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RESEARCH**

APPLICATION NUMBER:

208352Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Resubmission
Application Number(s)	NDA 208352 (INDs 64,623 and 109,300)
Priority or Standard	Standard
Submit Date(s)	November 25, 2019
Received Date(s)	November 25, 2019
PDUFA Goal Date	May 25, 2020
Division/Office	Division of Urology, Obstetrics and Gynecology (DUOG)
Review Completion Date	May 21, 2020
Established/Proper Name	Lactic acid, citric acid, and potassium bitartrate
(Proposed) Trade Name	PHEXXI
Class	Contraceptive vaginal gel
Applicant	Evoform, Inc.
Dosage form	Gel
Applicant proposed Dosing Regimen	5 grams of applicator instilled gel in vagina before each episode of vaginal intercourse
Applicant Proposed Indication(s)/Population(s)	Prevention of pregnancy in women who choose to use on-demand methods for their contraceptive needs
Recommendation on Regulatory Action	Approval

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Kimberly Shiley
Chief Regulatory Project Manager	Margaret Kober
Nonclinical Reviewer	Yangmee Shin, PhD
Nonclinical Team Leader	Kimberly Hatfield, PhD
Nonclinical Supervisor	Mukesh Summan, PhD, DABT
Office of Clinical Pharmacology Reviewer(s)	Li Li, PhD
Office of Clinical Pharmacology Team Leader(s)	Yanhui Lu, PhD
Clinical Reviewer	Anandi Kotak, MD, MPH
Clinical Team Leader	Gerald Willett, MD
Statistical Reviewer	Weiya Zhang, PhD
Statistical Team Leader	Mahboob Sobhan, PhD
Cross-Disciplinary Team Leader	Gerald Willett, MD
Deputy Division Director (designated signatory authority)	Audrey Gassman, MD

Additional Reviewers of Application

OPQ	Drug Substance: Jeff Mediwd, Donna Christner Drug Product: Venkat Pavuluri, Moo-Jhong Rhee Manufacturing: Cassandra Abellar, Joanne Wang Microbiology: Jesse Wells, Yarery Smith RBPM: Marquita Burnett ATL: Mark Seggel
OPDP	Jina Kwak, Matthew Falter
DMPP	Nyedra Booker, PharmD, MPH, Marcia Williams, PhD, LaShawn Griffiths, MSHS-PH, BSN, RN
OSI	Ling Yang, MD, PhD, FAAFP, Min Lu, MD, MPH, Kassa Ayalew MD, MPH
OSE/DMEPA Labeling Review Proprietary Name Review	Carol Holquist, RPh, Lolita White, PharmD Beverly Weitzman, PharmD, Briana Rider, PharmD, CPPS
Other	CDRH-OPEQ: Veronica Price

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
DMPP= Division of Medical Policy Programs
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Yangmee Shin, PhD	DPT - ORPURM	Sections: 5, 17.2, 17.4	Select one: ☒ _X_ Authored ☐ _ Approved
	Signature: Yangmee Shin -S Digitally signed by Yangmee Shin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yangmee Shin -S, 0.9.2342.19200300.100.1.1=1300163502 Date: 2020.05.20 17:40:47 -04'00'			
Nonclinical Team Leader	Kimberly Hatfield, PhD	DPT - ORPURM	Sections: 5, 17.2, 17.4	Select one: ☐ _ Authored ☒ _X_ Approved
	Signature: Kimberly P. Hatfield -S Digitally signed by Kimberly P. Hatfield -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Kimberly P. Hatfield -S, 0.9.2342.19200300.100.1.1=1300387215, Date: 2020.05.20 15:31:49 -04'00'			
Nonclinical Supervisor	Mukesh Summan, PhD, DABT	DPT - ORPURM	Sections: 5, 17.2, 17.4	Select one: ☐ _ Authored ☒ _X_ Approved
	Signature: Mukesh Summan -S Digitally signed by Mukesh Summan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mukesh Summan -S, 0.9.2342.19200300.100.1.1=2000337340 Date: 2020.05.20 16:11:38 -04'00'			
Clinical Pharmacology Reviewer	Li Li, PhD	OCP/DCEP	Sections: 6, 17.5	Select one: ☒ _x_ Authored ☐ _ Approved
	Signature: Li Li -S Digitally signed by Li Li -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Li Li -S, 0.9.2342.19200300.100.1.1=2000508577 Date: 2020.05.20 14:05:37 -04'00'			

Clinical Pharmacology Team Leader	Yanhui Lu, PhD	OCP/DCEP	Section: 6, 17.5	Select one: ☐ _ Authored ☒ _x_ Approved
	Signature: Yanhui Lu -S Digitally signed by Yanhui Lu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yanhui Lu -S, 0.9.2342.19200300.100.1.1=2001501324 Date: 2020.05.20 13:31:41 -04'00'			
OPQ, Application Technical Lead	Mark Seggel, PhD	OPQ/ONDP/DNDPII	Sections: 4.2	Select one: ☒ _x_ Authored ☒ _x_ Approved
	Signature: Mark R. Seggel -S Digitally signed by Mark R. Seggel -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mark R. Seggel -S, 0.9.2342.19200300.100.1.1=1300071539 Date: 2020.05.20 17:29:29 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Anandi D. Kotak, MD, MPH	ORPURM/DUOG	Sections: 3.1, 4.1, 4.4, 7, 8, 9, 10, 11, 12, 13, 17	Select one: ☒ Authored ☐ Approved
	Signature: Anandi D. Kotak -S Digitally signed by Anandi D. Kotak -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002629744, cn=Anandi D. Kotak -S Date: 2020.05.21 11:13:34 -04'00'			
Statistical Reviewer	Weiya Zhang, PhD	OB/DBIV	Sections: 8.1.2, 8.1.3, 8.3	Select one: ☒ Authored ☐ Approved
	Signature: Weiya Zhang -S Digitally signed by Weiya Zhang -S Date: 2020.05.20 13:37:55 -04'00'			
Statistical Team Leader	Mahboob Sobhan, PhD	OB/DBIII	Sections: 8.1.2, 8.1.3, 8.3	Select one: ☒ Authored ☒ Approved
	Signature: Mahboob Sobhan -S Digitally signed by Mahboob Sobhan -S Date: 2020.05.20 15:35:36 -04'00'			

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CI	confidence interval
CONRAD	Contraceptive Research and Development Group
CRF	case report form
CTCAE	common terminology criteria for adverse events
DHOT	Division of Hematology Oncology Toxicology
DUOG	Division of Urology, Obstetrics and Gynecology
EDC	electronic data capture
FDA	Food and Drug Administration
GLP	good laboratory practice
GRAS	generally recognized as safe
IND	Investigational New Drug
IP	investigational product
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intent to treat
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PK	pharmacokinetics
PRO	patient reported outcome
SAE	serious adverse event
TEAE	treatment emergent adverse event
UTI	urinary tract infection

1 Executive Summary

1.1. Product Introduction

The Applicant, Evofem, Inc., is resubmitting NDA 208352 for PHEXXI, which is a non-hormonal contraceptive vaginal gel that contains lactic acid, citric acid, and potassium bitartrate in a 5 g single pre-filled applicator. The gel is applied vaginally with the applicator before each act of intercourse. Although there may be multiple mechanisms of action, the principal effect for the product is thought to be maintenance of an acidic vaginal pH. Normally, the introduction of semen increases the pH, which allows for a more favorable environment for spermatozoa.

An IND for this product was originally submitted to the FDA by the Contraceptive Research and Development Group (CONRAD). The name given to the product originally was Acidform Gel. After withdrawal of the IND by CONRAD, the sponsor for this product became Evofem. Evofem's proposed name for the product at the time of the first NDA submission in 2015 was Amphora. The trade name Amphora was not found acceptable by FDA, and the Applicant proposed PHEXXI. Either PHEXXI or investigational product (IP) will be used to refer to the vaginal gel product in this review.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Effectiveness was demonstrated for PHEXXI in a single-arm, open-label, phase 3 U.S. study over seven cycles of use in women aged 18 to 35 years of age at risk for pregnancy - Trial AMP002. The primary endpoint was a seven-cycle cumulative pregnancy rate as calculated using the Kaplan-Meier method. The primary efficacy analysis called for the upper bound of the 95% confidence interval (CI) around the cumulative pregnancy percentage point estimate to be $\leq 21\%$.

The Applicant and the FDA statistical reviewer determined that the 7-cycle cumulative pregnancy rate was 13.7% with a 95% CI of (10.0%, 17.5%) based on 101 on-treatment pregnancies.

The Pearl Index was calculated as the secondary efficacy endpoint. Based on 101 on-treatment pregnancies over 7 cycles of exposure (in days), the Pearl Index was 27.5 (95% CI: 22.4%, 33.5%).

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

PHEXXI is a non-hormonal contraceptive consisting of lactic acid, citric acid, and potassium bitartrate in a 5 g single pre-filled applicator. The gel is applied vaginally with the applicator before each act of intercourse. Although there may be multiple mechanisms of action, the principal mechanism for the product is thought to be sperm immobilization due to the maintenance of an acidic vaginal pH. As noted in Section 1.2, the Applicant met its effectiveness goal in a single arm phase 3 trial by demonstrating a cumulative pregnancy rate of 13.7% over 7 cycles of use (life table method). The 95% two-sided CI for the cumulative pregnancy rate was 10.0%, 17.5%, respectively, based on 101 on-treatment pregnancies. The Pearl Index (pre-defined secondary endpoint) was also calculated using 101 on-treatment pregnancies and was 27.5 (95% CI = 22.4, 33.5). These effectiveness results are in the same range as nonoxynol-9 spermicidal Tier 3 products on the market and, therefore, are acceptable.

Although the contraceptive benefit of PHEXXI in terms of pregnancy rates is significantly less than that of hormonal methods, it does provide another contraceptive option. The safety profile is consistent with other topically applied vaginal products. The vaginal application just prior to intercourse allows for on-demand use which may benefit women with infrequent intercourse or if concomitant use with a barrier method is being considered.

Adverse events for this product in both women and their male partners are local in nature and consist primarily of genitourinary irritation. Women may primarily experience vulvovaginal burning and pruritus, while male partners may experience penile burning and pruritus. Urinary infections in women, including some cases of pyelonephritis were reported during the product's development and women with a history of repeated UTIs were excluded from the phase 3 trial. After review of the safety profile, the Division recommends a labeled Warning/Precaution for the product in women with frequent urinary tract infections.

In summary, the benefit for the product is comparable to other marketed on-demand non-hormonal vaginal contraceptives and balanced by a safety profile consistent with other vaginal products. Approval of PHEXXI is recommended for prevention of pregnancy in women who choose to use on-demand methods for their contraceptive needs.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Unintended pregnancy has major personal, societal, and health consequences for women and their families.	New contraceptive methods provide additional choices for women.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	- Current non-hormonal contraceptive treatment options include: - Barrier methods = male and female condom, diaphragm, cervical cap - Barrier/spermicide = sponge - Spermicide (nonoxynol-9) = cream, gel, foam, film, suppository - Intrauterine = copper intrauterine system (Paragard) According to the CDC chart of family planning methods, the aforementioned products vary in regard to effectiveness from a low pregnancy rate of 0.8% for the copper intrauterine system up to 28% for spermicides (rate in first year of typical use).	Non-hormonal products offer contraceptive options for women who cannot tolerate hormone therapies or have a history of health problems that contraindicate hormone use. Nonoxynol-9 is typically found in spermicides. Vaginal methods employing nonoxynol-9 have much higher pregnancies rates compared to hormonal products
Benefit	- Although the contraceptive benefit of PHEXXI is less than that of hormonal methods it does allow for on-demand use which may benefit those women with infrequent intercourse. The cumulative pregnancy rate by life table analysis was the primary endpoint. This rate was 13.7% (95% CI = 10.0%, 17.5%). The upper bound met the prespecified goal. - The Pearl Index was calculated as the secondary efficacy endpoint. Based on 101 on-treatment pregnancies over 7 cycles of exposure (in days), the Pearl Index was 27.5 (95% CI: 22.4%, 33.5%). - Pregnancy rates were not established for PHEXXI in conjunction with barrier contraceptives but PHEXXI was found to be compatible for use with the vaginal diaphragm and condoms.	PHEXXI represents a new on-demand non-hormonal vaginal contraceptive available for women in addition to nonoxynol-9 products.
Risk and Risk Management	PHEXXI had a safety profile in women consistent with other locally applied vaginal products. There appeared to be a relationship between PHEXXI and clinically significant urinary tract infections (cystitis and pyelonephritis). Discontinuation in 17 subjects occurred due to local adverse reactions in the vulvovaginal area (primarily burning, pruritus, mycotic infections, etc.) Vulvovaginal burning sensation and pruritus were the most common adverse	The safety profile for this vaginal contraceptive was acceptable and consistent with other vaginally applied products. Labeling will address the relationship to urinary tract infections.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	reactions reported in women. Male partners of female subjects in AMP002 did report some irritative symptoms; however, few discontinued due to these symptoms. Although interpretation of the AMP001 colposcopy substudy comparing PHEXXI to a vaginal contraceptive containing nonoxynol-9 is limited, there were no major vaginal ulcerations or lesions reported.	No other risk management programs or studies are needed.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that were submitted as part of the application include:	Section of review where discussed, if applicable
☐	Clinical outcome assessment (COA) data, such as	
☐	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
X	Patient preference studies (e.g., submitted studies or scientific publications)	See Section 8.1.3
☐	Other: (Please specify):	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify):	
☐	Patient experience data was not submitted as part of this application.	

2 Therapeutic Context

2.1. Analysis of Condition

Unintended pregnancy has significant personal, societal, and health consequences. Potential complications include the following:

- Missed opportunities for preconception care
- Late initiation of prenatal care
- Maternal mental health problems
- Relationship stress
- Substance abuse
- Economic and psychosocial distress
- Increased rates of preterm birth and low birth weight
- Decreased infant bonding
- Decreased breastfeeding
- Increased rates of child neglect

2.2. Analysis of Current Treatment Options

Current non-hormonal, non-surgical contraceptive options include:

- Barrier methods = male and female condom, diaphragm, cervical cap
- Barrier/spermicide = sponge
- Spermicide (nonoxynol-9) = cream, gel, foam, film, suppository
- Intrauterine = copper intrauterine system

Barrier Methods (classified as devices)

Barrier methods include the male and female condom, diaphragm and cervical cap. Poor sales have affected the availability of female condoms. Diaphragms and cervical caps require fitting by a health care provider.

Spermicides (classified as devices)

Nonoxynol-9 (N-9) as a spermicide attacks the acrosomal membranes of the sperm, thus interfering with sperm transport into the upper female reproductive tract. N-9 products are available in numerous forms as stand-alone products, incorporated into barrier methods such as the contraceptive sponge and used in conjunction with pure barrier methods. Studies have not shown any evidence that N-9 prevents vaginal acquisition of HIV infection by women from men. (Wilkinson 2002) In fact, there is concern that repeated and high-dose use of N-9 may lead to lesions which in turn may increase the risk of HIV transmission. Therefore, the CDC advises against the use of N-9 for those women at high risk for HIV. (Curtis 2016).

Intrauterine systems

The only non-hormonal intrauterine contraceptive system is Paragard, which is a T-shaped system with copper sleeves on the horizontal section and wound copper on the stem. Paragard is approved for up to 10 years in the United States.

Effectiveness of Non-hormonal, Non-surgical Methods

Non-hormonal, non-surgical contraceptive options have a wide range of effectiveness. Pregnancy rates for male condoms and female vaginal products range from 12% to 28% (number of unintended pregnancies within the first year of typical use for 100 women) on the CDC chart illustrating the effectiveness of family planning methods (Curtis 2013). Spermicides alone are listed at 28%. Copper intrauterine systems are far more effective with pregnancy rates around 0.8%.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

During the development phase by the original Applicant, CONRAD, this product received approval as a lubricant by the Center for Devices and Radiological Health (CDRH) but was never marketed. CONRAD did not perform phase 3 studies of the product as a contraceptive and eventually withdrew the IND. The subsequent developer, Evofem, did study the product in a non-inferiority phase 3 trial but did not receive approval for the product as a contraceptive upon original NDA submission in 2015. This resubmission is a complete response to deficiencies identified by the Division. This product is not marketed in any other country.

3.2. Summary of Presubmission/Submission Regulatory Activity

The timeline of presubmission and submission regulatory activity is presented below:

2002

- April 29 – Submission of IND 64,623 for Acidform Gel as vaginal contraceptive gel by CONRAD.

2004

- June – CDRH approved the gel as a personal lubricant under the 510 (k) approval pathway (K033776 -trade name “Instead Personal Lubricant”). However, it has never been marketed as a lubricant.

2010

- October 18 – The Division met with the new sponsor, Evofem, in a Pre-IND meeting to discuss development of this product, now named Acidform Gel, as a contraceptive product.

2011

- February 17 – Evofem opened a new IND 109300 and submits phase 3 trial protocol (AMP001), which is designed as a randomized non-inferiority trial with a comparator arm of an approved spermicide gel (with the active ingredient nonoxynol-9). At the time of the phase 3 protocol submission there had been 10 completed studies for Acidform Gel resulting in eleven publications. Authorization was provided to cross-reference its withdrawn IND 64,623 for preclinical, manufacturing, and clinical information.

2014

- December 9 – A pre-NDA meeting was held with the Applicant.
 - *Key Considerations Communicated to the Applicant by the Review Division*
 - The Division typically relies on the Pearl Index to evaluate contraceptive effectiveness

- Provide justification for the proposed non-inferiority margin
- Address the large discrepancy between the 7-cycle cumulative pregnancy rate (Kaplan-Meier) and the Pearl Index
- A Statistical Analysis Plan for the Phase 3 protocol (AMP001) was never submitted
- Justify the Kaplan-Meier methodology that “compressed” cycles following a cycle in which back-up or emergency contraception was used in order to provide contiguous cycles.

2015

- June 30 – Original NDA submission date containing supportive data from phase 3 study AMP001.

2016

- April 28 – Complete Response Letter
 - *Key Deficiencies*
 - Russian data not generalizable to the U.S. target population
 - Insufficient cycles for analysis of safety and efficacy (< 5,000 cycles)
 - Insufficient evidence of efficacy (failure to reach prespecified non-inferiority criterion)
 - Multiple chemistry, manufacturing, and controls deficiencies
 - *Key Recommendations*
 - Conduct a new non-inferiority trial versus nonoxynol-9 gel (agreement however could not be reached on a non-inferiority margin, and the proposal for an open labeled study was accepted by the Division)
 - Majority of new data from U.S. population and foreign data generalizable to U.S. population
 - Evaluable cycles should include only cycles in which trial subjects are at risk for pregnancy
 - Cycles that fall outside of the range consistent with ovulatory cycles should be excluded from efficacy analysis
 - Electronic diary is strongly encouraged
- October 31 – Type A End-of-Review Meeting
 - Sponsor was asked to submit a protocol for a new Phase 3 trial for review.

