants.

Preferred terms were mapped by this reviewer into clinically meaningful categories for AEs as shown in **Table 24**.

Table 24: Mapping of Preferred Terms

Preferred term	Defined Category
Vulvovaginitis chlamydial Vulvovaginitis trichomonal Trichomoniasis Molluscum contagiosum Gynecological chlamydia infection Anogenital warts Genital herpes Cervicitis trichomonal Chlamydial cervicitis Genitourinary chlamydia infection Gonorrhea Herpes simplex Urogenital trichomoniasis	Sexually transmitted infection
Urinary tract infection Urinary tract infection bacterial Urinary tract infection fungal Urinary tract infection staphylococcal Urinary tract infection viral Streptococcal urinary tract infection Cystitis Escherichia urinary tract infection	Urinary tract infection
Vaginal infection Vaginitis bacterial Vulvovaginitis	Vulvovaginitis (non-mycotic)
Dyspareunia Genital discomfort Genital pain Pruritus genital Vulvovaginal burning sensation Vulvovaginal discomfort Vulvovaginal dryness Vulvovaginal pain Vulvovaginal pruritus	Vulvovaginal discomfort
Vulvovaginal candidiasis Vulvovaginal mycotic infection	Yeast Vaginitis
Bladder discomfort Bladder pain Dysuria Micturition urgency Urinary tract pain Pollakiuria	Urinary discomfort

The most common AEs reported by subjects in AMP001 were yeast vaginitis, UTI, vulvovaginal discomfort and vulvovaginitis. These AEs were reported roughly equally between treatment arms, but were reported more commonly by US subjects compared to Russian Subjects. Other less commonly reported AEs included vaginal discharge, dysmenorrhea and urinary discomfort. AEs by preferred terms occurring in ≥ 2% of the ATD population (by country) are shown in Table 25**.**

Table 25: AMP001: All AEs ≥ 2% by, Treatment Arm, ATD population, by Country

Body System	Adverse Event	US %		Russia %	
		Amphora Gel (N=1,135)	N-9 Gel (N=1,160)	Amphora Gel (N=324)	N-9 Gel (N=316)
Infections and infestations	Yeast Vaginitis	14.6	17.9	10.4	14.9
	Urinary tract infection	13.6	20.3	7.4	5.1
	Vulvovaginitis (non-mycotic)	14.1	17.3	0.9	2.2
Reproductive system and breast disorders	Vulvovaginal discomfort	8.2	11.1	0.9	1.9
	Vaginal Discharge	3.2	4.0	0.9	0
Renal and urinary disorders	Urinary discomfort	1.6	3.8	0.9	0

Source: FDA table based on JMP analysis of adex.xpt NDA dataset with recoded PT as specified in Table 24.

Discomfort Questionnaire:

A discomfort questionnaire was completed by participants after Cycle 1, Cycle 3, and Cycle 7 and for the extension study, after Cycles 10 and 13. The questionnaire included an evaluation of symptoms of genitourinary discomfort including vulvovaginal irritation, burning, itching, rash, abnormal discharge (not counting gel), urinary, pain or difficulty. The reporting of discomfort was roughly equivalent by arm with fewer reports of "Any Discomfort" among participants at Russian sites. Among US participants, roughly one-third in each treatment arm experienced discomfort (see **Table 26** below).

Table 26: AMP001 "Any Discomfort" Reported by Country and Treatment Arm

US		Russia	
Amphora (N=1133)	N-9 (N=1161)	Amphora (N=324)	N-9 (N=316)
n (%)	n (%)	n (%)	n (%)
407 (35.9)	394 (33.9)	38 (11.7)	38 (12.3)

Source: Generated in JMP 12/29/2015 using Applicant's NDA analysis disc.xpt data set using ATD population as denominator.