2017

- January 11 – Applicant submits Special Protocol Assessment (SPA) request for AMP002 study protocol
 - Proposal for a second non-inferiority trial with 10% non-inferiority margin and active comparator arm (Nonoxynol-9 containing vaginal gel)

- February 24 – Review Division issues a Special Protocol Assessment No Agreement Letter
 - *Key Deficiencies*
 - Insufficient rationale for the proposed non-inferiority margin of 10% and sample size
 - The non-inferiority margin in AMP001 was set to 5.5%
 - Unspecified minimum number of subjects who will complete the full duration of use
 - Inadequate approach to collection of genitourinary adverse effects of interest
 - Statistical Analysis Plan did not include subgroup analyses by race/ethnicity, body weight, and body mass index (BMI)
 - Proposed approach is not feasible to demonstrate non-inferiority to active comparator
 - *Additional Considerations*
 - Investigators should note the presence of vulvar, vaginal, or cervical irritation on pelvic exam, including epithelial disruption, bleeding, petechiae, sloughing, or areas of obvious erythema and report the findings as an adverse event if considered to be a clinically significant change from baseline. Define and quantify what constitutes a “clinically significant change from baseline” in the protocol.
 - Subjects may need contraception between the end of the 7th study cycle and the Exit Visit. Provide contraceptive counseling and referral before the Exit Visit.
 - Specify how compliance with the eDiary is tracked.
 - Modify the definition of “on-treatment” pregnancy to state date of conception within seven days *after* last study product use.
 - Subjects who become pregnant should be discontinued from use of study drug as soon as pregnancy is confirmed.
 - Pregnant subjects should be followed to pregnancy outcome and not discontinued from the study until follow-up is complete.
 - Statistical Analysis Plan states “the primary efficacy endpoint is the cumulative probability of typical-use 7-cycle pregnancy” and is appropriate.
 - The proposed methods for determining evaluable cycles and imputing missing dates of cycles were acceptable. A large amount of imputed data would be a review issue.
 - The Applicant was asked to re-submit the protocol for review as a “Special Protocol Assessment – Resubmission” and advised to submit the Statistical Analysis Plan for review once agreement on study design was reached.
- March 17 – SPA No-Agreement Additional Clarification Question

- o The Applicant submits additional clarification question “Is the agency open to discussing a single-arm study design to meet efficacy requirements for AMP002.”
- o *Key Considerations Communicated to the Applicant by the Review Division*
 - Agree to discuss a single-arm study design
 - Propose an acceptable threshold for the upper bound of the 95% confidence interval (CI) around the Pearl Index (PI) and a narrow confidence interval.
 - Provide a rationale for the threshold selected and specify any assumptions you made.
 - Explicitly describe the assumptions made in calculating the sample size.
 - Ensure the study is well-conducted
 - Ensure subjects are at-risk for pregnancy throughout the study
 - Minimize premature discontinuations and loss to follow-up
 - Submit a meeting request with protocol for review
- April 3 – Applicant submits meeting request
- June 9 – Type A Meeting Preliminary comments provided
 - o *Key Considerations Communicated to the Applicant by the Review Division*
 - The proposed point estimate for the 7-cycle cumulative pregnancy rate of 16.5% with a prespecified upper bound of the 95% confidence interval of 21% is acceptable
 - Revise the formula for calculating the Pearl Index to apply to the proposed 7-cycle trial
 - The proposed sample size may be insufficient if the pregnancy rate is higher the proposed point estimate or if fewer than expected subjects complete the 7-cycle trial.
 - Justify an expected study completion rate of 35%
- November 20 – SAP submitted for review
 - o Biometrics Review deems SAP acceptable

2018

- October 29 – SAP amendments submitted
 - o Biometrics Review deems minor amendments to SAP acceptable

2019

- April 10 – Pre-NDA meeting containing a new phase 3 trial AMP002
- August 12 – Proprietary name of Amphora was found unacceptable
- November 29 – Complete response submission

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Two clinical site inspections occurred in support of this application. A high enrollment rate and high protocol violation rate formed the basis for selection of the two sites.

A Form 483 (Inspectional Observations – Voluntary Action Indicated) was issued for the first site due to investigational records not retained for a period of two years following approval of a drug's marketing application. In addition, 13 subjects were instructed to return for the end-of-study visit during the seventh cycle rather than 14 to 30 days after the seventh cycle, resulting in early discontinuation.

The second clinical site also received a Form 483 for:

1. An investigation that was not conducted in accordance with the signed statement of the investigator. For five subjects, accurate instruction on IP use was not provided to subjects prior to IP use. One of the five subjects had a positive serum pregnancy test at visit 5. The protocol deviations and the pregnancy were reported to the Applicant. The deviations were identified early in the study and staff were retrained on instructions to subjects.
2. Investigational drug disposition records were not adequate with respect to quantity and use by subjects. Discrepancies between the documented amount of IP returned and the amount of e-diary IP used entries were noted for five subjects. The clinical investigator indicated that the study coordinator had left the site and remaining staff had been retrained on maintaining drug disposition records. Discrepancies were relatively small and were identified and addressed by the clinical study monitor.
3. Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation. Specifically, the updated e-diary source data on IP use that was changed or updated by seven subjects was not updated in the electronic case report form (eCRF).

Based on the results of these inspections, the Office of Scientific Investigations concluded that both clinical sites appeared to be in compliance with Good Clinical Practice except for the observations noted above. The observations appeared unlikely to have a significant impact on the overall assessment of efficacy and safety of the product. Overall, data submitted by the two clinical sites appeared acceptable in support of this specific indication.

4.2. Product Quality

Evoform's 505(b)(2) New Drug Application 208352 for PHEXXI (lactic acid, citric acid, and potassium bitartrate) vaginal gel, as resubmitted on November 25, 2019, is recommended for APPROVAL from the OPQ perspective pending receipt of satisfactory final labeling.

Sufficient chemistry, manufacturing and controls information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, and purity of the drug product.

All drug substance and product-related manufacturing, packaging and testing facilities have acceptable drug CGMP status. An overall manufacturing inspection recommendation of APPROVE was issued on March 30, 2020. The recommendation remains current as of this review. Note that the (b) (4) cited as 'deficient' in the April 28, 2016 Complete Response Letter, has been withdrawn from the application and a new supplier of potassium bitartrate has been identified. The previous drug product manufacturer, (b) (4) has also been replaced by a new firm, (b) (4)

PHEXXI (previously referred to as AMPHORA) is supplied in a 5 g vaginal applicator and is thus a drug-device combination product under 21 CFR Part 3. CDRH-OPEQ has determined that all device-related deficiencies identified in the 2016 Complete Response Letter have been adequately addressed and the information provided is sufficient to support approval of the proposed applicator to deliver the drug product (see section 4.4, Devices and Companion Diagnostic Issues).

The proposed 30-month expiration dating period for drug product stored at 20°C to 25°C is supported by the available stability data.

The claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b) is acceptable.

Each pre-filled 5 g PHEXXI vaginal applicator contains 1.8% lactic acid, 1% citric acid and (b) (4)% potassium bitartrate in a gel base consisting of alginic acid and xanthan gum, benzoic acid (preservative), glycerin (humectant), sodium hydroxide (to adjust pH) and purified water. Since the time the application was previously reviewed, the formulation has been revised slightly. The percent of lactic acid has been revised from 1.76% (w/w) to 1.8% (w/w). This change was reportedly made in 2014 due to a change in the target raw material acceptance criterion for lactic acid solution from (b) (4)%. This difference is considered minor; the target pH of the formulation (b) (4) and acid neutralization test, a measure of buffering capacity, ((b) (4) mEq/g) are unchanged. All inactive ingredients have been found suitable for vaginal administration at the proposed levels. The compatibility of the formulation with the (b) (4) plastic applicator has been demonstrated.

Drug product microbiological quality is adequately ensured by control of raw material quality, manufacturing process environmental controls, the presence of effective levels of preservative (benzoic acid) as demonstrated by antimicrobial effectiveness testing (AET), and by microbial quality testing, at release and on stability, complying with the requirements of USP <1111> for nonsterile, vaginally administered drug products.

Questions regarding the appropriate nomenclature (and hence, identity) for the lactic acid component of the drug product have come up recently during the labeling review. Throughout the October 2015 version of the proposed prescribing information, the applicant referred to this active ingredient simply as lactic acid, although the structure provided in Section 11, Description, does show stereochemistry. With the November 2019 resubmission, Evofem included a stereochemical descriptor with 'lactic acid', i.e., 'L-lactic acid' throughout the labels and labeling. However, the established name (see USP and USAN Dictionary) does not include such a descriptor, and therefore cannot be used in the established name of the ingredient or of the product. The pKa of lactic acid is independent of stereochemistry. (b) (4)

At this time, it is recommended that all references to lactic acid stereochemistry be removed from the labeling.

See OPQ Quality Assessment #1 dated April 11, 2016 and OPQ IQA #2 dated May 21, 2020 for a detailed assessment of drug substance and drug product CMC.

4.3. **Clinical Microbiology**

Clinical Microbiology was not assessed for this clinical development program. See Section 4.2 for Product Quality Microbiology assessment.

4.4. **Devices and Companion Diagnostic Issues**

The Center for Devices and Radiologic Health biomedical engineer reviewer reviewed the device component of the pre-filled single-dose applicator in the current submission. In the previous review cycle, deficiencies were noted with respect to device description, bench testing, biocompatibility, and shelf life of the applicator. The Applicant indicated a change in delivery method in the current submission – the pre-filled single-dose applicator. The Applicant clarified the description of the applicator and provided additional testing to address device performance, biocompatibility, and stability over the intended shelf life. The Applicant has adequately addressed the CDRH engineering review issues. The information provided is adequate to support the approval of the proposed applicator to deliver the drug product.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Reference is made to Pharmacology and Toxicology review by Dr. Deepa Rao, filed in DARRTS on April 12, 2016. Pharmacology/toxicology recommended approval of the initial NDA submission for this vaginal gel based on the long history of use and common nature of each of the active ingredients, lack of novel excipients, and the lack of significant adverse events in nonclinical local irritation studies conducted.

In order to support the initial NDA via a 505(b)(2) pathway, Evofem was relying on Evofem-conducted clinical and nonclinical studies, as well as published literature and data from a 510(k) application for use of the gel as a lubricant (No. K033776). The Applicant's own studies included a 10-day vaginal irritation study in rabbits, a 3-day penile irritation study in rabbits, and a 5-day rectal irritation study in rabbits.

The Applicant's proposal for not conducting additional nonclinical studies with either individual active ingredients or the combination drug product was agreed at the pre-IND meeting on October 18, 2010, based on the following reasons:

- Ingredients of the proposed gel include three active small organic acids/acid salts (lactic acid, citric acid, and potassium bitartrate) that are common and/or endogenous pH buffering agents.
- The active ingredients are generally recognized as safe (GRAS)-listed substances with long history of use as inactive ingredients in other FDA-approved products.
- All excipients are also either GRAS-listed or are common ingredients that exist in other FDA-approved drug products at acceptable levels and routes of administration.
- Systemic absorption is unlikely based on chemical characteristics of the formulation that are designed to retain the formulation within the local vaginal environment.
- There is no significant toxicity of the combination gel in local toxicology studies.
- Systemic toxicology information is available to support the characterization of the active ingredients from published literature.

This product was given a Complete Response during the last review cycle based on a number of deficiencies, including those from the CDRH review team. In this resubmission, the Applicant included nonclinical studies to address the deficiencies issued by CDRH in the Complete Response letter. These included tests for cytotoxicity, sensitization, acute systemic toxicity, and 5-day vaginal irritation using the final, finished device to characterize the biocompatibility of the finished product. Compatibility with polyisoprene condoms was addressed as per ASTM D7661. Furthermore, an in vitro study conducted at ~25°C to evaluate the gel when used with other common vaginal products was repeated at 37°C, simulating body temperature. Refer to the CDRH review of these studies.

Taken together, there is no impediment to approval of this NDA via a 505(b)(2) pathway based on the lack of nonclinical issues identified for the vaginal gel during the review of the resubmission.

5.2. Referenced NDAs, BLAs, DMFs

- IND 109300; IND 064623; K033776 [Instead Intimate Lubricant, 510(k) clearance from CDRH]

The lubricant device was never marketed in the US.

Previously submitted nonclinical data and information were reviewed by Dr. Deepa Rao (NDA 208352 filed in DARRTS on April 12, 2016), Dr. Lynnda Reid (IND 064623 filed in DARRTS on May 23, 2002), and Dr. Kimberly Hatfield (filed in DARRTS on March 16, 2011, and May 3, 2019).

The following summary is based on the previous reviews and the Applicant's information provided within the original and the current submission.

5.3. Pharmacology

Each active ingredient in the combination gel is designed to work together to elicit the intended effect of prevention of pregnancy. However, it is unknown whether the absence of any active components would affect the efficacy of the product.

Although the exact mechanism of action of the combination gel is unknown, in vitro studies designed to support the use of the combination product as a vaginal contraceptive showed that the gel may produce a spermicidal effect through reduced sperm motility (partially reversible) possibly due to buffering of the local pH of the vagina (1-5), and may impede cervical mucus penetration by sperm (5). The gel may also have bioadhesive properties that would ensure retention in the vagina (3, 6) and retain viscosity on dilution to reduce leakage from the vagina (3, 4). Of note, the gel had no significant effect on sperm viability in vitro (5).

Overall, these data suggest that the effectiveness of the vaginal gel occurs via a combination of the pharmacological activities, although cessation of sperm motility may confer reduced fertilization potential. However, the duration of sperm immobilization that would result in sperm death is unknown (7-11).

Typical safety pharmacology studies were not conducted on the active ingredients based on the reasons above (i.e., GRAS-listed substances, long history of use).

5.4. ADME/PK

Evoform did not conduct ADME/pharmacokinetic/toxicokinetic studies to determine the systemic or local exposure of each ingredient (and/or its metabolites) individually or in

combination, per agreement at the pre-NDA meeting on December 9, 2014. The Division agreed to the Applicant's proposal for not assessing the ADME/pharmacokinetics based on the following reasons: chemical characteristics of the formulation that render unlikely systemic absorption of the active ingredients; the lack of significant toxicity in local irritation studies; and the general nontoxic nature of the individual active ingredients (i.e., GRAS-listed substances).

In addition, calculated hypothetical estimates (based on 100% absorption of lactic acid and citric acid from a single dose) still would not exceed the upper limit of normal endogenous serum concentrations of the organic acids. Systemic absorption would not be necessary for efficacy, given the local vaginal activities of the combination gel.

Potassium bitartrate, while not an endogenous product in animals, is not known to be absorbed following oral administration, but is broken down into tartaric acid, tartrate, and potassium ions within the gastrointestinal tract, although it is unknown whether exposure to the vaginal environment will result in a similar breakdown of potassium bitartrate. Based upon the available literature, if absorbed, it would either be excreted unchanged in urine or otherwise converted by intestinal flora into oxaloacetic acid, which may then be used by these cells as part of their normal metabolic processes or otherwise eliminated in the feces (24, 25, 35).

5.5. Toxicology

5.5.1. General Toxicology

No acute or chronic nonclinical toxicology studies were conducted with either the individual active components or the combination drug product. The Applicant provided a published literature summary of acute and repeat-dose toxicology studies for lactic acid or citric acid, and the degradation products of potassium bitartrate, tartaric acid, or sodium tartrate. For reference, the proposed vaginal gel will administer a clinical dose of lactic acid, citric acid, and potassium bitartrate at 90 mg, 50 mg, and 20 mg, respectively, in a 5 g gel.

Lactic acid: The major target organs were the lung, liver, kidney, gastrointestinal tract, and/or the central nervous system at high doses tested in rats after a single dose (>3000 mg/kg) or repeat-dose of 8 days (1300 mg/kg) following oral administration. Rabbits displayed test-site reactions (e.g., edema, erythema, blanching, necrosis, eschar formation, atonia, desquamation, and denuded areas) following a single dermal administration to abraded skin at 2000 mg/kg (46, 47, 53, 54).

Citric acid: LD₅₀ values were 42 mg/kg and 330 mg/kg in mice and rabbits, respectively, via intravenous administration, or 375 mg/kg in rats via intraperitoneal administration (monohydrate citric acid). No significant adverse effects were observed following repeated oral administration of citric acid in mice up to 1 year at 5%, in rats up to 1 year at 1.2%, in guinea pigs for 60 days at 5%, in rabbits for 150 days at 7.7% (sodium citrate), and in dogs for 120 days at 1380 mg/kg (48, 49, 55).

Sodium tartrate or tartaric acid: No significant effects were noted up to 4000 mg/kg following a single oral or intravenous administration of sodium tartrate in rabbits. Nephritis was observed with sodium tartrate in rabbits at ≥ 400 mg/kg and in dogs at 6000 mg/kg after a single subcutaneous administration or in rabbits at ≥ 1700 mg/kg after a single oral dose. No significant adverse effects were observed following oral administration of tartaric acid in rats for 2 years up to 1200 mg/kg, sodium tartrate in rabbits for 150 days at 2300 mg/kg, and sodium tartrate in dogs for 114 days at 990 mg/kg (50, 51, 53-55).

General toxicology; additional studies

Both lactic acid (0.5 mL of 80 - 88% solution in water) and citric acid (2 - 3%) were irritating to the skin, eye, and/or respiratory tract in animals (46-47).

One 10-day vaginal irritation study was conducted in rabbits with the proposed gel. There were two studies conducted with the prototype formulations that are closely related to the proposed formulation, but these formulations also contain the spermicidal agent nonoxynol-9. Two additional studies, a penile irritation study and a rectal irritation study in rabbits were submitted to CDRH under 510(k) No. K033776 by Instead Healthcare (currently Evofem). Based on results from these studies, the combination gel is considered a mild vaginal irritant, but not a rectal and penile mucosa irritant in rabbits. However, no evaluations were performed for other potentially exposed organs and tissues in the genitourinary tract and oral mucosa. A full review of these studies can be found under the original NDA review.

In clinical trials conducted with the combination gel in the United States, high incidences of adverse reactions and infections including the vulvovaginal burning sensation (18.0%), vulvovaginal pruritus (14.5%), vulvovaginal mycotic infection (9.1%), urinary tract infection (9.0%), vulvovaginal discomfort (9.0%), and bacterial vaginosis (8.4%) were reported in women using PHEXXI (see Clinical Safety Assessments for more details). Male partners of women using PHEXXI also experienced symptoms of mild to severe local discomfort (e.g., burning, itching, pain). It is unknown whether the repeated use of the combination gel may result in mucosal cell disruption and epithelial cell damage that can lead to increased transmission of and susceptibility to genitourinary tract infections (e.g., STDs, HIV, HPV), particularly, in the presence of the gel remaining throughout the post-treatment period of 6 days measured following a single vaginal dose in female subjects.

5.5.2. Genetic Toxicology

No genetic toxicology studies were conducted with the combination gel. Based on published literature provided, the individual active ingredients were negative in the Ames test or the chromosome aberration assay in vitro (47, 56, 57).

5.5.3. Carcinogenicity

No carcinogenicity studies were conducted with the combination gel. Based on published literature provided, no treatment-related tumors were noted with oral administration of lactic acid, citric acid, or tartaric acid in rats or rabbits.

Lactic acid: There were no tumor incidences observed at 2500 and 5000 mg/kg/day in rats fed calcium salt of lactic acid for 2 years or 0.1 - 0.7 g/kg lactic acid in 50 - 100 mL water twice daily in female rabbits for 13 months (47, 58).

Citric acid: There was no evidence of carcinogenicity in rats fed at 1200 and 2000 mg/kg/day for 2 years (48).

Potassium bitartrate: No tumor incidences were noted in rats fed tartaric acid up to 1200 mg/kg/day for 2 years (53).

Potassium bitartrate is not listed as a known or suspected carcinogen by the International Agency for Research on Cancer, the National Toxicology Program, or the California Environmental Protection Agency Office of Environmental Health Hazard Assessment (OEHHA, CA Prop 65) [International Agency for Research on Cancer, 2015; National Toxicology Program, 2014; State of California Environmental Protection Agency - Office of Environmental Health Hazard Assessment, 2015]. Potassium bitartrate is listed in the Select Committee on GRAS Substances database and has been given a type 1 conclusion by the Committee [Select Committee on GRAS Substances, SCOGS-107].

5.5.4. Reproductive and Developmental Toxicology

No data or information on fertility was provided with individual active ingredients or the combination gel product.

Based on published literature provided, there was no embryo-fetal developmental toxicity of orally administered lactic acid or citric acid in animal species tested.

Lactic acid: The only observed effect on the fetus was a statistically significant increase in delayed ossification of the parietal bones when pregnant CD-1 mice were dosed daily with 570 mg/kg lactic acid by oral gavage on gestation days 6 to 15. There were no effects on sex ratio when rats were fed stock diet supplemented with 2.5% or 5% lactic acid (47).

Citric acid: No effects on litter size or survival of pups were reported in mice receiving either 7500 mg/kg/day at pre-mating, during and after mating or 241 mg/kg/day during gestation days 6 – 15 (48).

There were no adverse effects on reproductive parameters nor any teratogenicity of dietary citric acid in a 90-day two-generation study with male and female rats fed 1.2% citric acid (48). There were no teratogenic or other adverse effects in rats with dietary dose of either 2500 mg/kg/day at pre-mating, during and after mating or 295 mg/kg/day during gestation days 6-15 (48).

There were no teratogenic or other adverse effects in female hamsters receiving 272 mg/kg/day during gestation days 6-10 nor in female rabbits receiving up to 425 mg/kg/day during gestation days 6-18 (48).

Potassium bitartrate: Potassium bitartrate is not considered to be teratogenic. The daily intake of tartrates added to foods is orders of magnitude below that which could be expected to cause toxicity in man.

5.5.5. Other Toxicology Studies

The following summarizes the nonclinical studies submitted to address the CDRH deficiencies in the Complete Response letter (see CDRH Review for more in-depth discussions).

Study Title: Interaction with Vaginal Over-the-Counter Products (Study EFM-C0001-GMR0079.00)

Methods: Miconazole, metronidazole, and tioconazole at 5g each and 2g RepHresh Vaginal Gel™ (in triplicate), were mixed with 5 g combination gel in a beaker for at least 5 minutes. The vaginal preparation mixtures were then incubated at $37 \pm 5^\circ\text{C}$ for 1 hour and were allowed to equilibrate to ambient conditions for at least 1 hour prior to testing of pH. Total acid titer was determined by weighing 8 ± 0.1 g of each mixture and following a specific method for acid neutralization.

Key Findings: The gel mixed with various prescription and over-the-counter products showed no significant shift in the pH while also maintaining resilient buffering capacity with the percent relative standard deviation of no greater than 0.2% and 2.5% for pH and acid neutralization, respectively.

Study Title: Report Summary for Compatibility of [PHEXXI] (Lot No. 99000053) with Polyisoprene Condoms (No. 1503005)

Methods: Negative control condoms were conditioned at 40°C but were not exposed to the gel and compared to condoms conditioned at 40°C while being treated with the gel. Additionally, baseline analyses were performed on the condoms (tested directly from their packages), as well as a positive control group to validate the laboratory's test technique. Mineral oil was used in the positive control group for the polyisoprene condoms.

Key Findings: The gel-treated polyisoprene condoms and the baseline and negative control polyisoprene condoms had comparable mean and standard deviations for all parameters assessed. None of the condoms assessed at baseline or treated with any of the substances leaked or had difficulty with the clamping mechanism.

Study Title: ISO Acute Systemic Injection Test (Study No. 36516, GLP)

Methods: Female albino Swiss mice (n=5/group) were injected systemically (intravenous for saline or intraperitoneal for sesame oil) with extracts of the test article (50 mL/kg) in standard solutions (normal saline and sesame oil). The animals were observed for signs of toxicity immediately after injection and at 4 hours, 24 hours, 48 hours, and 72 hours post-injection.

Key Findings: The vehicle control treated animals had no signs of toxicity at any of the observation periods, and no animals lost weight in excess of 10%. None of the test article treated animals were observed with clinical signs at observation periods. There were no significant body weight changes over the course of the study.

Study Title: ISO Guinea Pig Maximization Sensitization Test (Study No. 37687, GLP)

Methods: Eleven male albino guinea pigs (per extract) were intradermally injected with the test article extract (0.1 mL/site) and Freund's Complete Adjuvant, and six guinea pigs (per extract) were injected with the corresponding control blank and Freund's Complete Adjuvant. On day 6, the dorsal site was re-shaved and sodium lauryl sulfate in mineral oil was applied. The day after the sodium lauryl sulfate application, the test animals were topically (0.3 mL) patched with the appropriate test extract, and the control animals were patched with the corresponding control blank. The patches were removed after 48 ± 2 hours of exposure. Following an approximate 2-week rest period, the animals were topically patched with the appropriate test extract and corresponding control blank. The patches were removed after 24 ± 2 hours of exposure. The dermal patch sites were observed for erythema and edema 24 ± 2 hours and 48 ± 2 hours after patch removal. Each animal was assessed for a sensitization response based upon the dermal scores.

Key Findings: None of the negative control animals challenged with the control vehicles were observed with a sensitization response >0 . None of the animals challenged with the test article extracts were observed with a sensitization response >0 . By contrast, grades of 1, 2, or 3 were observed in the positive control animals at the 24-hour and 48-hour scoring periods.

Study Title: ISO Mucosal (Vaginal) Irritation Test (Study No. 37795, GLP)

Methods: The test article (1 mL) extracted in normal saline and sesame oil was administered to 3 New Zealand White rabbits per extraction vehicle for five consecutive days. Control vehicle was administered to three animals for five consecutive days. During the 5-day exposure, the vaginal tissue was observed and scored for erythema, exudate, and edema. After the 5-day exposure, the animals were sacrificed and the vaginal tissue was removed. The tissue was observed macroscopically and scored for irritation and injury (erythema, exudate, edema) to the epithelial layer. The tissue was sectioned to include the cervical, central, and caudal portions, placed in 10% neutral buffered formalin and submitted for histopathological evaluation. A numerical comparison of the test and control tissue microscopic scores was conducted to categorize the irritation reaction as indicated in ISO 10993-10 guidelines.

Key Findings: Both control and test article animals had daily vaginal scores of 0 to 2 with more frequent erythema score of 2 in the test group compared to the normal saline control group. Macroscopic observations conducted at necropsy had more animals with mild to moderate vascular congestion in the test article group compared to the sesame oil control group.

Study Title: MEM Elution GLP Report (Study #894986-S01, GLP)

Methods: An extract of the test article (88.6 cm²/29.5 mL) in the Minimum Essential Media was added to cell monolayers and incubated at 37 ± 1°C with 5 ± 1% CO₂ for 72 ± 3 hours. The cell monolayers were examined and scored based on the degree of cellular destruction.

Key Findings: The test article received a 0 reactivity grade.

6 Clinical Pharmacology

6.1. Executive Summary

The Office of Clinical Pharmacology, Division of Cardiometabolic, and Endocrine Pharmacology has reviewed the information contained in NDA 208352 and recommends approval of this NDA.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

PHEXXI is a non-hormonal contraceptive spermicidal gel. No pharmacokinetic (PK) study was conducted for PHEXXI.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

PHEXXI contains 90 mg lactic acid, 50 mg citric acid, and 20 mg potassium bitartrate in a 5 g gel. PHEXXI is recommended to be used within 1 hour before sexual intercourse.

Therapeutic Individualization

N/A

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Systemic exposures of lactic acid, citric acid, and potassium bitartrate following the vaginal administration of PHEXXI were not determined based on the following considerations:

1) As PHEXXI exerts its contraceptive effect at the site of application in the vagina, systemic exposures of these active ingredient are not expected to be relevant to contraceptive efficacy;
2) lactic acid, citric acid, and potassium bitartrate are generally recognized as safe (GRAS). In addition, they are commonly used in FDA approved vaginally applied products. The proposed doses of these compounds in [PHEXXI] are similar to or lower than the doses used in other vaginal products. Therefore, there is no significant safety concern on the proposed dose of PHEXXI.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. Study EVO-002 demonstrated that PHEXXI lowered vaginal pH from baseline in a dose-dependent manner at 3, 4, or 5g dose (See Appendix Section 16.5 and Section 8). In addition, several literatures, reported that an increased PHEXXI dose (2 ~ 5 g) correlated to increased sperm immobilization without significant tolerability issues. Therefore, the 5 g dose of PHEXXI was selected for phase 3 Studies AMP001 and AMP002.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. It is recommended that PHEXXI be used no more than 1 hour before sexual intercourse. This is consistent with the instruction of use from phase 3 studies AMP001 and AMP002.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

N/A

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No. Clinical drug-drug interaction study with PHEXXI was not conducted, considering the low risk of DDI between PHEXXI and systemically absorbed medications. The Applicant conducted an in vitro study to evaluate the effect of other vaginal drugs on the pH and buffering capacity of PHEXXI. In the study, PHEXXI was mixed with commonly used vaginal products including miconazole vaginal cream, metronidazole vaginal gel, RepHresh vaginal gel, and tioconazole ointment at 37°C for 1 hour. No significant shift was found in the intended pH and the buffering capacity of the PHEXXI in the presence of the products mentioned above, indicating that concomitant use of these vaginal product is unlikely to affect the performance of PHEXXI.

Question on clinically relevant specifications (TBD)?

N/A

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 1 summarizes the clinical studies conducted in support of this application.

Table 1. Listing of Clinical Studies for PHEXXI

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
AMP-002	03243305	Multi-center Open-label Single arm	Phexxi inserted in the vagina at least 1 hour prior to each act of intercourse	Primary: Contraceptive efficacy as defined by the 7-cycle cumulative pregnancy rate by KM method Secondary: 1. Contraceptive efficacy as defined by the Pearl Index 2. Adverse Events 3. Pregnancy outcomes 4. Efficacy in the MITT population by the KM and PI 5. Primary analysis repeated with expanded cycle length of 21-42 days. 6. Effect of dosing time with respect to time of sexual intercourse	7 cycles	1384	Healthy, sexually active women ages 18-35 At risk of pregnancy Desired contraception Single male sex partner	112 sites US only

NDA/BLA Multi-disciplinary Review and Evaluation NDA 208352
Lactic acid, citric acid, and potassium bitartrate (PHEXXI)

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Studies to Support Safety								
AMP-001	01306331	Multi-center Open-label Randomized Controlled	Treatment Arm: Phexxi inserted in the vagina at least 1 hour prior to each act of intercourse Active Comparator Arm: Conceptrol Vaginal Gel (100mg N-9/2.5mL) inserted in the vagina at least 1 hour prior to each act of intercourse	Primary: Contraceptive efficacy as defined by the 7-cycle cumulative pregnancy rate by KM method Secondary: 1. Adverse Events 2. Safety of IP over 13 cycles of use 3. Acceptability of IP compared to Conceptrol Vaginal Gel 4. Incidence of lesions detected by colposcopy (subset) 5. Incidence of UTIs, BV, and yeast vaginitis (subset) 6. Asymptomatic yeast colonization (subset) 7. Vaginal <i>E. coli</i> colonization (subset)	7 cycles Optional 13 cycle extension	3389	1. Healthy, sexually active women ages 18-35 At risk of pregnancy Desired contraception Single male sex partner 2. Healthy sexually active women ages 36-45 (subset)	2 countries: US – 49 sites Russia – 13 sites
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)								
EVO-002	02693418	Phase 1 Randomized Double-blind Placebo-controlled Multi-center 5 treatment arms	Group A: single vaginal dose of IP – 5 grams (PHEXXI) Group B: single vaginal dose of IP – 4 grams Group C: single vaginal dose of IP – 3 grams Group D: single dose of hydroxyethylcellulose gel – 4 grams Group E: no intervention	1. Change in vaginal pH from baseline 2. Duration of change in vaginal pH	Single dose 7 days follow-up	100	Healthy female volunteers ages 18-45	1 country – US only 2 sites

IP = investigational product (PHEXXI is the 5 g product); KM = Kaplan-Meier life table analysis; PI = Pearl Index; MITT = modified intent-to-treat; UTI = urinary tract infection; BV = bacterial vaginosis; N-9 = nonoxynol-9
Source: NDA 208352 resubmission; Section 5.2 Tabular listing of all clinical studies

7.2. Review Strategy

The overall approach to review of this application includes assessment of efficacy based on study AMP002, and assessment of safety based on studies AMP001 and AMP002. In addition, the phase 1 study EVO-002 is briefly discussed.

Although the Applicant previously submitted the efficacy results from AMP001 in support of this application, methodologic flaws preclude use of these findings. In the first review cycle, the reviewing division (DBRUP) observed marked disparities in pregnancy, discontinuation, loss to follow-up and adverse event reporting rates between the U.S. and Russian cohorts. As a result, the Division determined that the results from the Russian cohort were not generalizable to the U.S. population, and therefore evaluated the data from the U.S. cohort of AMP001 only. Upon evaluation of the U.S. cohort, the Division noted a high proportion of non-evaluable cycles and a high premature discontinuation rate, resulting in fewer than 5,000 evaluable cycles as requested. As a result, the Applicant failed to achieve its prespecified non-inferiority criterion.

The Applicant was advised to address deficiencies identified in AMP001 in the design of a new clinical trial to assess the pregnancy rate in women using PHEXXI versus a nonoxynol-9 spermicide gel. Key Agency recommendations included:

1. The majority of the data should come from the U.S. population.
2. Any foreign data submitted should be generalizable to the U.S. population (i.e. comparable efficacy results, rates of study completion, adverse event reporting).
3. The statistical analysis plan should be pre-specified and submitted for review and comment prior to database lock.
4. Evaluable cycles should include only cycles in which trial subjects are at risk for pregnancy.
5. Ovulatory cycles should be well-defined. Cycles that fall outside the range consistent with ovulatory cycles should be excluded from the efficacy analysis.¹

The Applicant proposed a second non-inferiority trial with a proposed 10% non-inferiority margin. However, the Applicant was not able to provide appropriate justification for their trial design and statistical analysis plan. After further discussion, the Division agreed to an open-label, single arm phase 3 trial consistent with the development pathway for other contraceptive products (AMP002).

Because of the statistical concerns that arose in the Division's review of AMP001, the review of efficacy in this review cycle and the basis for approval is limited to AMP002 only. Adverse event data collection inadequacies precluded substantive review in the first review cycle. However, some safety data from AMP001, such as serious and significant adverse events, still inform the safety profile of PHEXXI. Therefore, the review of safety will primarily focus on findings in

¹ NDA 208352 Written Correspondence to the Sponsor – Complete Response, April 28, 2016.

AMP002, with some consideration given to the U.S. cohort of the PHEXXI-treated arm of AMP001, and minimal consideration given to the Russian cohort of the PHEXXI-treated arm of AMP001. No new foreign data has been submitted for review in the current review cycle.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. EVO-002

Overview and Objectives

EVO-002 was a Phase 1 randomized, double-blind, placebo-controlled, multi-center pilot study to determine the effect and duration of Acidform gel [PHEXXI]² on vaginal pH.

The study primarily aimed to assess the change in vaginal pH from baseline to post-administration after one dose of PHEXXI, placebo, or no treatment. The study also aimed to measure the duration of effect of the assigned treatment. Secondly, the study aimed to measure the effect of the treatment on asymptomatic bacterial vaginosis based on Amsel criteria; as well as the effect on the vaginal microbiome.

Trial Design

EVO-002 compared the effect of a single dose of PHEXXI on vaginal pH. Three doses (3g, 4g, or 5g) were compared to placebo and no treatment. Subjects and the study biostatistician were blinded to treatment assignment.

EVO-002 enrolled 105 healthy female volunteers at two U.S. sites. The study also enrolled at least 13 subjects in each treatment group of either African American or Hispanic descent to account for variations in vaginal pH by ethnicity. Key enrollment criteria are described below.

Key Inclusion Criteria

The following criteria were inclusionary:

1. Female subjects between 18 years and 45 years of age, inclusive
2. Negative pregnancy test
3. Able and willing to comply with all study procedures and available for all study visits
4. Abstain from sexual intercourse or use of any intravaginal products or devices for 24 hours prior to enrollment and for the duration of the study
5. Menstrual cycle regularity
6. Test negative for bacterial vaginosis or positive for bacterial vaginosis but asymptomatic

² PHEXXI was clinically developed under the names Acidform and Amphora.

Key Exclusion Criteria

The following criteria were exclusionary:

1. Symptoms of urinary tract infection, symptomatic bacterial vaginosis, vulvovaginal candidiasis, or sexually transmitted infection reported or observed, or based on laboratory testing
2. Regular use of douches, vaginal medications or suppositories, feminine sprays, genital wipes or contraceptive spermicides, or report abnormal vaginal discharge within 48 hours prior to screening
3. Menstruating or expect to menstruate during the study
4. Current use of contraceptives that are directly delivered to the vaginal mucosa, such as NuvaRing
5. Pregnant or breastfeeding
6. Participation in any study within 30 days prior to signed consent
7. Medical conditions or drug or alcohol dependence that would interfere with study protocol

Study Endpoints

Change in vaginal pH and duration of the change from baseline served as primary endpoint measures. Amsel criteria and vaginal microbiome assessment served as secondary endpoint measures. Adverse event data collection also occurred.

Study Procedures

Subjects enrolled in the study were randomly assigned to one of five treatment groups:

- Group A: Acidform (5g)
- Group B: Acidform (4g)
- Group C: Acidform (3g)
- Group D: Placebo (4g)
- Group E: No treatment (speculum exam only)

Subjects underwent baseline screening for vaginal pH, Amsel criteria, vital signs, vaginal comfort, HIV test and speculum exam. Research staff obtained direct vaginal pH readings at 1 hour and 6 hours post-treatment while subjects were domiciled. Subjects obtained subsequent pH readings with training on the use of self-collection vaginal swabs. Self-collection occurred at 12 hours and 24 hours and days 2 through 7 post-treatment.

Research staff performed vaginal pH, microbiome collection and Amsel criteria assessments 24 hours post-treatment. Subjects were then discharged from the inpatient facility. Appendix 16.7 illustrates the study schematic and flow.

Statistical Analysis Plan

Efficacy findings summarized vaginal pH, including change from baseline, for each evaluation time point by treatment group and overall. Findings also summarized vaginal pH and change from baseline for all active treatment groups combined.

Comparisons across treatment groups occurred using analysis of variance (ANOVA). Post-ANOVA pairwise comparisons of each study treatment compared to placebo and compared to no treatment also occurred.

Protocol Amendments

Protocol amendments submitted to the Agency outlined procedures for microbiome assessment as an exploratory endpoint. No other significant protocol amendments occurred.

8.1.1.1. Study Results - Efficacy

Compliance with Good Clinical Practices

The Applicant attests to the conduct of EVO-002 in compliance with Good Clinical Practices.

Financial Disclosure

The Applicant certifies that the Clinical Investigators who participated in EVO-002 did not enter into any identifiable, disclosable financial arrangements with Evofem, Inc., whereby the value of compensation to the investigator could have been affected by the outcome of the study.

Patient Disposition

A total of 105 subjects enrolled and assigned to one of five treatment groups. Randomization occurred in a 1:1:1:1:1 scheme. Five subjects discontinued the study: three subjects were lost to follow-up; two subjects discontinued due to the start of their menstrual cycle. No subjects discontinued due to adverse events. Table 2 summarizes subject disposition for EVO-002.

Table 2. EVO-002 Subject Disposition

	Acidform (5 g) n = 22	Acidform (4 g) n = 21	Acidform (3 g) n = 21	Placebo (4 g) n = 20	No- Treatment n = 21
Number of subjects					
Total Enrolled	22	21	21	20	21
Total Randomized	22	21	21	20	21
Total Treated	22	21	21	20	21
Included in Safety Population	22 (100%)	21 (100%)	21 (100%)	20 (100%)	21 (100%)
Completed	21 (95.5%)	19 (90.5%)	19 (90.5%)	20 (100%)	21 (100%)
Discontinued	1 (4.5%)	2 (9.5%)	2 (9.5%)	0	0
Reasons for Discontinuation					
Adverse Event	0	0	0	0	0
Protocol Violation	0	0	0	0	0
Withdrawal of Consent	0	0	0	0	0
Lost to Follow-Up	1 (100%)	2 (100%)	0	0	0
Other	0	0	2 (100%)	0	0

The Safety Population included all subjects who received any amount of study treatment, and all subjects who were randomized to the no-treatment group.

Percentages for primary categories are based on the number of subjects who were enrolled to the indicated treatment group. Percentages for subcategories are based on the number of subjects in the primary category being described. Percentages for reasons for discontinuation are based on the total number of subjects who discontinued among those subjects enrolled in the treatment group being summarized.

Source: Listings 16.2.1.1 and 16.2.1.2.

Source: NDA 208352, EVO-002 Study Report Body, Table 3, page 27 of 41, eCTD SN: 0034.

Protocol Deviations

Protocol deviations were broadly categorized as:

- Procedures not performed
- Procedures performed outside the allotted window
- Deviations to inclusion/exclusion criteria
- Other

Of the significant protocol deviations, one subject reported a urinary tract infection (UTI) and should have been discontinued from the study. Two subjects left after the 6-hour post-treatment evaluations. One subject failed to attend the Day 7 final assessment. One subject worked in the clinical research unit and later enrolled in the study (subject had previously recorded vital signs and performed urine pregnancy test for two subjects); and one subject was related to a sub-investigator who signed on to the study several weeks later. The reported protocol deviations do not appear to have affected the outcome of the study. Table 3 outlines protocol deviations in EVO-002.

Table 3. EVO-002 Protocol Deviations

	Procedure Not Performed	Procedure Performed Out of Window	Inclusion/Exclusion Criteria Deviations	Other
Number of subjects (%)	19 (18.1%)	41 (39.0%)	3 (2.9%)	5 (4.8%)
Number of events	43	117	3	5

Source: NDA 208352, EVO-002 Study Report Body, Table 4, page 28 of 41, eCTD SN: 0034.

Demographics of Study Population

Treatment groups were overall similar by age. Treatment groups differed slightly in racial distribution. Table 4 summarizes the demographics and baseline characteristics of the study population.