Reviewer's Comments:

- ***The overall safety profile of Amphora gel is acceptable. There was an extremely low rate of SAEs in all arms. There were no deaths. The rate of AE reporting was similar between Amphora and N-9 treatment arms in both countries. There were few discontinuations due to AEs reported. Differences in AE reporting in Russian compared to US AEs biased toward a more favorable safety profile for Amphora gel if the Russian data were pooled with the US data. There were markedly fewer AEs reported among Russian participants and the common AEs. Among the Russian subgroup, there was a markedly lower incidence rate of expected AEs such as vaginal discharge, vulvovaginal discomfort, vulvovaginitis (non-mycotic) and urinary tract infection.***
- ***The AEs observed with Amphora gel are consistent with what is expected for treatment-related AEs for a spermicidal gel with one exception: other safety studies with lower discontinuation rates report a higher frequency of vulvovaginal discomfort among participants. As previously mentioned, this is likely due to the lack of collection and reporting of AEs experienced within the first hour after application of the gel as well as a lack of reporting of AEs among participants who were lost to follow-up.***

7.4.2 Laboratory Findings

Chemistry

Clinical laboratory tests were performed at the Screening Visit and at study completion in both studies and included the following (refer to for a complete schedule of assessments):

- Serum Chemistry: Sodium, potassium, calcium, chloride, glucose, uric acid, creatinine, blood urea nitrogen, ALT, AST, total protein, albumin, lipid panel, alkaline phosphatase, gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), and inorganic phosphorus, cholesterol
- Hematology: Hemoglobin, hematocrit, red blood cell count, platelets, white blood cell count and differential
- Dipstick urinalysis
- Pap test
- Urine culture
- Chlamydia and gonorrhea test

In the US cohort, based on the All Treated population, approximately 8% of women in both treatment arms started with normal serum cholesterol at baseline and had elevated cholesterol at the exit visit.

Clinical chemistry results in the 7- and 13-cycle phases did not provide any evidence of a significant safety signal for Amphora gel. The clinical chemistry laboratory parameters showed

some variability with respect to the distribution of subjects in the below normal, normal, and above normal groups. However, these changes in distribution generally represented no more than 1% of the participants. The shift tables did show a shift from normal to high cholesterol in 7 percent of the population for both Amphora and N-9 arms, but otherwise there were no consistent shifts with respect to a single treatment group across multiple chemistry tests or consistent changes with respect to any other single lab analyte across treatment arms.

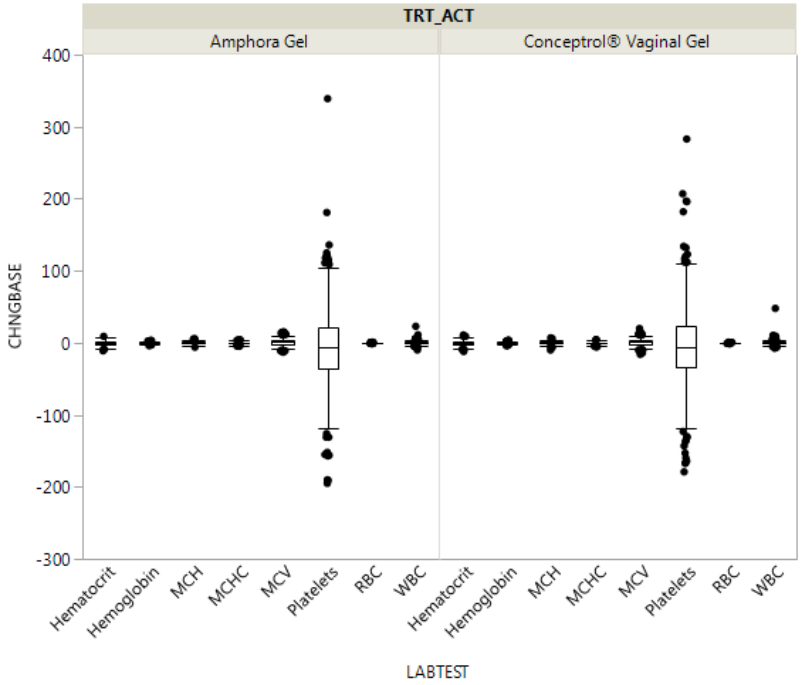
Reviewer's Comments:

- ***For the combined phase 3 data, mean changes were small and not clinically significant across treatment groups. There were no clinically significant safety findings for the Amphora group.***
- ***It is unclear why such a large proportion of the population had a shift from normal to high cholesterol. This is a non-systemically absorbed product and the shift occurred in a balanced fashion across treatment arms, so is unlikely to represent a safety signal from use of this drug product.***

Hematology

There were no significant differences between treatment arms in the mean change from baseline in hematology parameters before and after treatment (see **Figure 5**).