Table 4. EVO-002 Demographics of Study Population

	Acidform (5 g) n = 22	Acidform (4 g) n = 21	Acidform (3 g) n = 21	Placebo (4 g) n = 20	No-Treatment n = 21
Age (years)					
n	22	21	21	20	21
Mean (SD)	31.62 (7.11)	28.57 (7.20)	28.12 (5.40)	30.42 (6.47)	30.21 (6.45)
Median	30.30	27.10	26.40	31.20	30.00
Min, Max	(20.4, 45.6)	(18.8, 44.5)	(19.0, 38.9)	(19.7, 45.0)	(22.1, 46.0)
Gender					
Male	0	0	0	0	0
Female	22 (100%)	21 (100%)	21 (100%)	20 (100%)	21 (100%)
Race					
White	10 (45.5%)	6 (28.6%)	11 (52.4%)	11 (55.0%)	7 (33.3%)
Black or African American	10 (45.5%)	11 (52.4%)	8 (38.1%)	6 (30.0%)	12 (57.1%)
American Indian/Alaskan Native	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Asian	1 (4.5%)	0	1 (4.8%)	0	1 (4.8%)
Other	1 (4.5%)	4 (19.0%)	1 (4.8%)	3 (15.0%)	1 (4.8%)
Ethnicity					
Hispanic or Latino	6 (27.3%)	6 (28.6%)	2 (9.5%)	6 (30.0%)	3 (14.3%)
Not Hispanic or Latino	16 (72.7%)	15 (71.4%)	19 (90.5%)	14 (70.0%)	18 (85.7%)

Percentages are based on the number of subjects in the indicated treatment group.

Source: NDA 208352, EVO-002 Study Report Body, Table 5, page 29 of 41, eCTD SN: 0034.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Treatment groups did not differ in baseline characteristics.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Research staff administered the single dose of assigned treatment.

Efficacy Results – Primary Endpoint

Vaginal pH at the 5g dose decreased from baseline by a mean of 0.59 (SD 0.50) at 6 hours, 0.76 (SD 0.57) at 12 hours, and 0.72 (SD 0.55) at 24 hours ($p < 0.0001$), before gradually returning to baseline by Day 6. A similar reduction in mean vaginal pH occurred at the 4g dose (0.72 [SD 0.57] at 12 hours), with a smaller reduction at 24 hours compared to the 5g dose (0.50 [SD 0.54] vs. 0.72 [SD 0.50]). The 3g dose of PHEXXI also demonstrated a decline in vaginal pH by 0.58 (SD 0.70) at 12 hours before gradually returning to baseline. The nadir for all three doses occurred at 12 hours post-treatment. The mean vaginal pH for subjects receiving active gel remained below baseline at Day 6. Decline in mean vaginal pH was not seen in subjects who received either placebo or no treatment.

Data Quality and Integrity

Data quality and integrity issues were not identified.

Efficacy Results - Secondary and other relevant endpoints

EVO-002 evaluated the exploratory endpoint of the effect of PHEXXI on Amsel criteria. Four subjects (19%) in the 5g treatment group had positive Amsel findings at baseline. None had positive Amsel findings at Day 1, and one had positive Amsel findings at Day 7 (end of study).

Dose/Dose Response

EVO-002 evaluated the change in vaginal pH in response to three different doses of PHEXXI. The 5g dose demonstrated the largest and most sustained mean decrease in vaginal pH compared to the 4 g and 3 g doses.

Durability of Response

EVO-002 demonstrated the mean decrease in vaginal pH was most significant up to 24 hours after dose administration. The nadir occurred at 12 hours post-treatment, with a gradual return to baseline by Day 6.

Persistence of Effect

Persistence of effect was not evaluated for this single-dose study.

8.1.1.2. Study Results – Safety

Adverse event data was collected to inform the safety profile of PHEXXI.

Treatment Exposure

Of 105 subjects enrolled in the study, 84 received treatment (including placebo). Twenty-one subjects received speculum exam only; 22 subjects received the 5g dose; 21 subjects each received the 4 g and 3 g doses; 20 subjects received placebo.

Adverse Event Categorization

Adverse events categorization utilized MedDRA v17.0 or higher.

Routine Clinical Tests

Routine clinical tests performed included baseline evaluation of vaginal pH and HIV testing. HIV testing was not repeated at the end of the study.

Adverse Events

Deaths or serious adverse events did not occur during EVO-002. None of the reported treatment-emergent adverse events (TEAEs) resulted in treatment modification or withdrawal from the study.

Sixty-eight subjects (64.8%) reported TEAEs. Of these, vaginal discharge was the most frequently reported. Vaginal discharge occurred in 50.0% to 68.2% of subjects per treatment arm and in 14.3% of subjects in the no-treatment arm. Gel-associated discharge “peaked” on Day 2.

The second most frequently reported TEAE of vulvovaginal pruritis occurred in nine subjects across treatment arms. Three subjects in the 5 g arm and three subjects in the placebo arm represented the highest frequency of pruritis. An inactive ingredient in the placebo formulation may be a mild vulvovaginal irritant.

Conclusions

EVO-002 demonstrates that the 5 g dose (PHEXXI) lowers the vaginal pH most significantly in the first 24 hours after administration, with the maximum effect occurring at 12 hours post-treatment. Evaluation of the effects of PHEXXI on Amsel criteria are inconclusive. In conclusion, PHEXXI may be a mild vulvovaginal irritant but appears to be overall safe.

8.1.2. Study AMP002

Overview and Objectives

AMP002 was a single-arm, open-label, phase 3 study designed to evaluate the safety and efficacy of PHEXXI for prevention of pregnancy. AMP002 primarily aimed to evaluate the cumulative contraceptive efficacy of PHEXXI over seven cycles of use. Secondary objectives included evaluation of contraceptive efficacy by the Pearl Index, evaluation of safety and assessment of pregnancy outcomes.

Exploratory objectives listed by the Applicant included subject satisfaction, pregnancy intendedness and dosing time deviations for study drug-associated pregnancies.

Trial Design

AMP002 was conducted at 112 U.S. sites over seven cycles in women ages 18-35 at risk for pregnancy. Eligible subjects underwent a 60-day screening period before receiving study drug. Subjects received instruction on product use, daily e-diary entries, and symptom reporting. Subjects used study drug until seven cycles were completed, or pregnancy occurred. Cycles defined as evaluable included those where intercourse with study product use occurred, and back-up methods were not used. Non-evaluable cycles were not replaced by additional cycles.

Key eligibility criteria are described below.

Key Inclusion Criteria

To be enrolled in the study, subjects were required to:

1. Be healthy sexually-active women at risk for pregnancy and desiring contraception.
2. Be between 18 and 35 years old, inclusive.
3. Have regular menstrual cycles of 21 to 35 days duration, inclusive.
4. Have a single male sex partner for 23 months at the time of enrollment.
5. Have a negative urine pregnancy test at enrollment.
6. Be willing to engage in at least three acts of heterosexual vaginal intercourse per cycle.
7. Be willing to use the study drug as the only method of contraception over the course of the study.
8. Be willing to keep a daily e-diary to record information regarding coitus, study drug use, concomitant medication or vaginal product use, menses, and signs and symptoms data for self and male partner.

Key Exclusion Criteria

Excluded subjects fulfilled the following criteria:

1. Three or more UTIs in the year preceding date of consent
2. UTI or sexually transmitted infection by urine culture or vaginal swab at the time of screening
3. Used vaginal or systemic antibiotics or antifungals in the 14 days prior to enrollment unless receiving treatment for infections diagnosed at enrollment
4. History of recurrent vaginal infections/disorders (as defined by $\geq$ four occurrences in the previous year or $\geq$ three occurrences in the previous six months)

Study Procedures

Subjects attended five visits: visit 1 (screening), visit 2 (enrollment), visit 3 (during the second study cycle), visit 4 (during either the fifth or sixth study cycle), and visit 5 (14 to 30 days after seventh study cycle). Clinical site staff contacted subjects by telephone between visit 3 and visit 4 to monitor adverse events (AEs), concomitant medications (CMs), sexual activity, use of back-up contraception, compliance with study drug and electronic diary (e-diary), need for an unscheduled visit and confirmation of contact information. Table 30 in the appendix outlines the study schedule of assessments.

Subject satisfaction, including sexual satisfaction, was measured through a questionnaire distinct from the daily e-diary entries. Subjects' satisfaction with PHEXXI as a birth control method was elicited using a Likert scale. The Female Sexual Function Index questionnaire was also administered. Subjects also answered questions regarding pregnancy intendedness based on a Likert scale.

Drug Accountability

Study drug was shipped by the Applicant to each clinical site. Each investigator maintained accurate accountability records and documented drug dispensing in the electronic data capture (EDC) system. Subjects received a minimum of one carton containing 10 pre-filled applicators of PHEXXI. Subjects were instructed to return all unused pre-filled applicators or wrappers of used or partially used product at each study visit. All unused drug was returned to the Applicant at the end of the study for disposal.

Laboratory Procedures

The following laboratory procedures were conducted according to the schedule of assessments (see Appendix 16.8):

Table 5. Laboratory Procedures

Local Laboratory or Site	Central Laboratory
Dipstick urinalysis (study test kit to be provided)	CBC differential
Urine culture	Clinical chemistry
Urine pregnancy test (study test kit provided)	Serum pregnancy test
Pap test	HIV
Wet Mount Analysis	Chlamydia
Vaginal pH	Gonorrhea

Source: NDA 208352, AMP002 Protocol/Amendment, Table 2, page 91-2 of 263,eCTD SN: 0034.

Emergency Contraception

Subjects were eligible to receive emergency contraception on request, or obtain her own over-the-counter, in the event of suspected risk of pregnancy.

Concomitant Medications

E-diary entries queried subjects on the use of concomitant medications and health products. Subjects were advised to avoid douching during the study. If douching did occur, subjects were advised to wait at least 6 hours after the last act of intercourse and record product use in the e-diary. Use of lubricants or vaginal preparations before or during intercourse was prohibited. If use did occur, e-diary documentation was required.

Study Endpoints

The primary endpoint of the study was seven-cycle cumulative pregnancy rate calculated using the Kaplan-Meier method.

The secondary endpoints include efficacy measured by the Pearl Index, adverse events, and pregnancy outcomes.

Exploratory endpoints proposed by the Applicant included subject satisfaction (including sexual satisfaction) with PHEXXI, pregnancy intendedness, and dosing time deviations for study drug-associated pregnancies.

Statistical Analysis Plan

Analysis Population

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

Safety Population was a subset of ITT subjects who used at least one application of the study product.

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

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

The mITT population is the primary analysis population for the efficacy analysis.

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

Sample Size Determination

The applicant used simulation methods to evaluate the likelihood of various sample sizes providing enough information to test the primary hypothesis (one-sided type 1 error of 0.025) and enough use cycles of PHEXXI gel to address other regulatory requirements. The 6-month (183 day) cumulative pregnancy percentage was estimated using Kaplan-Meier methods.

The sample size determination assumed the following:

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

With 1,349 participants aged 18 through 35 years (inclusive), the study would have 90% power to ensure that the upper limit of the 95% CI of the cumulative seven-cycle pregnancy rate was less than or equal to 21%. The expected number of completers was 515 and the expected

number of cycles evaluable for safety was at least 3143.

Primary Efficacy Analysis

The primary efficacy endpoint was the cumulative percentage of typical-use seven-cycle pregnancy.

The primary hypothesis was whether subjects using PHEXXI vaginal gel have a seven-cycle cumulative pregnancy percentage less than or equal to 21%, that was,

$$H_0: \pi_A > 21 \% \text{ vs. } H_A: \pi_A < 21 \%$$

where π_A represented the 7-cycle cumulative pregnancy percentage for PHEXXI. The Kaplan-Meier estimate and its 95% CI (based on Greenwood's method) of the seven-cycle cumulative pregnancy percentage of women in the mITT population were calculated. If the upper bound of the 95% CI was $\leq 21\%$, then the null hypothesis would be rejected and the conclusion would be that the -cycle cumulative pregnancy percentage was $\leq 21\%$.

Secondary Efficacy Analysis

The Pearl Index was defined as the number of pregnancies in 100 woman-years of method use. The primary method of analysis for Pearl index used by the applicant was Number of pregnancies * 365.25 * 100/ Total number of days at risk, as this study used natural women cycles and the days varied from subject to subject. Year-based Pearl Index and its two-sided 95% CI were presented, assuming a Poisson distribution.

The statistical analysis plan (SAP) did not specify the duration of exposure that would serve as the basis for calculation of the Pearl Index. Upon review of this submission, the Review Division determined that the Pearl Index would be calculated based on the same number of on-treatment pregnancies and cycles of exposure (i.e. 7 cycles) as the primary efficacy endpoint.

Protocol Amendments

Three protocol amendments occurred prior to study initiation. The first amendment incorporated feedback from the Institutional Review Board regarding consent of male partners. Subsequent amendments incorporated feedback from the Review Division. Table 6 summarizes the relevant protocol amendments:

Table 6. Summary of AMP002 Protocol Amendments

Version Number	Effective Date	Summary of Changes
1	05 May 2017	Original Protocol
2	08 June 2017	Section 4.1.3: Moved Partner Requirements from the inclusion/exclusion criteria to the screening procedures based on IRB comments Clarifications to partner information collection throughout
3	19 June 2017	Section 5.4.3: Added grading criteria for valvar, vaginal or cervical AEs Section 5.6: Lock-out period statement added for eDiary Section 6.6: Corrected typo in “on-treatment” definition Section 9.1: Revised the Pearl Index formula Section 9.2: Sample size increased from 1157 (85% power) to 1349 (90% power) Section 9.8.3: Added an additional sensitivity analysis Table 1: Clarified footnote “a”
4	01 Nov 2017	Section 6.4 – Clarified that subjects who become pregnant are not discontinued Section 9.2 – Updated the expected number of completers and evaluable cycles for 1394 participants Section 9.8.3 - Adjusted dosing time intervals

Source: NDA 208352, AMP002 Protocol and/or Amendment, Table 4: Summary of Amendments, page 53 of 263, eCTD SN: 0034.

8.1.3. Study Results

Compliance with Good Clinical Practices

The Applicant attests to the conduct of AMP002 in compliance with Good Clinical Practices.

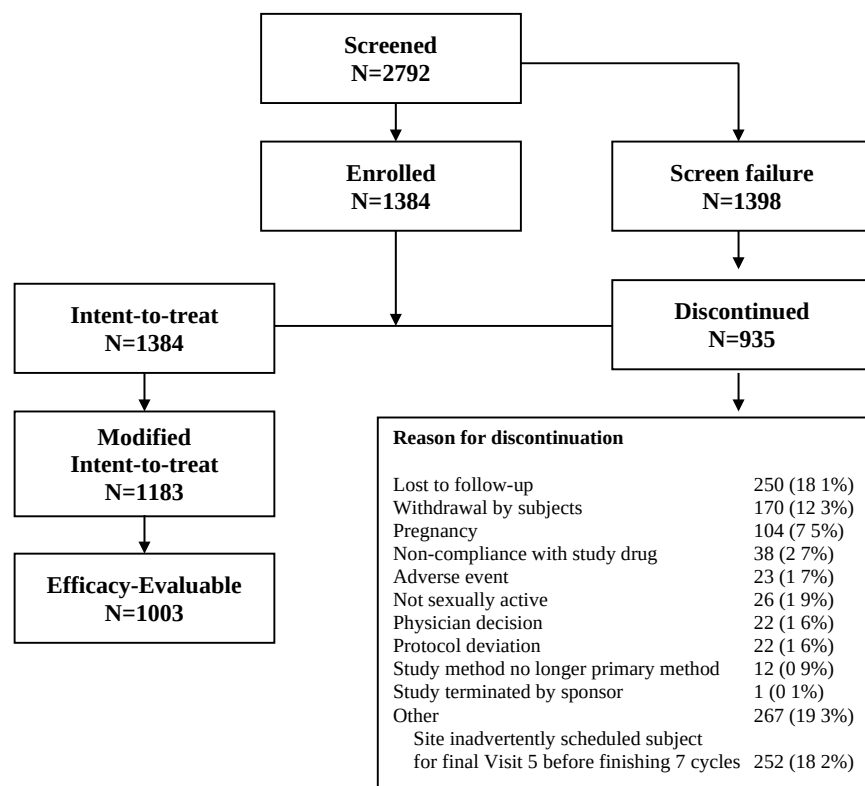
Financial Disclosure

The Applicant certifies that the Clinical Investigators who participated in AMP002 did not enter into any identifiable, disclosable financial arrangements with Evofem, Inc., whereby the value of compensation to the investigator could have been affected by the outcome of the study.

Patient Disposition

Of the 2,792 subjects who were screened for the study 1,384 subjects were enrolled in the study and included in the ITT population. Of the ITT population, 1,183 subjects were in the mITT population. Of the ITT population, 935 (67.6%) subjects discontinued the study early. The most common reasons for early study discontinuation were other reasons (19.3%), lost to follow-up (18.1%), withdrawal by subjects (12.3%), and pregnancy (7.5%). See details in Figure 1.

Figure 1. Subject Disposition



Source: AMP002 clinical study report, Applicant Figure 2, page 52 of 87 and statistical reviewer's summary.

The early discontinuation rate of 67.6% is higher than expected for a contraceptive trial. However, the Applicant reports that one study site inadvertently scheduled subjects' exit visit too early. These subjects were therefore only enrolled for six cycles instead of seven. These early discontinuations due to site error represent 18.2% (252/1,384) of all early discontinuations. Discontinuations due to all other causes 683/1,384 (49.3%) are comparable to other contraceptive spermicide trials (Raymond 2004, Grimes 2013).

Importantly, we note that losses to follow-up could result from subjects who became pregnant and chose not to inform the investigators. This could result in an under-estimation of the true pregnancy rate in the trial.

Protocol Violations/Deviations

A total of 76.4% (1,058/1,384) of subjects had protocol deviations. The most frequent protocol deviations were due to: 1) deviation from protocol-defined procedures, and 2) withdrawal criteria. Table 7 lists the AMP002 protocol deviations.

Table 7. AMP002 Protocol Deviations*

Deviation Category	Amphora (N = 1384) n (%)
Total Number of Subjects With any Criteria Deviations	1058 (76.4)
Procedures/Tests	809 (58.5)
Withdrawal Criteria	557 (40.2)
Visit Schedule	256 (18.5)
Investigational Product Administration/Study Treatment	119 (8.6)
Informed Consent	39 (2.8)
Inclusion/Exclusion Criteria	18 (1.3)
Adverse Events/Serious Adverse Events	2 (0.1)
Other	1 (0.1)

A subject with more than 1 reported deviation in each unique deviation category was counted once. Percentages for subcategories may sum to more or less than 100%.

ITT = Intent-to-Treat, N = number of subjects in the ITT population, n = number of subjects included in the deviation category.

Source: [Table 14.1.5](#).

*Amphora = PHEXXI

Source: NDA 208352, AMP002 Study Report Body, Table 4: Protocol Deviations, eCTD SN: 0034.

The majority of protocol deviations were minor (2,783/3,190, 87.2%). Of the major protocol deviations (406/3,190, 12.7%), 17 were missed pregnancy tests (urine or serum). Eight of these occurred in visit 5 (end of study). No single subject had more than one missed pregnancy test. No single subject missed both a urine and serum pregnancy test. For this study, protocol deviations do not appear to have affected overall conclusions regarding efficacy. However, on-treatment pregnancies may have been missed as a result of missed pregnancy tests at the final visit.

Table of Demographic Characteristics

Subjects' demographics and baseline characteristics in the mITT population are shown in **Table 8**. The subjects' mean age was 27.8 years old; 70.6% of the subjects were white, 23.7% were black or African American, 2.5% were Asian, and 3.3% were others; 41.8% subjects were Hispanic or Latino origin. Mean body mass index was 28.6 kg/m². The demographic and baseline characteristics of the mITT population were consistent with those of the ITT population (see **Table 29** in the appendices).