Figure 5: AMP001: Actual Numeric Change from Baseline in Hematology Labs by Treatment Arm, US population



Source: JMP extracted data from Applicant's NDA analysis dataset lab-H.xpt, US population

Reviewer's Comment:
Amphora did not show any evidence of a hematologic safety signal in this phase 3 study.

7.4.3 Vital Signs

Vital signs measured during the phase 3 trial included height, weight and blood pressure (BP) at the screening visit, each subsequent visit, and at the exit visit. There were no clinically significant differences observed in the change from baseline by treatment group. There was a significant difference noted between arms in the change from baseline in Visit 8 for diastolic BP; however, this was not a clinically significant difference as the blood pressure change was still within normal limits and it was likely due to chance.

When evaluating the data, it was noted that there were a large proportion of subjects who had zero change from baseline with respect to systolic or diastolic blood pressure. This change was consistent across treatment groups and by country.

An Information Request was sent to the sponsor to address the concern regarding the zero change from baseline in blood pressure findings. They provided the following response:

> *"Based on the distributions of systolic and diastolic blood pressures we agree a change from baseline of 0 was the most common response. Even though a change of 0 was the*

most common change from baseline value, the proportion of assessments with a change of 0 was relatively low (17.1% for systolic and 19.3% for diastolic). The Russian sites had a change of 0 more frequently than US sites, but we believe that is due to the fact that Russian sites used an analog blood pressure cuff (which may have led to rounding of the BP in some situations (for instance, 120/80 instead of 124/82)). Our submission includes more detailed reports that provide the distribution of data across country, treatment and study visit."

Reviewer's Comment:
There were no clinically significant changes in vital signs in the Amphora treatment arm. There are no safety signals identified in vitals. Evofem adequately addressed the concerns related to the zero change from baseline. The data integrity was also assessed during OSI site investigations and there was no evidence of fraudulent activity observed. This is a healthy patient population and this may have contributed to these findings.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not indicated or performed during the phase 3 clinical trial.

7.4.5 Special Safety Studies/Clinical Trials

7.4.5.1 Colposcopy Subset:

Cervicovaginal colposcopy was performed at baseline and at each visit for a subset of participants. Colposcopy technicians were blinded to study assignment. This study was designed to evaluate for possible cervicovaginal erosion. The results from this study are shown in **Table 27** and **Table 28** below. The number of lesions was similar by treatment arm.

Table 27: Summary of Colposcopy Lesions by Treatment Group (CS Subset)

Lesions on Colposcopy	Amphora (N=74)	Conceptrol (N=70)	Overall (N=144)
	n (%)	n (%)	n (%)
0 1-2 3-4 5-6 7-8	50 (69.4) 13 (18.1) 6 (8.3) 2 (2.8) 1 (1.4)	44 (66.7) 12 (18.2) 5 (7.6) 5 (7.6) 0	94 (68.1) 25 (18.1) 11 (8.0) 7 (5.1) 1 (0.7)

Source: Applicant-provided study report Table 14.3.5.6

Table 28: Summary of Colposcopy Lesions by Size, Diagnosis and Treatment Group (CS Subset)

Suspicious Lesion found?	Size of Lesion	Diagnosis	Amphora Gel N = 74 n (%)	Conceptrol Vaginal Gel N = 70 n (%)
No	<5mm	Erythema	0	1 (1.4)
Yes	<5mm	Abrasion	1 (1.4)	2 (2.9)
Yes	<5mm	Ecchymosis	3 (4.1)	3 (4.3)
Yes	<5mm	Edema	1 (1.4)	0
Yes	<5mm	Erythema	3 (4.1	11 (15.7
Yes	<5mm	Grossly white finding	0	4 (5.7)
Yes	<5mm	Laceration	2 (2.7)	1 (1.4)
Yes	<5mm	Other	14 (18.9)	14 (20.0)
Yes	<5mm	Petechiae	11 (14.9)	9 (12.9)
Yes	>10mm	Edema	0	2 (2.9)
Yes	>10mm	Erythema	4 (5.4)	4 (5.7)
Yes	>10mm	Grossly white finding	2 (2.4)	2 (2.9)
Yes	>10mm	Peeling	0	1 (1.4)
Yes	5-10mm	Ecchymosis	1 (1.4)	1 (1.4)
Yes	5-10mm	Erythema	6 (8.1)	13 (18.6)
Yes	5-10mm	Laceration	3 (4.1)	0
Yes	5-10mm	Other	3 (4.1)	2 (2.9)
Yes	5-10mm	Peeling	1 (1.4)	1 (1.4)

Source: Applicant's NDA colp.xpt analysis dataset. JMP extracted data 12/30/2015 by R Zopf.