Table 8. Demographics and Baseline Characteristics (mITT Population)

Subject Characteristic	PHEXXI (N = 1183) n (%)
Age (years)	
Mean (SD)	27.8 (4.5)
Median	28
Min, Max	18, 35

Subject Characteristic	PHEXXI (N = 1183) n (%)
Race	
White	835 (70.6)
Black or African American	280 (23.7)
Asian	29 (2.5)
American Indian or Alaska Native	5 (0.4)
Native Hawaiian or Pacific Islander	2 (0.2)
Other	32 (2.7)
Ethnicity	
Hispanic or Latino origin	495 (41.8)
Not Hispanic or Latino origin	681 (57.6)
Not Reported	7 (0.6)
BMI at Screening (kg/m ²)	
Mean (SD)	28.6 (7.8)
Median	26.7
Min, Max	13.2, 66.8

Source: Table 14.1.6.2 in Study AMP002 clinical study report and statistical reviewer's analysis.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Other baseline disease characteristics or concomitant drugs that could influence interpretation of study outcomes are not relevant to this application.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

AMP002 study protocol stipulated that subjects participating in the study should not be excluded from analysis if “imperfect” use of the product occurred per FDA’s advice. All subjects who documented acts of vaginal intercourse with investigational product use are included in the efficacy analysis.

As discussed, subjects were instructed to avoid douching throughout the trial, but to document in the e-diary if vaginal douches were used. Douching was not specifically prohibited. Use of other vaginal products such as antifungals or antimicrobials were documented in the e-diary.

Data Quality and Integrity

The data definition file for study AMP002 is acceptable after the applicant for clarification from the information request.

Efficacy Results – Primary Endpoint

The applicant reported 101 pregnancies in AMP002 and the primary analysis using the Kaplan-Meier method was based on 101 on-treatment pregnancies that occurred in the first seven cycles.

The Review Division identified an additional five pregnancies in the study population. Five documented pregnancies occurred in Cycle 8. The estimated date of conception for each of the five pregnancies was within 7 days of last product use. See Appendix 16.9 for a complete listing of adjudicated pregnancies.

The seven-cycle cumulative pregnancy rate in the mITT population estimated by the Kaplan-Meier method is 13.7% (95% CI: 10.0%, 17.5%) (**Table 9**). The upper bound of the 95% confidence interval is smaller than 21%.

Table 9. 7-cycle Pregnancy Rate by Kaplan-Meier Method (mITT Population)

PHEXXI (N=1183)	
Number of pregnancies	101
Cumulative pregnancy rate (95% CI)	13.7% (10.0%, 17.5%)

Source: Table K.14.2.1 in the applicant's response in SDN # 49 and statistical reviewer's analysis.

Sensitivity analysis for the primary endpoint using cycle information from subjects' e-diary only

Reviewers noticed that a menses case report form (CRF) page to capture the start date of each menses was implemented in the study when about 96% of the subjects had finished the study treatment. An information request was sent for clarification. The applicant clarified that the data recorded in this designated menses CRF page was from sources including e-diary, study specific source documents, and/or the patient medical record. This menses CRF page in the EDC, as for all EDC pages, was 100% verified against source documents. The data clarification request process for e-diary corrections was stopped at the time of implementing the new menses CRF page. The e-diary data was not corrected after September 2018.

To compare the difference between the cycle information captured in the e-diary and the individual menses CRF page, the seven-cycle cumulative pregnancy rate based on e-diary only was estimated. Based on the e-diary, the seven-cycle cumulative pregnancy rate in the mITT population estimated by the Kaplan-Meier method is 14.5% (95% CI: 10.8%, 19.6%) (**Table 10**). The upper bound of the 95% confidence interval is smaller than 21%.

Table 10. 7-cycle Pregnancy Rate by Kaplan-Meier Method Based On e-diary Only (mITT Population)

PHEXXI (N=1183)	
Number of pregnancies	101
Cumulative pregnancy rate (95% CI) ^a	14.6% (10.8%, 19.6%)

Source: Statistical reviewer's analysis based on the applicant's submitted dataset ADTTES in SDN # 49.

Efficacy Results – Secondary and Other Relevant Endpoints

Based on the 101 on-treatment pregnancies that occurred in the first seven cycles, the Pearl Index in the mITT population was 27.5% (95% CI: 22.4%, 33.5%) per 100 woman-years (**Table 11**).

Table 11. Estimated Pregnancy Rate by Pearl Index (Per 100 Women-Year) (mITT Population)

	PHEXXI (N=1183)
Number of pregnancies	101
Number of women-years at risk	360.9
Pearl Index (95% CI)	27.5% (22.4%, 33.5%)

Source: Table K.14.2.5 in the applicant's response submitted in SND # 49 and statistical reviewer's analysis.

^a Pearl Index estimate is (number of pregnancies × 100)/total number of women-years at risk. Number of women-years=Number of women-days/365.25.

The seven-cycle pregnancy rate estimation by subgroups of age, race, ethnicity, and BMI is presented in **Table 12**. The results by the subgroup are consistent with the overall analyses results, in general. For the non-Hispanic subjects, the cumulative pregnancy rate is numerically higher than the Hispanic subjects (17.5% versus 9.0%).

Table 12. 7-Cycle Cumulative Pregnancy Rate by KM Method by Subgroup (mITT Population)

Subgroup	Category	Number of Pregnancies	Cumulative Pregnancy Rate (95% CI)
Age (years)	≥ 18 - ≤30 (N=805)	71	12.8% (9.8%, 15.8%)
	> 30 - ≤35 (N=378)	30	14.8% (6.9%, 22.8%)
Race	White (N=835)	74	14.0% (9.4%, 18.6%)
	Non-white (N=348)	27	12.7% (7.6%, 17.9%)
Ethnicity ^a	Hispanic (N=495)	22	9.0% (2.3%, 15.6%)
	Non-Hispanic (N=681)	79	17.5% (13.6%, 21.5%)
BMI ^b	< 30 (N=784)	64	13.9% (8.5%, 19.2%)
	≥ 30 (N=398)	37	14.0% (9.5%, 18.4%)

Source: Tables K.14.2.1.A, K.14.2.1.B, K.14.2.1.C, K.14.2.1.D, K.14.2.E, K.14.2.1.F, K.14.2.1.G, and K.14.2.1.H in the applicant's submission SDN # 49 and statistical reviewer's analysis.

^a Seven subjects did not report ethnicity.

^b One subject did not have height and BMI information in the database.

Dose/Dose Response

AMP002 was not designed to evaluate dose response.

Durability of Response

AMP002 was not designed to evaluate durability of response and dosing instructions require repeated dosing after each episode of vaginal intercourse.

Persistence of Effect

AMP002 was not designed to evaluate persistence of effect. Based on the mechanism of action, persistence of effect after vaginal intercourse would not be expected.

Efficacy Results – Secondary or exploratory Clinical Outcome Assessment (PRO) endpoints

Safety outcomes are discussed in Section 8.2.

Results of exploratory endpoints regarding subject satisfaction with PHEXXI as a method of birth control, female sexual function index, and pregnancy intendedness are briefly discussed here. However, these patient reported outcomes were not previously discussed with the

Review Division. Therefore, a clinical assessment of the questionnaires was not performed and these data are not included in labeling.

Additional Analyses Conducted on the Individual Trial

Additional efficacy analysis has not been conducted on AMP002.

Assessment of Efficacy Across Trials

A single clinical trial - AMP002 - forms the basis for PHEXXI's efficacy as a contraceptive vaginal gel. Therefore, assessment of efficacy across trials is not relevant to this application.

8.1.4. Integrated Assessment of Effectiveness

Contraceptive efficacy for PHEXXI was demonstrated by the seven-cycle cumulative pregnancy rate and supported by the Pearl Index over 7 cycles of exposure. Sensitivity analyses indicate that the statistical issues identified in the course of the review have not significantly affected the overall efficacy assessment.

8.2. Review of Safety

8.2.1. Safety Review Approach

This review addresses the safety of PHEXXI in the "as treated" population, i.e. all subjects who received at least one dose of study drug. Therefore, drug exposure from studies EVO-002, AMP001, and AMP002 are included. Adverse event findings from EVO-002 were previously discussed (see Section 8.1.1.2).

Adverse events analysis will include an overview of serious or significant adverse events in AMP001 and AMP002 that inform product labeling. However, detailed analysis of adverse events applicable to the target population in the US will only include the US cohort of AMP001 and AMP002. The Russian cohort of AMP001 will not be included in the detailed analysis for the following reasons: 1) the extremely low rate of adverse events in the Russian cohort of AMP001 precludes generalizability to the target population; and 2) the inadequate trial conduct and safety data collection in AMP001 precludes substantive review.

Despite the demographic similarity between AMP002 and the US cohort of AMP001, adverse event data are considered separately. In the first review cycle, the primary clinical reviewer noted that the Applicant did not collect adverse event data within the first hour after product use, nor did the Applicant collect genitourinary adverse event data specifically, as previously requested by FDA. For example, in AMP001, the preferred term "vulvovaginal discomfort" was frequently documented without further characterization of the nature of the "discomfort." In contrast, AMP002 documented the preferred term "vulvovaginal pain." AMP002 collected additional parameters such as timing of onset, duration, and intensity per FDA's advice. As a

result of these considerations, direct comparison of adverse event frequencies is limited.

Additional safety findings from study AMP001 were previously reviewed in detail by the DBRUP Medical Officer in the first review cycle. Specifically, a colposcopy substudy was performed in the Russian cohort and revealed no difference in cervicovaginal lesions by treatment arm. See Section 8.2.8 for further discussion. Additionally, a male partner safety and tolerability study revealed no significant safety findings as discussed in Section 8.2.8.

In summary, while adverse event data from both Russian and US cohorts of AMP001 will be considered, this review emphasizes the safety findings of AMP002.

8.2.2. Review of the Safety Database

Overall Exposure

A total of 2824 subjects were exposed to PHEXXI at the 5 g dose across all studies. Study EVO-002 enrolled 100 subjects randomized to 5 study arms. However, only one study arm (20 subjects) received the 5 g dose of the study drug used in the clinical trials. The remaining groups received 3 grams, 4 grams, placebo, or no treatment and therefore are not included in the overall exposure numbers.

Where 2824 subjects used the study drug at least once, and a median of five applications per cycle occurred, the safety database approximates 19,000 cycles of exposure. Therefore, the safety database provides an adequate basis for conclusions regarding the safety of PHEXXI. Table 13 below summarizes the safety database for PHEXXI.

Table 13. Overview of the Safety Database for PHEXXI

Safety Database for PHEXXI ¹			
Individuals (and male partners) exposed to the study drug in this development program for the indication under review			
N=2824			
(N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	PHEXXI (n= 2804) ⁵	Active Control ² (n= 1659)	Placebo ^{3,4} (n= 20)
Phase 1 Trial			
Single dose	20	0	20
Phase 3 Trial			
Active control, multiple dose			
AMP001 Russia	324	318	0
AMP001 USA	1143	1341	0
Subtotal	1485	1659	0
Phase 3 ⁶ Trial			
Single arm, open-label, multiple dose	1339	0	0
Subtotals			
Russia	324	318	0
USA	2480	1341	20
Grand Totals	2804	1659	20

¹ PHEXXI = one pre-filled single dose applicator containing 5 grams of lactic acid (1.8%)/citric acid (1%)/potassium bitartrate (0.4%) gel.

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² Subjects in Study AMP001 were randomized to treatment with the study product or Conceptrol® Vaginal Gel (a nonoxynol-9 spermicide gel) as the active control.

³ Subjects in Study EVO-002 were randomized to 1 of 5 study arms, one of which was the placebo arm.

⁴ Excludes male partners.

⁵ Subjects who participated in PHEXXI clinical trials more than one time are counted once in number of exposures.

⁶ All subjects in AMP002 received PHEXXI; AMP002 conducted in US only.

Relevant characteristics of the safety population:

Study AMP001 included subjects from 2 countries: USA and Russia. The demographic composition of these cohorts differed significantly by age, race, and body mass index. The Russian cohort was younger (mean age 26.8 years vs. 27.7 years), primarily White (100.0% vs. 65.6%), and had lower mean BMI (21.71 kg/m² vs. 28.31 kg/m²) compared to the US cohort. Study AMP002 was conducted at US sites only and more closely represented the expected target population: mean age 27.6 years, 69.5% White, and mean BMI 28.8 kg/m².

While the demographic differences between the US and Russian cohorts of AMP001 and AMP002 are not expected to impact the safety profile of PHEXXI, differences in study conduct and data collection limit the generalizability of AMP001.

Adequacy of the safety database:

Overall, the safety database provides sufficient information to generalize results to the target population in the US. AMP002 was conducted in US sites only, and adequately represents the target population. In addition, adverse event data collection generally followed FDA's advice and is sufficient for analysis.

The primary clinical reviewer conducted a thorough review of AMP001 in the first review cycle. The inadequacies pertaining to collection and reporting of product-related adverse events in AMP001 included:

1. Failure to collect data on adverse events occurring within one hour after product use.
2. Screening and treating all subjects for genitourinary infections regardless of the presence of symptoms.
3. Marked differences in adverse reaction reporting rates exist between the US and Russian cohorts.

Although the topical method of application and local mechanism of action of this product are unlikely to be affected by demographic factors, the methodologic differences between studies AMP001 and AMP002 limit pooled analyses of the safety data. Therefore, the safety data are presented separately for each of 3 cohorts: 1) Russian cohort of AMP001; 2) US cohort of AMP001; and 3) full cohort of AMP002 (conducted at US sites only). In addition, the overall safety profile based on all available information across studies is discussed.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no identified issues regarding data integrity and submission quality that impacted

review of the safety database in the current submission.

Categorization of Adverse Events

Overall, categorization of adverse events in AMP002 occurred in a manner consistent with CFR 312.32. The definitions of serious adverse events (SAEs) were acceptable. Adverse events that began or worsened in severity after at least one dose of study drug were defined as treatment-emergent adverse events. Adverse events were coded by preferred term and system organ class consistent with MedDRA v17.0 or higher. Preferred term and system organ class were assigned using standard terminology based on the verbatim description documented by the investigator. Research staff performed adverse event assessments at each scheduled visit as well as by telephone between Visits 3 and 4 (see Table 30 Schedule of Assessments in Section 16.8).

Symptom severity assessment followed standard terminology according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Mild symptoms correlated to CTCAE grade 1; moderate to CTCAE grade 2; and severe to CTCAE grade 3 or higher. Causality assessment performed by the Investigator included description of the most likely cause of an adverse event. The causal description then followed the World Health Organization Uppsala Monitoring Centre causality categories:

- Certain/Definite
- Probable/Likely
- Possible
- Unlikely
- Not assessable

Adverse event data collection with respect to genitourinary adverse events of interest generally followed the advice from the Review Division. The reported genitourinary AEs of interest included: burning, itching, pain, and “other.” The adverse event category of “other” is non-specific and fails to adequately capture symptoms of interest to the Review Division. Additionally, “vulvovaginal pain” fails to characterize the nature of pain, which can vary in quality (i.e. sharp, stabbing vs. dull, aching).

For adverse events of interest, such as pyelonephritis, the Review Division has assigned causality conservatively. As is FDA’s practice, all adverse event causality has been determined by the Review Division independent of the Investigators’ assessment of causality.

Collection and categorization of adverse events in AMP001 was inadequate as previously discussed. The inadequacies of AMP001 data collection are discussed in context throughout this review. Refer to Dr. Zopf’s Primary Clinical Review for a detailed review.

Routine Clinical Tests

Routine clinical tests performed at the investigator site included dipstick urinalysis, urine culture, urine pregnancy test, pap smear, wet mount, and vaginal pH. Central laboratory tests

included CBC with differential, clinical chemistry, serum pregnancy test, HIV, chlamydia, and gonorrhea testing.

Safety labs including HIV testing were collected at baseline and end of study. Pap tests were performed at the baseline visit per current guidelines. Dipstick urinalysis and urine pregnancy test were performed at every site visit. Chlamydia and gonorrhea testing were performed at Visits 1, 3, 4, and 5 (exit visit). Refer to Table 30 in the Appendix for the specific timing of each assessment.

8.2.4. Safety Results

Deaths

No deaths were reported during clinical trials for this product.

Serious Adverse Events

Sixteen subjects reported serious adverse events in AMP002. Of these, one event (cystitis and vaginal mass requiring hospitalization) was likely related to the study product. The event of vaginal mass and cystitis is described in detail below.

Vaginal Mass and Cystitis:

Subject AMP002- (b) (6) was a 36-year-old G₁P₁ who was contacted by the study site for a missed appointment on January 10, 2018. The subject reported study product use on December 6th, 9th, and 29th, 2017. The subject reported the adverse events of cystitis (Grade 2), unspecified vaginal mass (Grade 3) which was excised, and a motor vehicle accident (Grade 1). Per subject report, each event occurred on the same day – (b) (6) days after last study product use. The subject was hospitalized on the same day of the events. The subject withdrew consent from participation in the study during the phone call with the study site and declined to release her medical records. Therefore, additional details are not available. The investigator assessed the event of “cystitis” and “vaginal mass” as likely related to study product use. The Applicant assessed the relatedness as “unknown.”

The Review Division concludes that the adverse event “cystitis” is related to study product use. An incubation period of 7 days would be expected before urinary tract infections become clinically apparent. Insufficient information is available to inform the causality of “vaginal mass.”

Status Epilepticus

One subject with a pre-existing seizure disorder experienced status epilepticus during the study. Subject AMP002- (b) (6) was a 31-year-old G₄P₃ who enrolled in AMP002 on October 11, 2017. On (b) (6), the subject was hospitalized due to “seizures.” The subject had been taking levetiracetam and phenytoin for known seizure disorder. The Applicant states this history was not reported to the investigator. The subject received Versed and

Dilantin and was admitted to the ICU for stabilization. The subject was discharged home on (b) (6) with driving restrictions.

The subject was prescribed levetiracetam and lacosamide for outpatient management of seizure disorder. The subject's medications were reviewed by the investigator. The investigator determined that the subject's seizure medications were non-teratogenic and allowed the subject to continue in the study. On January 16, 2018 the subject had a positive pregnancy test. A pelvic ultrasound on January 19, 2018 revealed a gestational sac with yolk sac but no fetal pole consistent with 4 weeks 1-day gestation. The estimated date of conception was January 4, 2018. The pregnancy was classified as "on-treatment." The subject was subsequently lost to follow-up. The adverse event "status epilepticus" was assessed as unrelated to study drug.

Despite the investigator's review of the subject's medical history and medications after the adverse event of status epilepticus, the Review Division has concerns regarding the subject's continued participation in the study. While levetiracetam may have evidence to support its safety, lacosamide's safety profile is concerning. Per lacosamide USPI, increased embryofetal and perinatal mortality; growth deficits; and neurodevelopmental toxicity have been observed in rats. The Risk Summary states "there are no adequate data on the developmental risks associated with the use of [lacosamide] in pregnant women."

Additionally, a study participant with uncontrolled seizure disorder should have been considered a withdrawal criterion. Failure to discontinue the subject from the study increased the risk to the subject as well as a future pregnancy. The lack of follow-up information on this subject is concerning.

Peritoneal Hemorrhage and Uterine Rupture resulting in Intrauterine Fetal Demise

Subject AMP002- (b) (6) – a 29-year-old G5P4 - enrolled in AMP002 on November 29, 2017. A positive home urine pregnancy test was reported on March 2, 2018, which was confirmed by the site on March 6, 2018. An ultrasound on March 7, 2018 revealed a single live intrauterine pregnancy at 10 weeks 3 days gestation. The estimated date of conception was January 4, 2018 and the pregnancy was classified as "on-treatment."

On (b) (6) at 20 weeks gestational age, the subject presented with sudden onset of right shoulder pain followed by severe diffuse abdominal pain. An abdominal ultrasound revealed fluid in the peritoneum and a single live intrauterine pregnancy with fetal heart rate 135 beats per minute. The subject underwent laparoscopy where large hemoperitoneum was identified and evacuated. A small rupture at the right uterine cornu was identified with extrusion of placental tissue. The procedure was converted to exploratory laparotomy. A hysterotomy was performed, the placenta and fetus were removed, and the defect in the uterine wall was repaired. The subject required hemodynamic resuscitation with multiple transfusions of packed red blood cells and cryoprecipitate. The subject was discharged home once stable.

Per the narrative submitted by the Applicant, “she had had two previous vaginal deliveries. A fibroid was thought to have complicated her antenatal care.” The event was assessed as unrelated to study drug.

The Review Division concurs that the SAE is unrelated to study drug. These events are potentially the result of a cornual implantation.

Uterine rupture

Subject AMP002 (b) (6) – a 30-year-old G9P8 – enrolled in AMP002 on January 25, 2018. Her past medical history was significant for chronic hypertension and depression. Her obstetric history was significant for three prior cesarean deliveries (2012 – low transverse cesarean for breech; 2015 – classical cesarean for twins; 2017 – cesarean for breech and macrosomia) and preeclampsia. The subject had a positive home pregnancy test on February 15, 2018 which was confirmed by the site on February 22, 2018. An ultrasound on February 28, 2018 revealed a single live intrauterine pregnancy consistent with 6 weeks 2 days gestation. The pregnancy was assessed as “on-treatment.” The estimated date of conception was January 29, 2018.

On (b) (6), at 39 weeks 0 days gestational age, the subject presented to labor and delivery for induction of labor. The pregnancy had been complicated by gestational hypertension and gestational diabetes. The subject had been advised to have a scheduled repeat cesarean delivery at 36 weeks; however, the subject refused. Labor induction was initiated with low dose oxytocin.

During the labor induction, the subject reported intermittent abdominal pain despite an epidural. At this time the cervix was 5 cm dilated. Pitocin was increased. The subject was 6 cm dilated for several hours with increased pain and dizziness. The fetal heart tracing had small variable decelerations and an emergency cesarean section was advised. The cervix was 9 cm dilated. The fetal heart tracing showed prolonged decelerations.

The subject then underwent a repeat low transverse cesarean section for suspected uterine rupture. Blood and fetal feet were within the peritoneal cavity upon laparotomy. A male infant was delivered with birth weight 6 lbs. 9 oz. Apgar scores were 8 and 9. A large uterine rupture was identified from the right side of the fundus extending down through the cervix into the vagina and into the right broad ligament. Estimated blood loss was 2 liters. Cystoscopy and cystotomy through the dome of the bladder were performed due to concern for possible bladder and right ureteral injury. A stitch was identified in the right posterior wall of the bladder and was repaired. The subject received 2 units of packed red blood cells, 2 units of fresh frozen plasma, and 10 units of platelets.

The SAE of “uterine rupture” was assessed as unrelated to study drug by the investigator and the Applicant.

The Review Division concurs that the SAE of “uterine rupture” is unrelated to study drug. However, the subject’s enrollment in the study given her prior medical and obstetric history

(especially history of classical caesarean section) is concerning. Enrollment in the study increased the risks to the subject and any potential pregnancy and contradicts the principles of Good Clinical Practice (International Council on Harmonisation).

Dropouts and/or Discontinuations Due to Adverse Effects

Seventeen subjects (1.3%) discontinued participation in AMP002 due to adverse events likely related to PHEXXI. Of these discontinuation events, subjects most frequently reported vulvovaginal burning sensation as the reason for discontinuation (n=9, 52.9%). Other reported reasons for discontinuation related to product use included: vulvovaginal pruritis, genital paresthesia, vulvovaginal discomfort, vulvovaginal mycotic infection, vulvovaginal pain, and vulvovaginal ulceration.

Significant Adverse Events

Urinary Tract Infections, Cystitis, and Pyelonephritis

Urinary tract infections and pyelonephritis occurred at higher than expected rates in a population of overall healthy females. A total of 237 subjects had documented urinary tract infections across studies. However, as previously discussed, the frequency of urinary tract infection in AMP001 differed from AMP002 (14.7% vs. 5.7%). Clinically significant infections of the bladder and upper urinary tract included preferred terms “cystitis,” “pyelonephritis,” and “kidney infection.”

Table 14 details the adverse events of “cystitis,” “pyelonephritis,” and “kidney infection.”

Table 14. Subjects Using PHEXXI With Urinary Tract Infections & Pyelonephritis

USUBJID Country Age	Treatment Start Date	Preferred Term	Serious AE	Applicant Assessment of Causality	Medical Officer Assessment of Causality	Additional Comments
AMP001- USA 22	(b) (6) 24-May-2012 12-Jul-2013	Pyelonephritis	N	UNRELATED	Related	
AMP001- USA 30	(b) (6) 12-Feb-2013 26-Jun-2013	Pyelonephritis	Y	UNRELATED	Related	Received antibiotics then admitted for unremitting pain one week later
AMP001- USA 24	(b) (6) 30-Jun-2013 23-Jun-2013	Cystitis	N	UNRELATED	Unrelated*	*Symptoms occurred before treatment start date
AMP001- USA 39	(b) (6) 13-Jul-2012 28-Dec-2012	Pyelonephritis	Y	POSSIBLY RELATED	Related	Simultaneously treated for wound cellulitis
AMP001- RUS 33	(b) (6) 18-Jul-2012 27-May-2013	Cystitis	N	UNRELATED	Related	
AMP001- RUS 29	(b) (6) 31-Jul-2012 7-Aug-2013	Cystitis	N	UNRELATED	Related	
AMP002- USA 35	(b) (6) 9-Dec-2017 2-Jul-2018	Kidney infection	N	UNLIKELY	Related	
AMP002- USA 29	(b) (6) 4-Jan-2018 1-Feb-2018	Kidney infection	N	UNLIKELY	Related	
AMP002- USA 35	(b) (6) 5-Dec-2017 5-Jan-2018	Cystitis	Y	PROBABLE/ LIKELY	Related	Simultaneously treated for "vaginal mass"
AMP002- USA 30	(b) (6) 28-Dec-2017 16-May-2018	Kidney infection	N	POSSIBLE	Related	Narrative states "treated"

NDA 208352. AMP001 ADEX, AMP002 ADAE, ISS ADTEX. Clinical Reviewer Analysis.

Of the ten (10) subjects listed in Table 14, the Review Division determined nine (9) subjects had infections of the bladder or upper urinary tract that could be reasonably attributed to PHEXXI use. Three subjects had cystitis; 6 subjects had pyelonephritis. Subject AMP001- (b) (6) was diagnosed and treated for cystitis prior to the treatment start date. Therefore, the Review Division considers this event unrelated to PHEXXI use.

The Review Division requested additional details in an Information Request to further investigate the relationship between the timing of onset of urinary tract infections and the timing of last product use. However, the requested details were not provided in the Applicant's response. Based on treatment exposure data located in the submission, we conclude that these nine cases are related to product use.

Although post-coital urinary tract infections are common, regular use of spermicides is also an independent risk factor for urinary tract infections in reproductive-aged women (Scholes 2000, Hooton 1996). Additionally, the eligibility criteria specified that a current or history of recurrent urinary tract infection was exclusionary.

Because of the high number of cystitis and pyelonephritis cases and the use of an enriched trial population, the increased risk of urinary tract infections and pyelonephritis warrants a **Warning & Precaution** in prescription labeling. Women with a history of recurrent urinary tract infection or urinary tract abnormalities should avoid using PHEXXI.

The Applicant subsequently revised the frequency of cystitis and pyelonephritis to include all ten cases listed in Table 14. Product labeling reflects the Applicant's revision.

Drug Hypersensitivity:

Subject AMP001- (b) (6) was a 22-year-old yo Caucasian female enrolled at a Russian site in AMP001. On day 4 of study participation, the subject's case report form indicates an adverse event of "allergy" that was later recoded as "allergies due to [PHEXXI]." Per the CRF, the subject was treated with "chloropyramine 0.025 grams once a day" for 2 days. Additionally, the subject self-treated with "solcoseryl gel 5 grams twice a day topically to the vulva" for 5 days. The adverse event was assessed as "non-serious" and "moderate severity." The subject was discontinued from the study due to the adverse event.

Sufficient details are lacking regarding the nature and extent of the allergic reaction. Additional limited details describing the event were provided by the Applicant. This event is described in Section 6 [Adverse Reactions] of product labeling.

Treatment Emergent Adverse Events and Adverse Reactions

Overview of Adverse Reactions

Of the most frequently reported adverse reactions in women using PHEXXI, the vulvovaginal symptoms “burning sensation” and “pruritis” were commonly reported in both AMP001 and AMP002. **Table 15** lists adverse reactions occurring with a frequency $\geq 2\%$ in women using PHEXXI (excluding AMP001 Russian cohort).

Table 15. Frequency of Adverse Reactions in US Women Using PHEXXI ($\geq 2\%$)*

Preferred Term	Number of Subjects (n)	% of Total (N=2480) [†]
Vulvovaginal burning sensation	447	18.0
Vulvovaginal pruritus	359	14.5
Vulvovaginal mycotic infection**	226	9.1
Urinary tract infection [‡]	224	9.0
Vulvovaginal discomfort	224	9.0
Bacterial vaginosis	209	8.4
Vaginal discharge	137	5.5
Genital discomfort	102	4.1
Dysuria	76	3.1
Vulvovaginal pain	51	2.1

* Excludes Russian cohort of AMP001.

** Includes preferred terms vulvovaginal mycotic infection and vulvovaginal candidiasis.

[†] Safety population of all US sites (AMP001 US cohort + AMP002).

[‡] Includes preferred terms urinary tract infection, streptococcal urinary tract infection, Escherichia urinary tract infection, and urinary tract infection bacterial.

Source: NDA 208352. ISS ADAE. Clinical Reviewer Analysis.

AMP002

Study subjects in AMP002 most frequently reported vulvovaginal burning sensation (n=266, 19.9%) and vulvovaginal pruritis (n=149, 11.1%). Women using PHEXXI also reported ($\geq 2\%$): urinary tract infection, vulvovaginal pain, vulvovaginal mycotic infection, and bacterial vaginosis. **Table 16** lists adverse reaction frequencies among women using PHEXXI in AMP002.

Table 16. Frequency of Adverse Reactions in AMP002 ($\geq 2\%$)

Preferred Term	Number of Subjects (n)	% of Total (N=1330)
Vulvovaginal burning sensation	266	19.9
Vulvovaginal pruritus	149	11.1
Urinary tract infection*	76	5.7
Vulvovaginal pain	51	3.8
Vulvovaginal mycotic infection**	48	3.6
Bacterial vaginosis	37	2.8

* Includes preferred terms urinary tract infection, streptococcal urinary tract infection, Escherichia urinary tract infection, and urinary tract infection bacterial.

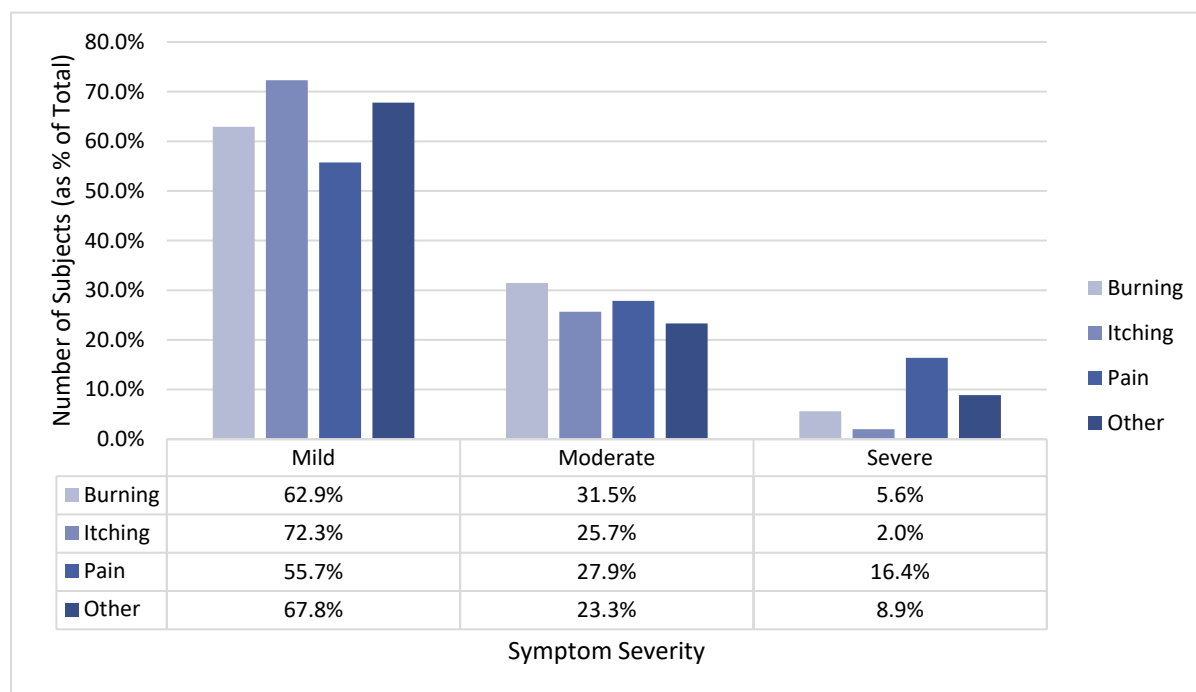
** Includes preferred terms vulvovaginal mycotic infection and vulvovaginal candidiasis.

Source: NDA 208352. AMP002 ADAE. Clinical Reviewer Analysis.

Genitourinary symptoms of interest were further characterized by timing of onset, severity, and duration. These symptoms included burning, itching, pain, and “other.”

Among women experiencing burning, itching, pain, or “other” symptoms, the majority were mild (grade 1) or moderate (grade 2) intensity as seen in **Figure 2**.

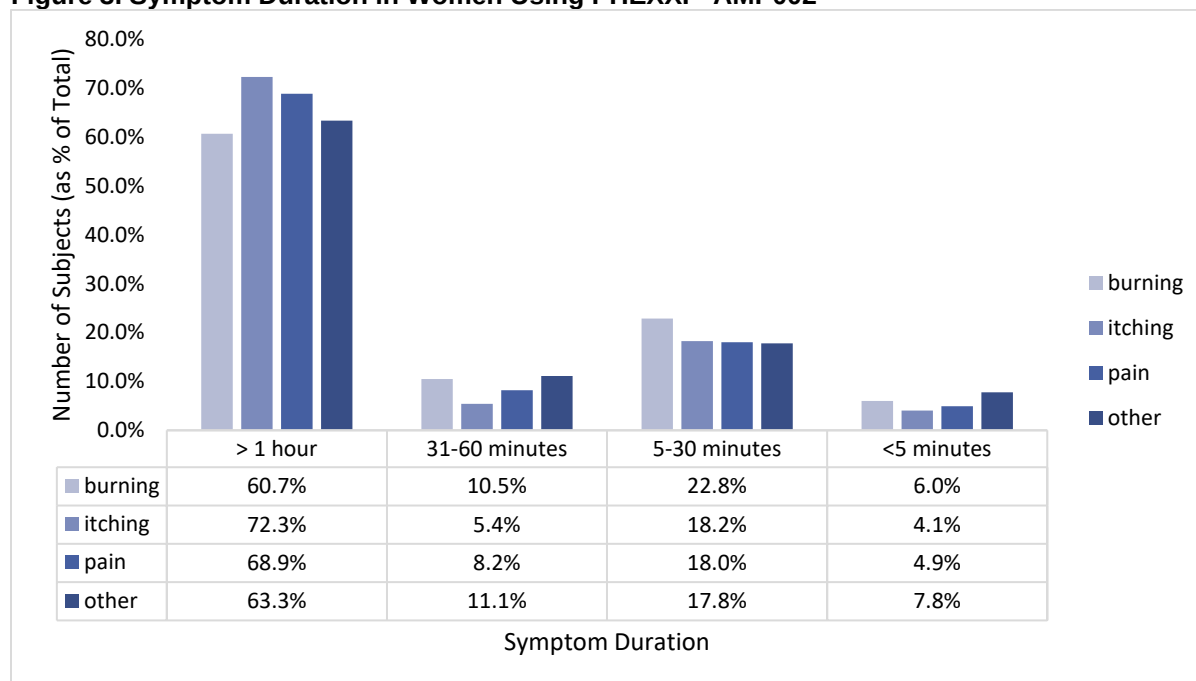
Figure 2. Symptom Severity in Women Using Phexxi - AMP002



Source: NDA 208352. AMP002 ADFA. Clinical Reviewer Analysis.

The vast majority of women reported symptoms lasting more than one hour, as shown in **Figure 3** below.

Figure 3. Symptom Duration in Women Using PHEXXI - AMP002



Source: NDA 208352. AMP002 ADFA. Clinical Reviewer Analysis.

Burning

The majority of women with burning symptoms reported mild (n=168, 62.9%) or moderate (n=84, 31.5%) intensity. Severe symptoms occurred infrequently (n=15, 5.6%). Onset typically occurred within 30 minutes of product use (<5 minutes [n=104, 39.0%]; 5-30 minutes [n=97, 36.3%]). The majority of women reported burning lasting more than one hour (n=162, 60.7%). Few women reported burning duration less than five minutes (n=16, 6.0%).

Itching

Nearly three-quarters of women with itching symptoms reported mild intensity (n=107, 72.3%) and duration greater than one hour (n=107, 72.3%). Only eight women (5.4%) reported itching less than five minutes duration. The majority of women reported symptom onset either within 30 minutes (n=78, 52.7%) or more than hour after (n=54, 36.5%) product use.

Pain

Slightly more than half of women with pain symptoms reported mild intensity (n= 34, 55.7%). The remainder reported moderate (n=17, 27.9%) or severe (n=10, 16.4%) intensity. Onset typically occurred within 30 minutes of product use (n=37, 60.7%). Nearly a third of subjects reported onset greater than one hour after product use (n=20, 32.8%). The majority experienced greater than one-hour duration (n=42, 68.9%), with only five subjects (8.2%) reporting symptoms subsided in less than five minutes.

Other

The majority of women experiencing “other” symptoms reported mild intensity (n=61, 67.8%) and greater than one-hour duration (n=57, 63.3%). Timing of onset varied in women with “other” symptoms. The majority of women reported onset occurring less than 30 minutes after product use (5-30 minutes [n=25, 27.8%]; < 5 minutes [n=22, 24.4%]). Slightly more than a third reported onset greater than one hour after product use (n=36, 40.0%).

In AMP002, product-related symptoms appear to be mild and self-limited. Although adverse event reporting generally followed the Agency’s advice, non-specific categories such as “pain” and “other” provide limited value in understanding the participants’ experience with the product. However, no additional safety concerns arise from these results.

AMP001

The most frequently reported adverse reactions in AMP001 included preferred terms associated with vulvovaginal complaints such as burning and itching, as well as vaginal infections. As previously discussed, inadequate adverse event data collection methods severely limits interpretability of adverse reaction frequencies in AMP001. Therefore, adverse reaction frequencies are only superficially presented here. **Table 17** lists the frequencies of adverse reactions (≥ 2%) in AMP001.

Table 17. Frequency of Adverse Reactions in AMP001 (≥ 2%)

Preferred Term	Number of Subjects (n)	% of Total (N=1465)
Vulvovaginal pruritus	229	15.6
Vulvovaginal discomfort	217	14.8
Vulvovaginal burning sensation	200	13.7
Vulvovaginal mycotic infection*	180	12.3
Bacterial vaginosis	173	11.8
Urinary tract infection	162	11.1
Vaginal discharge	121	8.3
Genital discomfort	102	7.0
Dysuria	70	4.8

*Includes preferred terms vulvovaginal mycotic infection and vulvovaginal candidiasis.

Source: NDA 208352, ISS ADAE – AMP001 subset, Clinical Reviewer Analysis

Table 18 and Table 19 list the **adverse reaction frequencies for the Russian and US cohorts of AMP001.**

Table 18. Frequency of Adverse Reactions in AMP001 - Russian Cohort

Preferred Term	Number of Subjects (n)	% of Total (N=324)
Vulvovaginal candidiasis	39	12.0
Vulvovaginal burning sensation	19	5.9
Vulvovaginal pruritus	19	5.9
Urinary tract infection	14	4.3
Vulvovaginal discomfort	11	3.4
Vaginal discharge	7	2.2

Source: NDA 208352, ISS ADAE – AMP001 subset, Clinical Reviewer Analysis.

Table 19. Frequency of Adverse Reactions in AMP001 - US Cohort

Preferred Term	Number of Subjects (n)	% of Total (N=1134)
Vulvovaginal pruritus	210	18.5
Vulvovaginal discomfort	206	18.2
Vulvovaginal burning sensation	181	16.0
Vulvovaginal mycotic infection*	178	15.7
Bacterial vaginosis	172	15.2
Urinary tract infection	148	13.1
Vaginal discharge	114	10.1
Genital discomfort	100	8.8
Dysuria	67	5.9
Vulvovaginal erythema	26	2.3

*Includes preferred terms vulvovaginal mycotic infection and vulvovaginal candidiasis.

Source: NDA 208352, ISS ADAE – AMP001 subset, Clinical Reviewer Analysis.