Reviewer's Comment:
Lesions observed on colposcopy were similar by treatment arm. Approximately two-thirds of participants observed in the colposcopy study did not have any lesions. Amphora appears no more or less irritating to the cervico-vaginal area than N-9 gel.

7.4.5.2 Use in Male Subjects

Male tolerance of Amphora gel was evaluated under IND 109,300. A randomized double-blind, single-center phase I trial was performed in circumcised and uncircumcised men to compare K-Y Jelly Personal Lubricant with Amphora gel.22 Each participant was instructed to apply 2 mL of the study product to his penis at bedtime, to wash it off 6-10 hours later and to record any symptoms on a diary card. A follow-up exam of the genital area was performed and participants were assessed for AEs and completed an acceptability questionnaire.

Results were:

- Thirty-five out of 36 men completed all seven uses of gel on seven consecutive days and completed the study.
- The Amphora gel was left on for an average of 10.0 h (range 5.7–21.4, SD 1.5) and K-Y Jelly for 9.9 h (range 5.7–18.1, SD 1.8) before being washed off.
- Two men out of 24 (8.3%) in the Amphora gel group reported a total of two product-related AEs, namely, tingling and dryness. Five men out of 12 (41.7%) in the K-Y Jelly group reported a total of 9 AEs, including itching, tingling, burning, and dryness. All AEs were considered mild except for two episodes of itching occurring in a volunteer using K-Y Jelly that were recorded as being of moderate severity and were associated with prolonged gel exposure of about 12 h.
- On follow-up genital exam, 2 out of 24 Amphora gel and one out of 11 K-Y gel users were found to have a lesion on the penis. One Amphora user was a circumcised male with a small 1 mm ulceration and the other was an uncircumcised male with an area of small vesicles. All findings were painless and resolved within 2 weeks.
- Overall, comfort and easy use were the aspects best liked about Amphora gel. Gel consistency was the aspect least liked by 8 out of 23 (34.8%) users of Amphora gel. Taking a long time to dry was one of the aspects least liked about Amphora gel by 4 out of 24 users (17.4%).
- There were two participants in the Amphora gel group with laboratory values that were normal at enrollment and abnormal at follow-up (elevation in eosinophil percentage and glucose).
- A majority (about 70%) of all gel users did not think that they would be able to tell if their partners used the gel. About 91% of men in the Amphora gel group would not object to their partner using the gel in the future.

In the AMP001 trial, partner discomfort was assessed in the subject diary at each visit. When evaluating partner-reported discomfort after use of the study product, partner discomfort was greatest after Cycle 1 (5.4% Amphora and 5.7% N-9). By Cycle 3, reports of partner discomfort had subsided (3.5% Amphora and 2.9% N-9) and by Cycle 7, partner discomfort was reported in <2% of subjects' partners (1.6% Amphora and 1.5% N-9). At the final evaluation, partner-reported discomfort was similar across the two treatment groups, with 3% of subjects' partners reporting discomfort during the study (3.5% Amphora and 2.9% N-9). In the Amphora extension phase, after Cycles 10 and 13, discomfort was reported by 1% of subjects' partners. There were 14 participants who withdrew from the study due to their partners disliking the study method for contraception. Of these, 7 were assigned to the Amphora treatment arm and 7 were assigned to the N-9 treatment arm.

Reviewer's Comment:
The product safety and tolerability profile in male users is acceptable; however, the data are limited. Given that this is a topical gel with GRAS-listed active ingredients, it is unlikely that the product would pose a safety risk to male partners. Furthermore,

the safety profile in male users is likely more favorable than the results indicate, as a shorter duration of exposure is expected than that in the male tolerability study.