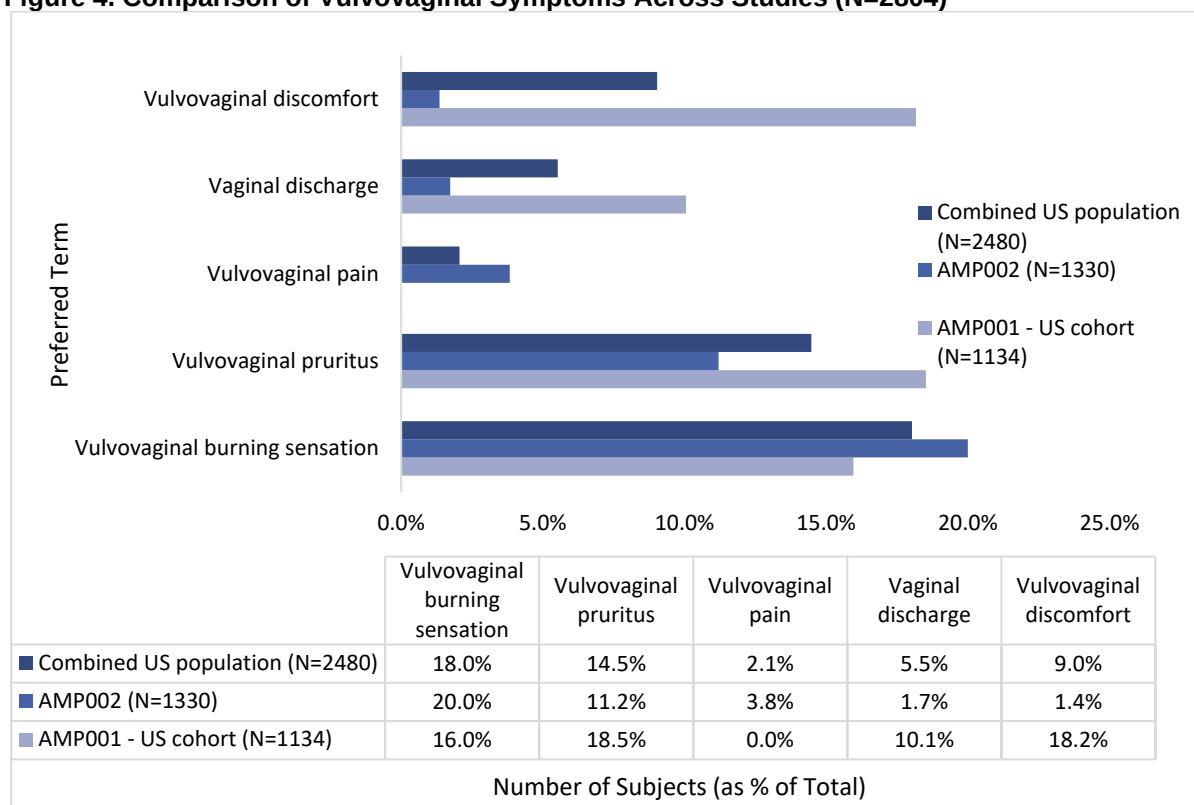
See NDA 208352 Primary Clinical Review dated May 2, 2016 for further discussion of AMP001.

Comparison of Adverse Reaction Frequencies Across Studies

Comparison of adverse reaction frequencies across studies reveals the impact of study design and methodology on adverse event data collection and analysis. Not only were genitourinary infections significantly over-reported in AMP001, other genitourinary adverse effects of interest were significantly under-reported.

Figure 4 illustrates the distribution of vulvovaginal symptoms between the US cohort of AMP001 and AMP002.

Figure 4. Comparison of Vulvovaginal Symptoms Across Studies (N=2804)

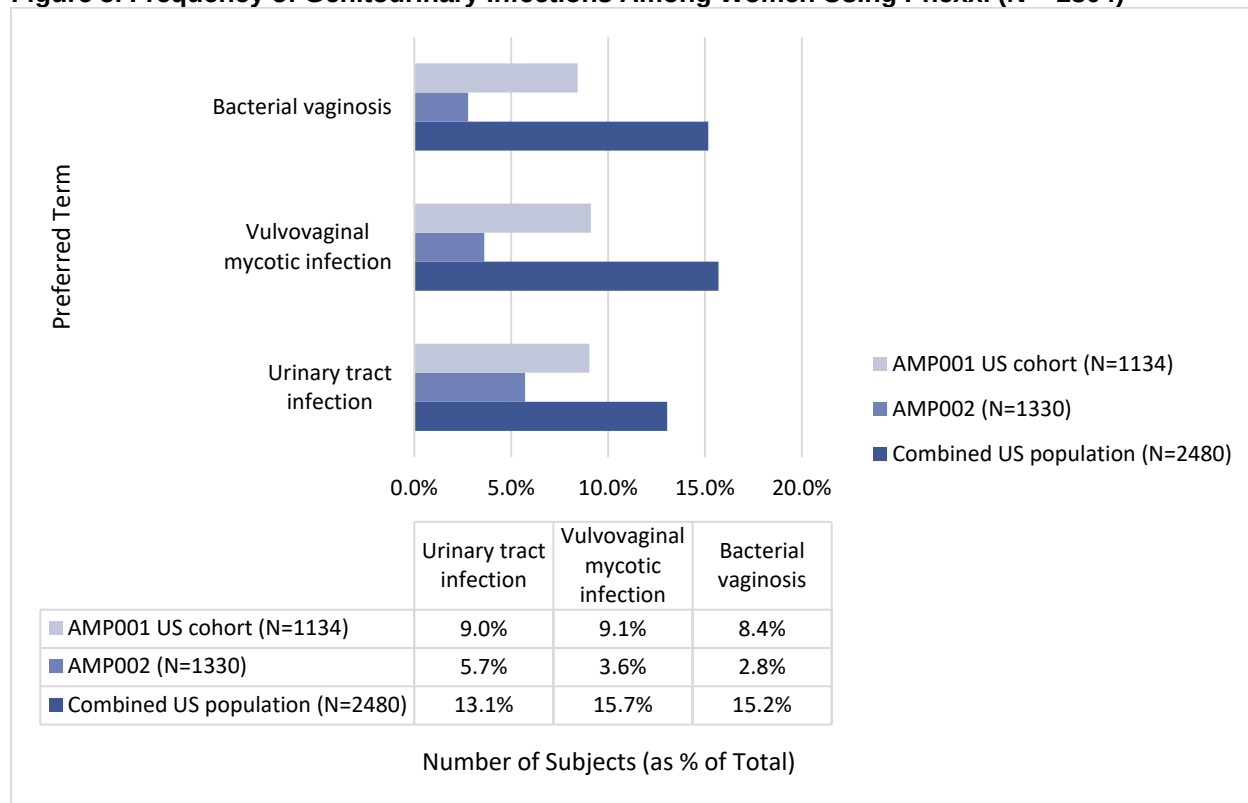


Source: NDA 208352. ISS ADAE. Clinical Reviewer Analysis.

There appears to be consistency with only a few common symptoms: both populations frequently reported vulvovaginal burning sensation and vulvovaginal pruritis.

The frequency of urinary and vaginal infections across studies also differs markedly, as illustrated in **Figure 5**. Differences in genitourinary infection assessments account for this disparity. Study personnel routinely sampled vaginal swabs at each follow-up visit in AMP001, whereas in AMP002, study personnel evaluated subjects for genitourinary infections only if symptomatic per FDA's advice.

Figure 5. Frequency of Genitourinary Infections Among Women Using Phexxi (N = 2804)



Source: NDA 208352. ISS ADAE, AMP001 ADAE, AMP002 ADAE. Clinical Reviewer Analysis.

Male Partner Symptoms

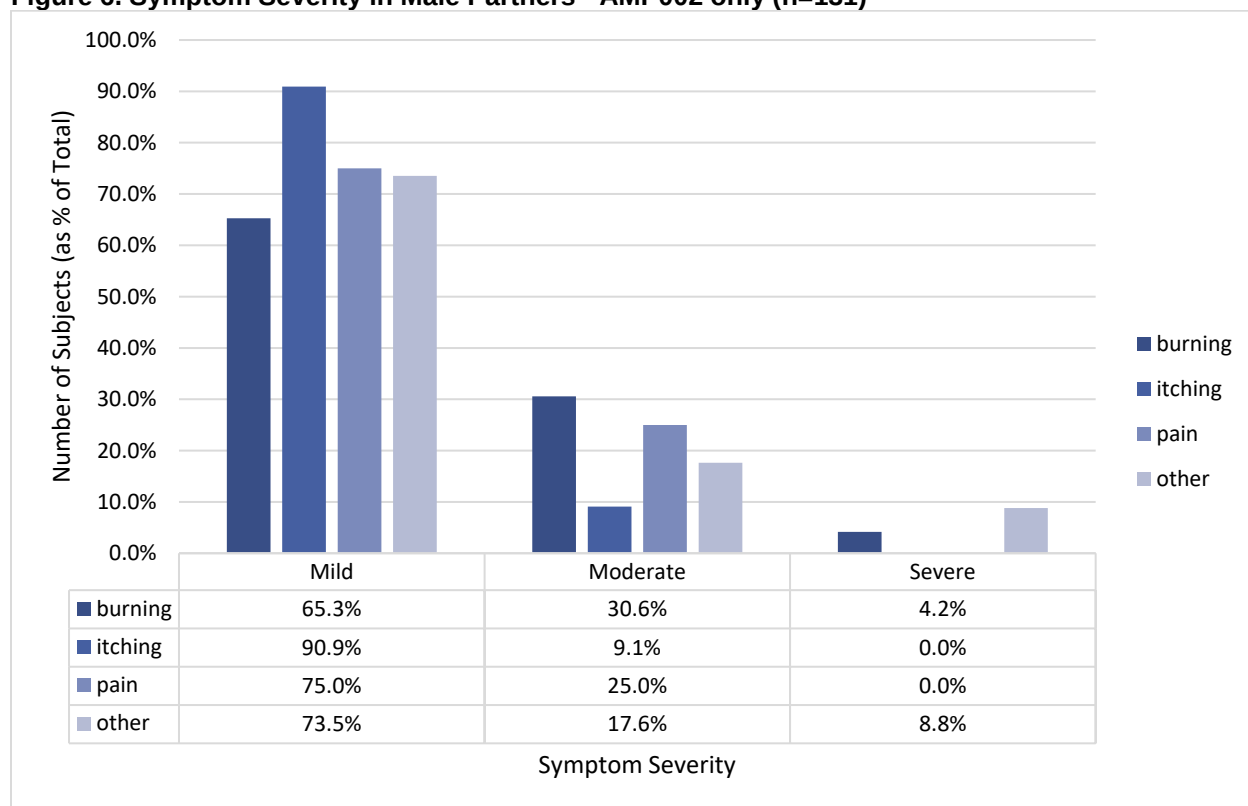
AMP002

Male partner symptom evaluation in AMP002 focused on adverse reactions of interest. Genitourinary symptoms of interest included: burning, itching, pain, and “other.” As with female study participants, further characterization of symptoms included timing of onset, severity, and duration. Study subjects reported adverse reactions experienced by their male partners in the eDiary.

A total of 131 of 1330 subjects (9.8%) reported male partner symptoms. Of these, 55.0% (n=72) reported burning, 33.6% (n=44) reported itching, 3.1 % (n=4) reported pain, and 26.0% reported “other” symptoms (n=34).

The majority of male partners reported mild symptoms, as seen in **Figure 6**.

Figure 6. Symptom Severity in Male Partners - AMP002 only (n=131)



Source: NDA 208352. AMP002 ADFA. Clinical Reviewer Analysis.

Burning

Approximately two-thirds of male partners with burning (n=47, 65.3%) reported mild symptoms, whereas nearly one-third (n=22, 30.6%) reported moderate intensity. Onset typically occurred within 30 minutes of product use (5-30 minutes [n=39 54.2%]; < 5 minutes [n=8; 11.1%]). Nearly one quarter of male partners reported onset greater than one hour after

product use (n=16, 22.2%). More than half of male partners reported duration less than 30 minutes (5-30 minutes [n=26, 36.1%]; <5 minutes [n=14, 19.4%]), whereas approximately one-third of male partners reported burning symptoms lasting more than one hour (n=27, 37.5%).

Itching

The majority of male partners with itching symptoms reported mild intensity (n=40, 90.9%). Most male partners experienced onset either within 30 minutes (n=17, 38.6%) or after one hour (n=18, 40.9%). Roughly two-thirds reported itching duration greater than one hour (n=28, 63.6%), whereas nearly one-third reported 5-30 minutes duration (n=14, 31.8%).

Pain

Of 4 male partners reporting pain, the majority reported mild intensity (n=3, 75.0%), onset within 30 minutes of product use (n=3, 75.0%), and duration greater than one hour (n=3, 75.0%).

Other

Nearly three-quarters of male partners with “other” symptoms reported mild intensity (n=25, 73.5%). Onset typically occurred within 30 minutes of product use (5-30 minutes [n=20, 58.8%]; <5 minutes [n=7, 20.6%]). Duration of symptoms varied. More than a third of male partners reported duration between 5 and 30 minutes (n=14, 41.2%); almost a third reported duration greater than one hour (n=11, 32.4%); and the remaining reported duration less than five minutes (n=9, 26.5%).

Overall, PHEXXI appears to be well-tolerated by male partners in AMP002. The majority of genitourinary symptoms experienced by male partners were mild and self-limited. As with the study participants’ adverse event reporting, the categories of “pain” and “other” are non-specific and fail to provide insight into bothersome symptoms other than “burning” and “itching.” Two subjects reported discontinuation of study product use due to partner symptoms.

AMP001

Male partner tolerability in AMP001 was described in detail by the primary clinical reviewer in the first review cycle. Female subjects were asked to enter male partner symptoms in the eDiary after Cycles 1, 3, and 7. Symptoms of “partner discomfort” were elicited with a “yes/no” response. Additional information regarding the nature of the discomfort (i.e. burning, itching, etc.), as well as timing of onset and duration of symptoms, were not elicited. Seven PHEXXI-treated subjects and seven nonoxynol-9 treated subjects discontinued study participation due to male partner symptoms.

The lack of interpretable data due to inadequate data collection methods and adverse event assessments was a review issue in the first review cycle. Therefore, the male partner tolerability assessment based on AMP001 has not been used to inform labeling.

Laboratory Findings

Safety laboratory values at baseline and end of study were similar. A contraceptive vaginal gel without systemic absorption would not be expected to affect serum laboratory parameters.

Vital Signs

Vital signs – including blood pressure and weight – at baseline and end of study were similar.

Electrocardiograms

Not applicable as PHEXXI is not systemically absorbed.

QT

Not applicable as PHEXXI is not systemically absorbed.

Immunogenicity

Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

Submission-specific safety issues were not identified during this review cycle.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

See Section 8.2.4 for analysis of safety.

8.2.8. Specific Safety Studies/Clinical Trials

Colposcopy Substudy

A colposcopy substudy in the Russian cohort of AMP001 evaluated the potential for cervicovaginal erosions with PHEXXI use. The primary clinical reviewer reviewed this study in detail in the first review cycle. The primary reviewer noted absence of lesions in two-thirds of participants.³ The number and severity of lesions did not differ between treatment arms (PHEXXI vs. nonoxynol-9). The highest number of lesions observed was “7-8” in a PHEXXI-treated subject. The correlation between number of cervicovaginal lesions and number of vaginal intercourse acts with study product use was not evaluated.

The lower than expected frequency of observed lesions in the nonoxynol-9 (a known vulvovaginal irritant) comparator arm raises concerns that vaginal irritation/inflammation was

³ Zopf, R. NDA 208352 Primary Clinical Review. May 2016.

under-reported in the AMP001 colposcopy substudy. Therefore, interpretation of this study's findings is limited. Results from this study were not used to inform labeling. However, no significant cervicovaginal findings were reported. A colposcopy substudy was not repeated in AMP002.

Male Subject Exposure in Phase 1 Trial

A randomized, double-blind, single-center phase 1 trial evaluated male tolerance of Phexxi under IND 109300. The results of this study were reviewed in detail by the primary clinical reviewer in the first review cycle.

In summary, two out of 24 subjects reported tingling and dryness associated with PHEXXI use compared to five out of 12 subjects reporting itching, tingling, burning and dryness in the comparator arm (an over-the-counter lubricant). On follow-up genital exam, two out of 24 PHEXXI users and one out of 11 comparator product users were found to have lesions on the penis. Both were small and painless and resolved spontaneously within 2 weeks.

The primary reviewer concluded that the safety and tolerability profile of Phexxi in male subjects was acceptable. Given the limited scope of this Phase 1 trial, results were not used to inform labeling. However, male partner tolerability incorporated in labeling was derived from AMP002. See Section 8.2.4 and 8.2.11 for further discussion and labeling recommendations.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable.

Human Reproduction and Pregnancy

PHEXXI is not expected to affect human reproduction. It is intended to immobilize sperm if intercourse occurs within one hour of product application. The sperm-immobilizing effects of PHEXXI are reversed after sperm are re-suspended in fresh medium in pre-clinical studies.⁴ Additionally, EVO-002 demonstrated that vaginal pH begins returning to baseline 12 hours after dose administration (see Section 8.1.1) and achieves baseline pH by Day 6 after a single use.⁵

Observational outcomes of on-treatment pregnancies indicate that PHEXXI does not increase the risk of congenital birth defects. A total of 112 pregnancies were reported in the safety population. Of these, 41 (36.6%) resulted in live birth, 27 (24.1%) ended by elective termination, and 19 (17.0%) ended in spontaneous abortion. Twenty-four (24, 21.4%)

⁴ NDA 208352, Module 2.6.2 Nonclinical Pharmacology Written Summary, eCTD SN:0034.

⁵ NDA 208352, Module 5.1. EVO-002 Study Report Body, eCTD SN: 0034.

pregnancies were lost to follow-up. One (0.9%) intrauterine death occurred as a result of uterine rupture. See Section 8.2.4 for a detailed discussion.

Of the pregnancies resulting in live-birth, the average birth weight was 3300 grams. One infant was born with Trisomy 21 and atrial septal defect. Maternal outcomes classified as serious adverse events included: preeclampsia (n=1); premature rupture of membranes (n=1); and placental abruption (n=1).

Pediatrics and Assessment of Effects on Growth

PHEXXI is not indicated for use in the pediatric and premenarcheal adolescent populations. The product is not anticipated to affect adolescent growth.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose and abuse potential are not anticipated with this product.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

PHEXXI is not currently marketed anywhere in the world.

Expectations on Safety in the Postmarket Setting

The safety profile of PHEXXI appears favorable overall. Adverse events in clinical trials were primarily due to irritation of the genitourinary tract. An increased risk of sexually transmitted diseases was not observed during AMP001 and AMP002. Significant safety concerns in the postmarketing environment are not anticipated.

8.2.11. Integrated Assessment of Safety

A total of 2804 women and their male partners participating in two clinical trials informs the overall safety profile of PHEXXI. As previously discussed, the study populations, trial design, and adverse event collection procedures differed significantly between AMP001 and AMP002. However, nearly 19,000 exposures across two 7-cycle studies and one 13-cycle extension provide sufficient information for overall safety conclusions. Key safety issues identified in the clinical program are highlighted below.

Cystitis and Pyelonephritis

Urinary tract infection, cystitis, and pyelonephritis occur frequently in the general population, particularly among reproductive-age women. Spermicide use is a known independent risk factor for lower and upper urinary tract infections in women; the intravaginal and on-demand application of PHEXXI increases the risk of introducing microbial pathogens into the genitourinary tract with each use.

The frequency of cystitis and pyelonephritis in an enriched study population – a history of

recurrent UTI was exclusionary - warrants a **Warning and Precaution** to mitigate risk. Therefore, women with a history of recurrent urinary tract infections or known urinary tract abnormalities should avoid PHEXXI use.

Genitourinary Adverse Reactions

Women using PHEXXI most frequently reported symptoms of vulvovaginal discomfort including vulvovaginal burning sensation and vulvovaginal pruritis. Poor data quality limits interpretation of AMP001 findings. However, the majority of women in AMP002 reported mild and self-limited symptoms that typically occurred within thirty minutes of product use and lasted more than one hour.