7.4.5.3 Condom Integrity and Diaphragm Studies

Condom compatibility studies with condoms were performed with latex, polyurethane and polyisoprene condoms. Mechanical tests were conducted to assess the changes in airburst volume, airburst pressure, break force, and elongation of the condom in the absence or presence of Amphora gel. Mineral oil was used as a positive control. There were no significant differences found in any measured parameters after treating the condoms for 10 minutes, 30 minutes, and 24 hours.

Mechanical tests were performed on female diaphragms to assess changes in break strength and elongation of the diaphragm in the absence or presence of Amphora gel. There were no significant changes in any of the measured parameters. For full details, please refer to the CDRH review by Veronica Price dated March 16, 2016.

The applicant referred to published literature that evaluated use of Amphora gel with diaphragm versus a placebo gel with a diaphragm. A total of 48 women were exposed to Amphora gel in the dome of a diaphragm and instructed to wear the diaphragm continuously for four weeks. There was weekly follow-up to assess for subject experience, an examination, and AEs. No SAEs were reported. AEs were more common in women using Amphora (62% of all AEs) than in participants using placebo, with the highest number of AEs reported after the first week of use. Genitourinary AEs (irritation, burning, itching, frequent urination, discharge) were reported in 75% of Amphora with diaphragm users. More inflammation, discharge, ulcers, and cervicitis were present in the Amphora arm than placebo.

Reviewer's Comment:
Condom integrity has not been shown to be affected by Amphora gel in any of the condom types studied; diaphragm integrity was also not impacted. Use of condoms and diaphragms is compatible with Amphora gel.

7.4.5.4 Pap Smear Results

In the United States, approximately 94% of subjects in each treatment group had a normal Pap smear at baseline. Pap smear results were missing for approximately 20% of subjects in each treatment arm in the US. In Russia, there was only one subject out of 640 in the Amphora arm with an abnormal Pap smear result at baseline. The Russian cohort did not have any missing data. Of subjects who did have a change in Pap smear results, 3% in each treatment group had improvements in Pap smear findings at Cycle 7 as compared to baseline and 7-8% of subjects in each treatment group had worsening in Pap smear results. These results are presented in **Table 29**.

The majority of pap findings were minor in nature including Atypical Squamous Cells of Uncertain Significance (ASCUS), Low Grade Squamous Intraepithelial Lesion (LGSIL), BV, or candida seen on pap. There were six instances of High Grade Squamous Intraepithelial Lesion (HGSIL) occurring on the Amphora treatment arm (2 US and 4 Russia).

Table 29: Pap Smear at Baseline and Study Exit (7-cycle and 13-cycle phases)

Country		US		Russia	
Treatment Arm		Amphora (N=1135)	N-9 (N=1160)	Amphora (N=324)	N-9 (N=316)
Baseline Pap Result	Change From Baseline	n (%)	n (%)	n (%)	n (%)
Normal	No Change	761 (67.1)	741 (63.8)	319 (98.5)	310 (98.1)
Normal	Worsened	94 (8.3)	88 (7.6)	7 (2.2)	4 (1.3)
Abnormal	No Change	10 (0.9)	13 (1.1)	1 (0.3)	0
Abnormal	Improved	38 (3.4)	40 (3.4)	0	0

Source: Applicant's NDA analysis data set papt.xpt. JMP extracted data 1/4/2016 R Zopf. Denominator is the ATD population.

Reviewer's Comment:
The Pap smear results demonstrate the inconsistency between US and Russian data. The worsening pap result in 8-9% of the women is consistent with what is expected in a population of sexually-active reproductive-age women and does not present a safety concern.

7.4.5.5 Yeast Vaginal Culture Subset (YVCS)

The Yeast Vaginal Culture Subset (YVCS) was made up of 73 Amphora and 79 N-9 gel subjects from US sites. The pathogens evaluated by quantitative vaginal culture included H_2O_2+ Lactobacillus, H_2O_2– Lactobacillus, H_2O_2 unknown Lactobacillus, *Gardnerella vaginalis*, *Staphylococcus aureus*, *E. coli*, enterococcus, *Candida albicans*, other yeast, and anaerobic gram negative rods. Cultures were performed at Baseline, after Cycles 3 and 7 and Cycles 10 and 13 for the participants in the extension study. The results of the quantitative cultures were similar at baseline and post-treatment, with no clear pattern of increase or decrease in pathogens within or across treatment groups.

Semi-quantitative cultures were performed for the same subset and time points as the quantitative cultures. These cultures included evaluation for *Eschecheria coli (E.coli)* and yeast at baseline and follow-up visits. The incidence of yeast at baseline was similar among the participants at Baseline (19.4% Amphora and 18.1% N-9 gel). By Cycle 7, a higher proportion of N-9 subjects had yeast compared to Amphora participants (17.8% Amphora and 33.3% N-9 gel).

At baseline the incidence of *E.coli* was slightly higher among Amphora participants (37.3% Amphora vs. 25.0% N-9 gel). By Cycle 7 the incidence remained slightly higher among Amphora participants but had decreased from Baseline (28.9% Amphora and 21.4% N-9 gel).

Reviewer's Comment:
The findings of the YVCS study do not indicate any clinical concerns related to the vaginal microbiome; however, this sub-study was exploratory in nature and not powered to detect treatment differences.

7.4.6 Immunogenicity

No immunogenicity studies were performed.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose-dependency for AEs was not studied in AMP001 as the product was used in a single dose on an as-needed basis. In one of the Applicant-submitted supporting studies, a partially blinded placebo-controlled safety trial demonstrated that 65% of women using Amphora gel 5 mL twice daily reported genitourinary AEs including irritation, burning, itching, frequent urination, and discharge.[26]

Reviewer's Comment:
Women using Amphora gel in the published safety study had a higher rate of AE reports than the women in the AMP001 trial. This may indicate that women may experience an increase in genitourinary AEs with more frequent use of Amphora gel.

7.5.2 Time Dependency for Adverse Events

Due to the sporadic use of this product by participants based on sexual activity, exploration for time-dependency of adverse events was not performed.

7.5.3 Drug-Demographic Interactions

This product is indicated for use only in women of childbearing age. No other special populations were studied. There is no evidence in the current medical literature that the safety or efficacy of spermicidal gels is significantly affected by race or ethnicity.

7.5.4 Drug-Disease Interactions

No drug-disease interactions were studied.

7.5.5 Drug-Drug Interactions

See Section 7.2.3 for a description of an *in vitro* study to evaluate the effects of over-the-counter gels and antifungal treatments.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity trials were indicated or performed. There are no new molecular entities in this product and the three active ingredients are GRAS-listed.

7.6.2 Human Reproduction and Pregnancy Data

Pregnancy outcomes are presented in **Table 30** below. Of the 155 pregnancies reported in the Amphora treatment group, 64 (41.3%) resulted in a full-term birth, 35 (22.6%) ended by induced abortion and 16 (10.3%) ended in spontaneous abortion. Two pregnancies (1.3%) resulted in a pre-term birth (both in the US), 1 (0.6%) ended with a still-birth and 1 (0.6%) was an ectopic pregnancy. The outcome of 24.5% of the pregnancies was unknown. Of the pregnancies occurring in the Amphora arm, 147 (95%) occurred in the US. In Russia, there were three full term deliveries, three induced terminations, and two spontaneous terminations.

In the N-9 treatment group, of the 129 reported pregnancies, 126 (98%) occurred in the US, 41 (31.8%) resulted in a full-term birth, 33 (25.6%) ended by induced abortion and 17 (13.2%) ended in spontaneous termination. Two pregnancies (2.3%) resulted in a pre-term birth and 3 (2.3%) were ectopic pregnancies. The fetal status was unknown for approximately a fourth of all subjects who became pregnant during the study (23.2% Amphora and 24.8% N-9).

Infant assessments were the same across the two treatment groups: average fetal weight was 7.5 pounds, average fetal height was 20 inches, mean Apgar score was 8.0 at 1 minute and 9.0 at 5 minutes, and median gestational age was 39 weeks in each treatment group. There were three infant abnormalities noted in live births from subjects treated with Amphora; an infant was missing the top two lateral incisors and lower left incisor, an infant had an umbilical hernia, and an infant was born with five infantile hemangiomas.

Table 30: Pregnancy Outcome in ATD Population by Country and Treatment Arm

	US		Russia	
	Amphora	N-9	Amphora	N-9
Pregnancy Outcome	**n (% of pregnancies)**	**n (% of pregnancies)**	**n (% of pregnancies)**	**n (% of pregnancies)**
Full term birth	61 (41.5)	40 (31.7)	3 (37.5)	1 (33.3)
Induced termination	32 (21.8)	31 (24.6)	3 (37.5)	2 (66.7)
Unknown	36 (24.5)	32 (25.4)	0	0
Spontaneous termination	14 (9.5)	17 (13.5)	2 (25.0)	0
Pre-term birth	2 (1.3)	3 (2.4)	0	0
Ectopic	1 (0.7)	3 (2.4)	0	0
Still birth	1 (0.7)	0	0	0
Total	147 (100)	126	8 (100)	3 (100)

Source: Applicant's NDA pout.xpt analysis dataset. JMP extracted data on 1/4/2016 by R. Zopf

Reviewer's Comment:
According to the Centers for Disease Control, birth defects affect 3% of all babies born in the US each year. Birth defects were present in 1.9% of pregnancies in the Amphora arm. The incidence of spontaneous abortion and stillbirth in this study are consistent with the rate in the general population. This does not present a safety concern related to pregnancy. However, the data quality are poor given that roughly a quarter of subjects have unknown pregnancy outcomes. This introduces some uncertainty in the safety analysis of pregnancy information.

7.6.3 Pediatrics and Assessment of Effects on Growth

All applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The Applicant requested a partial waiver from the requirements of the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) for all (b) (4) males (b) (4) and premenarcheal females, as they are not at risk of pregnancy. The onset of menarche marks the beginning of the biological capacity to for women to bear children; prior to menarche pediatric females, even if sexually active, are not capable of bearing children.

The applicant proposed that the use of Amphora gel in pediatric post-menarcheal females (≤ 17 years of age), would be addressed by extrapolation of efficacy and safety data from the clinical trial, AMP001 because studies to examine the use of Amphora gel would be impossible or highly impracticable in pediatric males and premenarcheal females (≤ 17 years of age) populations (PREA, section 505B(a)(4)(B)(i) of the Act), as they are not biologically capable of pregnancy. Similarly, the safety and efficacy profile of the Amphora gel is expected to be the

same for post-menarcheal adolescent females < 18 years of age as it is for females ≥ 18 years of age.

There are no pediatric-specific formulation development plans for the proposed Amphora gel product. Amphora gel is suitable for use in both adults and post-menarcheal females ages ≤ 17 years of age.

Reviewer's Comments:

- ***The Initial Pediatric Study Plan (iPSP) was submitted on May 11, 2015. DBRUP agreed to this plan on May 22, 2015.***
- ***Labeling*** (b) (4)
- ***The safety and efficacy profile of the Amphora gel is expected to be the same for post-menarcheal adolescent females < 18 years of age as it is for females ≥ 18 years of age.***
- ***The review of the Applicant's waiver/extrapolation request by the Pediatric Research Committee (PeRC) was deferred to the next review cycle.***

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There are no drug abuse potential issues with spermicidal gel, nor are there concerns about withdrawal or rebound. The potential for either intentional or accidental overdose with Amphora gel is viewed as unlikely, and is not likely to cause serious effects if it occurred.

7.7 Additional Submissions / Safety Issues

120-day Safety Report: A brief 120 day safety report was submitted on September 2, 2015. The original safety data on pregnancy and infant outcomes provided in the NDA covered through March 31, 2015. This safety update covered the period from the original NDA submission up until September 2, 2015. The report included only follow-up pregnancy and infant outcomes.

These data were not collected on a large portion of participants due to loss to follow-up. There were no additional congenital anomalies identified in this reporting period. The safety information gathered over this reporting period from participants who had participated in AMP001 does not raise any new safety signals.

8 Postmarket Experience

There is no postmarket experience available at this time as the product is not marketed anywhere in the world.

9 Appendices

9.1 Literature Review/References

A literature review was performed using Pub Med, Web of Science and Google Scholar to identify references relevant to the evaluation of safety and efficacy of spermicidal products. Relevant details were included in this review.

References:

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9.2 Labeling Recommendations

Deferred to the next review cycle.

9.3 Advisory Committee Meeting

An Advisory Committee Meeting is not required for this application as there were no scientific issues requiring outside expertise.

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/s/

REGINA R ZOPF
04/26/2016

LISA M SOULE
04/26/2016
I concur with Dr. Zopf's conclusions and recommendation for a Complete Response action for NDA 208-352.