The colposcopy substudy provides limited information regarding the irritation potential of PHEXXI. The very low frequency of cervicovaginal lesions in both the PHEXXI- and nonoxynol-9-treated arms suggests PHEXXI's irritation potential may be underreported. Only one PHEXXI-treated subject had 7-8 lesions. It is unclear why nonoxynol-9-treated subjects did not have a higher frequency of irritation lesions. The relationship between number of lesions and number of acts of vaginal intercourse with product use has not been evaluated.

Conclusions regarding vulvovaginal safety in the clinical development program are also supported by nonclinical studies. A 10-day rabbit vaginal irritation study showed PHEXXI to be a mild vaginal irritant.

The totality of the evidence indicates that PHEXXI is at most a mild to moderate vulvovaginal irritant. While study methods and possible under-reporting limit interpretation of AMP001, the more robust methods for data collection in AMP002 provide interpretable information to inform labeling.

Male Partner Safety and Tolerability

Male partners of female subjects using PHEXXI in AMP002 most frequently reported mild burning and itching related to product use. The majority of male partners reported symptom onset within 30 minutes and duration less than 30 minutes.

Conclusions regarding male safety and tolerability are further supported by low discontinuation rates. Of 2804 subjects with male partners in the Phase 3 clinical trials, seven PHEXXI-treated subjects in AMP001 and two PHEXXI-treated subjects in AMP002 discontinued study participation due to male partner symptoms.

Interpretation of male partner safety and tolerability findings in AMP001 is limited by poor data quality and does not inform labeling. The finding of small self-limited penile lesions in two male subjects in the Phase 1 assessment did not give rise to additional concerns given the results were comparable to the over-the-counter lubricant-treated group. Therefore, AMP002 provides sufficient support for PHEXXI's overall safety and tolerability in male partners of women using

PHEXXI. AMP002 findings are the basis for labeling of genitourinary adverse reactions in male partners.

Drug Hypersensitivity

One subject experienced a local vulvovaginal hypersensitivity reaction attributable to PHEXXI during AMP001 according to the submitted case report forms and narrative. Additional limited details were provided. In the absence of additional details of the case, we are unable to determine if a single or multiple components of PHEXXI are implicated in the hypersensitivity reaction.

Integrated Assessment of Safety Conclusions

The totality of evidence throughout the clinical development program informs the overall safety profile of PHEXXI. Conclusions regarding important safety concerns – i.e. an increased risk of urinary tract infections, cystitis, and pyelonephritis, are based on significant findings in both Phase 3 trials – AMP001 and AMP002, and are addressed in labeling.

However, the second Phase 3 trial - AMP002 - provides the most robust assessment of adverse reactions experienced by users of PHEXXI and primarily informs labeling of adverse reactions. Based on these findings, PHEXXI appears to be, at most, a mild to moderate irritant of the genitourinary tract in women and their male partners. Overall, PHEXXI does not appear to pose serious safety risks to a healthy population.

8.3. Statistical Issues

One statistical issue was identified in the study. A menses CRF page to capture the start date of each menses was implemented in the study when about 96% of the subjects had finished the study treatment. The applicant clarified that the data recorded in this designated menses CRF page was from sources including e-diary, study specific source documents, and/or the patient medical record. This menses CRF page in EDC, as for all EDC pages, were 100% verified against source documents. The data clarification request process for e-diary corrections was stopped at the time of implementing the new menses CRF page. The e-diary data was not corrected after September 2018.

To compare the difference between the cycle information captured in the e-diary and the individual menses CRF page, the 7-cycle cumulative pregnancy rate based on e-diary only was estimated. Based on the e-diary, the 7-cycle cumulative pregnancy rate in the mITT population estimated by the Kaplan-Meier method is 14.5% (95% CI: 10.8%, 19.6%). When the menstrual cycle information on the designated menses CRF page is used, the 7-cycle cumulative pregnancy rate in the mITT population estimated by the Kaplan-Meier method is 13.7% (10.0%, 17.5%). The upper bound of the 95% confidence interval from both estimates are smaller than 21%. It demonstrated that the study results were not affected by the menstrual cycle information collected from the menses CRF page or the subjects' e-diary.

8.4. Conclusions and Recommendations

PHEXXI prevents pregnancy at a rate expected for a non-hormonal contraceptive vaginal gel. PHEXXI may cause some mild-to-moderate irritation of the genitourinary tract in women and some mild symptoms in male partners as well. In some women, PHEXXI may increase the risk of cystitis and pyelonephritis. PHEXXI's overall efficacy and safety profiles are acceptable with labeling recommendations to mitigate the risk of cystitis and pyelonephritis.

9 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting has not been requested by the Applicant or deemed necessary by the Division for this application.

10 Pediatrics

A partial waiver was granted for pediatric males age ≤ 17 years as well as for premenarcheal females. Therefore, pediatric trials were not conducted. The efficacy and safety profile are not expected to differ for postmenarcheal adolescent females. PHEXXI is not expected to affect adolescent growth. Therefore, efficacy and safety findings can be extrapolated to the adolescent postmenarcheal female population.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

A WARNING AND PRECAUTION (Section 5 of USPI) is recommended to mitigate the risk of cystitis and pyelonephritis in women who have a history of recurrent urinary tract infection or urinary tract abnormalities.

The potential for local hypersensitivity reactions is described in Section 6 – Adverse Reactions.

Other Prescription Drug Labeling

Section 14 describes the efficacy of PHEXXI as the agreed-upon primary endpoint of the 7-cycle cumulative pregnancy rate as determined by Kaplan-Meier life-table analysis. Efficacy is also described by the secondary endpoint of the Pearl Index: the number of pregnancies per woman-years of exposure.

Efficacy and safety considerations are described in the Patient Package Insert. The Review Division recommends a graphic to illustrate contraceptive efficacy.

Labeling discussions were held with the Applicant. The Review Division requested the following items:

1. The Limitations of Use statement must be added to the Highlights of Prescribing Information section.
2. The description of lactic acid must be “lactic acid” throughout the prescribing information per USP monograph. All instances of “L-lactic acid” must be removed.

In addition, the Sponsor provided updated numbers on the frequency of cystitis and revised the Pearl Index.

Labeling was agreed to by the Applicant and the Review Division.

12 Risk Evaluation and Mitigation Strategies

Risk evaluation and mitigation strategies are not necessary for this product.

13 Postmarketing Requirements and Commitment

Postmarketing requirements and commitments are not necessary for this product and there are no outstanding safety issues that need to be addressed.

14 Deputy Division Director Comments

I concur with the review team’s determination that PHEXXI should be approved.

15 Deputy Division Director (Clinical) Comments

I agree that adding another option represents a benefit for women of reproductive age seeking contraception. The agreed to labeling represents expected benefit and safe use information for providers and patients.

16 Appendices

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16.3. Financial Disclosure

In compliance with 21 CFR part 54, the Applicant certifies that no financial arrangements with the investigators have been entered into whereby the value of compensation to the investigator could be affected by the outcomes of the studies.

Covered Clinical Study (Name and/or Number): AMP002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>718</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>N/A</u> Significant payments of other sorts: <u>N/A</u> Proprietary interest in the product tested held by investigator: <u>N/A</u> Significant equity interest held by investigator in S Sponsor of covered study: <u>N/A</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

16.4. Nonclinical Pharmacology/Toxicology

No carcinogenicity studies were conducted with the combination gel.

16.5. OCP Appendices (Technical documents supporting OCP recommendations)

Study EVO-002

Title: A Randomized, Placebo-Controlled Pilot Study to Determine the Effect and Duration of Acidform Gel [PHEXXI] on Vaginal pH

Objective:

The primary objective of this study was to assess the change in vaginal pH from baseline to post-administration of either one dose of PHEXXI (3, 4, or 5 g), placebo, or no-treatment, and to measure the duration of this change in vaginal pH

Study Design:

This was a randomized, single-dose, open label study in 105 healthy women. During the study, the subjects were randomized in a 1:1:1:1:1 ratio to one of the five treatment groups (at least 20/treatment group): PHEXXI at 5 g dose (Group A), 4 g dose (Group B), 3 g dose (Group C), 4 g placebo gel (Group D), or no-treatment (Group E). A direct vaginal pH reading from each subject was obtained by research staff prior to the speculum examination, as well as 1 hour, and 6-hours post-treatment (Day 0). Direct vaginal readings taken at the 1 hour and 6-hours post-treatment time points were taken on specimens collected from 2 different positions in the vagina, to allow for potentially incomplete distribution of PHEXXI or placebo immediately following administration. At the 6-hour post-treatment time points, subjects were trained on self-collecting vaginal swabs and how to perform the vaginal pH test. At 12-hours post-treatment, whilst still in the domiciliary clinic, subjects performed the vaginal pH test themselves using self-obtained swabs and recorded their results for clinician review. Subjects measured their vaginal pH and carried out microbiome collection at 24 ($\pm$ 4) hour intervals for 5 days (Days 2 to 6) as outpatients and recorded the pH test results, any change in vaginal comfort, and confirmation of having taken the microbiome swab in the diary provided. On Day 7 ($\pm$ 24 hours), subjects returned to the clinic with their diary and swab transport containers. Clinic staff measured subjects' vaginal pH (See **Figure 9**). The primary efficacy endpoint was change in vaginal pH from baseline to post-administration of one dose of either PHEXXI gel (3, 4, or 5 g), placebo gel, or no-treatment, and the duration of this effect.

Study Results:

The ages of study subjects ranged from 28 to 32 years old. Five subjects discontinued the study, all from PHEXXI treatment groups: 3 subjects were lost to follow-up and 2 subjects discontinued because menses came on during the study. No subjects discontinued the study due to an AE or SAE.

PHEXXI lowered vaginal pH in a dose-dependent manner with the greatest reduction in mean vaginal pH from baseline seen with the highest (5 g) dose. The mean pH reduction from baseline in PHEXXI groups was all significantly greater than that seen with placebo or no-treatment group. Peak reduction occurred at 12-hours post-administration. Subjects in the PHEXXI treatment groups continued to have mean reduction in vaginal pH at Day 7 compared

to baseline (**Figure 7** and **Figure 8**). Sixty-eight subjects (64.8%) reported a TEAE, none of which were serious, severe, or life-threatening, and did not lead to study discontinuation. TEAEs ranged from 61.9% to 76.2% across the treatment groups, including PHEXXI or placebo groups, and was 47.6% in the no-treatment group.

Figure 7. Mean Vaginal pH at Each Assessment Time Point

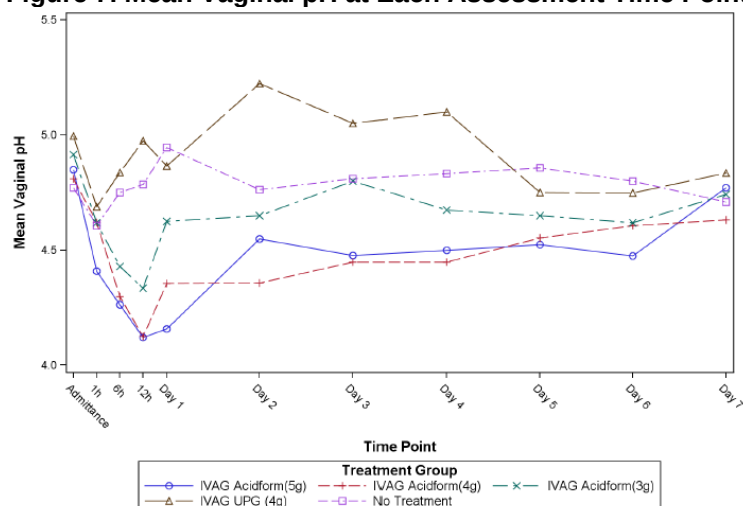
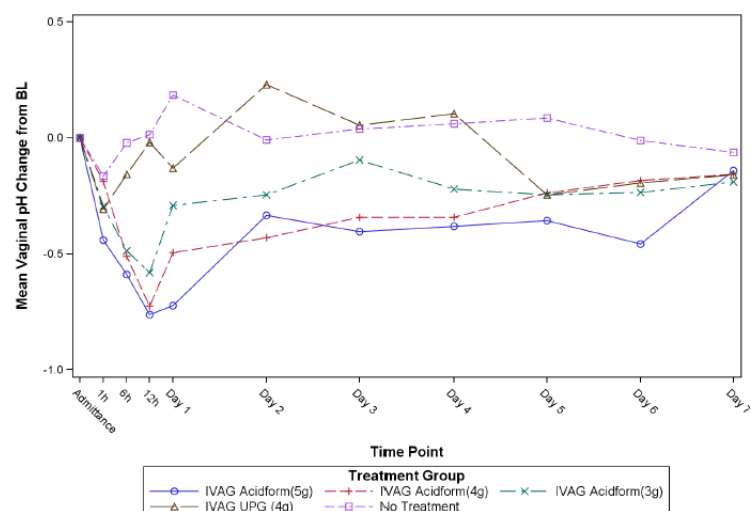


Figure 8. Mean Change from Baseline in Vaginal pH at Each Assessment Time Point



Conclusion:

Compared with placebo or no treatment groups, all PHEXXI treatment groups (3, 4 and 5 g gel) led to significantly greater reductions in vaginal pH with the greatest reduction in the highest PHEXXI dose group (5 g). Peak reduction occurred 12-hours post-administration. Subjects in the PHEXXI groups continued to have mean reduction in vaginal pH at Day 7 compared to baseline.

Reviewer's Comment:

The study design appears reasonable. We defer to the clinical reviewer Dr. Anandi Kotak for review on safety and pharmacodynamic related findings.

Study EFM-COOO 1-GMP0031. 00

Title: Evaluation of Buffering Capacity of Amphora Gel [PHEXXI] (Report: EFM-C0001-GMR0079.00)

Objective:

The primary objective of this study was to determine the buffering capacity and pH of [PHEXXI] when presented as an approximately dose-equal mixture with each of four over-the-counter vaginal products

Study Design:

Three doses (3 x 5 g) of each vaginal product (Miconazol vaginal cream, Metronizadole vaginal gel, RepHresh vaginal gel, and Tioconazole ointment.

Table 20) were mixed with three doses of PHEXXI (and a total of four doses of each, in the case of RepHresh vaginal gel). Each mixture was dispensed into a beaker and mixed for at least 5 minutes, so the mixture is uniform. The 4 vaginal product - PHEXXI mixtures were then incubated at $37 \pm 5^{\circ}\text{C}$ for 1 hour. pH measurements were made with a surface probe as directed under the method in EFM-C0001-GTM0002.01. Temperature measurements record the controlled gel temperature during the pH measurement. Total acid titer in PHEXXI mixed with the four vaginal products was determined by accurately weighing about 8 ± 0.1 g of gel mixture and analyzed using test method EFM-C0001-GTM0006 and each mixture measured in triplicate. Given the weight ratios of gel and the vaginal products in the mixture preparation, results for buffering capacity were determined based on the proportional contribution of only the PHEXXI.

Table 20. Tested Drug Products*

Test Article	Approximate Single Dose (g)	Manufacturer	Lot #	Condition	Expiration	Received CMR	Disposition CMR
Amphora™ Gel	5	Evofem	99000071	Ambient	NA	8348	10922
Monistat 7, Miconazole Nitrate Vaginal Cream (2%)	5	Insight Pharmaceutical	R29608	Ambient	10/17	10748	10922
Metronidazole Vaginal Gel, 0.75%	5	Prasco	GGET	Ambient	6/17	6424	10922
RepHresh Vaginal Gel Personal Lubricant	2	Lil Drug Store Products	UC5029	Ambient	2/18	8934	10922
Monistat 1-Day, Tioconazole Ointment 6.5% Vaginal Antifungal	4.6	Insight Pharmaceutical	GAT0418	Ambient	12/17	10817	10922

*Amphora Gel = PHEXXI

Study Results:

- pH of [PHEXXI]

The pH of [PHEXXI] mixed with one prescription and three over-the-counter vaginal products were determined and results are listed in **Table 21** to **Table 24**. The pH of [PHEXXI] at initial testing was reported as 3.5. Mixtures of PHEXXI with Miconazole nitrate vaginal cream, Metronidazole vaginal gel, RepHresh vaginal gel conform to the pH release specification of 3.3 to 3.9. Mixture with Tioconazole ointment resulted in a pH value of 4.

Table 21. pH of PHEXXI Mixed With Miconazole Nitrate Vaginal Cream (2%) (CPR11342 ADR BI)

# Replicate	Temp.Obs'd (°C)	pH Value
1	24.8	3.7
2	24.8	3.7
3	24.8	3.7
	Average	3.7
	% RSD	0.2

Table 22. pH of PHEXXI Mixed With Metronidazole Vaginal Gel (CPR11342 ADRBI)

# Replicate	Temp.Obs'd (°C)	pH Value
1	24.8	3.7
2	24.8	3.7
3	24.8	3.7
	Average	3.7
	% RSD	0.2

Table 23. pH of PHEXXI Mixed With RepHresh Vaginal Gel (CPR11342 ADR BI)

# Replicate	Temp.Obs'd (°C)	pH Value
1	24.8	3.6
2	24.8	3.6
3	24.8	3.6
	Average	3.6
	% RSD	0.2

Table 24. pH of PHEXXI Mixed With Tioconazole Ointment (CPR11342 ADR BI)

# Replicate	Temp.Obs'd (°C)	pH Value
1	24.7	4.0
2	24.7	4.0
3	24.7	4.0
	Average	4.0
	% RSD	0.0

2. Buffering Capacity (Acid Neutralization)

Tables 25 to Table 28 show the buffering capacity when PHEXXI was mixed with Miconazole vaginal cream, Metronizadole vaginal gel, RepHresh vaginal gel and Tioconazole Ointment. All mixtures demonstrated a similar or greater acid neutralization than PHEXXI which has a specification of 0.33 to 0.45 mEq/g.

Table 25. Buffering Capacity of PHEXXI Mixtures With Miconazole Nitrate Vaginal Cream (2%) (CPR11342 ADR CI)

# Replicate	Total Weight of Sample (g)	Amphora Weight, (g)	NaOH(0.5N), mL	Colorimetric mEq/g
1	7.9325	3.9636	3.66	0.46
2	7.9448	3.9698	3.74	0.47
3	7.9643	3.9795	3.86	0.48
			Average	0.47
			% RSD	2.5

Table 26. Buffering Capacity of PHEXXI Mixtures With Metronizadole Vaginal Gel (CPR11342 ADR CI)

# Replicate	Total Weight of Sample (g)	Amphora Weight, (g)	NaOH(0.5N), mL	Colorimetric mEq/g
1	7.9486	3.9746	5.52	0.69
2	7.9494	3.9750	5.30	0.67
3	7.9501	3.9753	5.34	0.67
			Average	0.68
			% RSD	2.2

Table 27. Buffering Capacity of PHEXXI Mixtures With RepHresh Vaginal Gel (CPR11342 ADR CI)

# Replicate	Total Weight of Sample (g)	Amphora Weight, (g)	NaOH(0.5N), mL	Colorimetric mEq/g
1	7.9138	5.6457	6.34	0.56
2	7.9293	5.6568	6.34	0.56
3	7.9154	5.6469	6.44	0.57
			Average	0.56
			% RSD	1.0

Table 28. Buffering Capacity of PHEXXI Mixtures With Tioconazole Ointment (CPR11342 ADR C4)

# Replicate	Total Weight of Sample (g)	Amphora Weight, (g)	NaOH(0.5N), mL	Colorimetric mEq/g
1	7.9283	4.1417	3.22	0.39
2	7.9669	4.1619	3.20	0.38
3	7.9997	4.1790	3.20	0.38
			Average	0.38
			% RSD	0.8

Conclusion:

No adverse impact on the pH and buffering capacity of [PHEXXI] was observed when mixed with various vaginal products under conditions similar to body temperature. Therefore, it is unlikely that these vaginal products can affect the performance of [PHEXXI] when used concomitantly.

Reviewer's Comments:

- In the Complete Response letter from the previous review cycle, the review team pointed out a design deficiency of a previously conducted in vitro study that had the same objective with this study, i.e., the test conditions in this study included temperature of ~25°C, and advised the Applicant to address the impact of temperature on the stated results and justify the applicability of the results to likely in vivo effects at body temperature. In the current review cycle, the Applicant re-conducted this in vitro study and evaluated the interaction at 37°C to simulate in vivo effects at body temperature.*
- Mixture of [PHEXXI] with Tioconazole ointment resulted in a pH value of 4. Although this value is slightly higher than the pH release specification of 3.3 to 3.9, the pH shift is not considered as significant considering the buffering capacity of the mixture was not affected.*

16.6. Additional Analyses

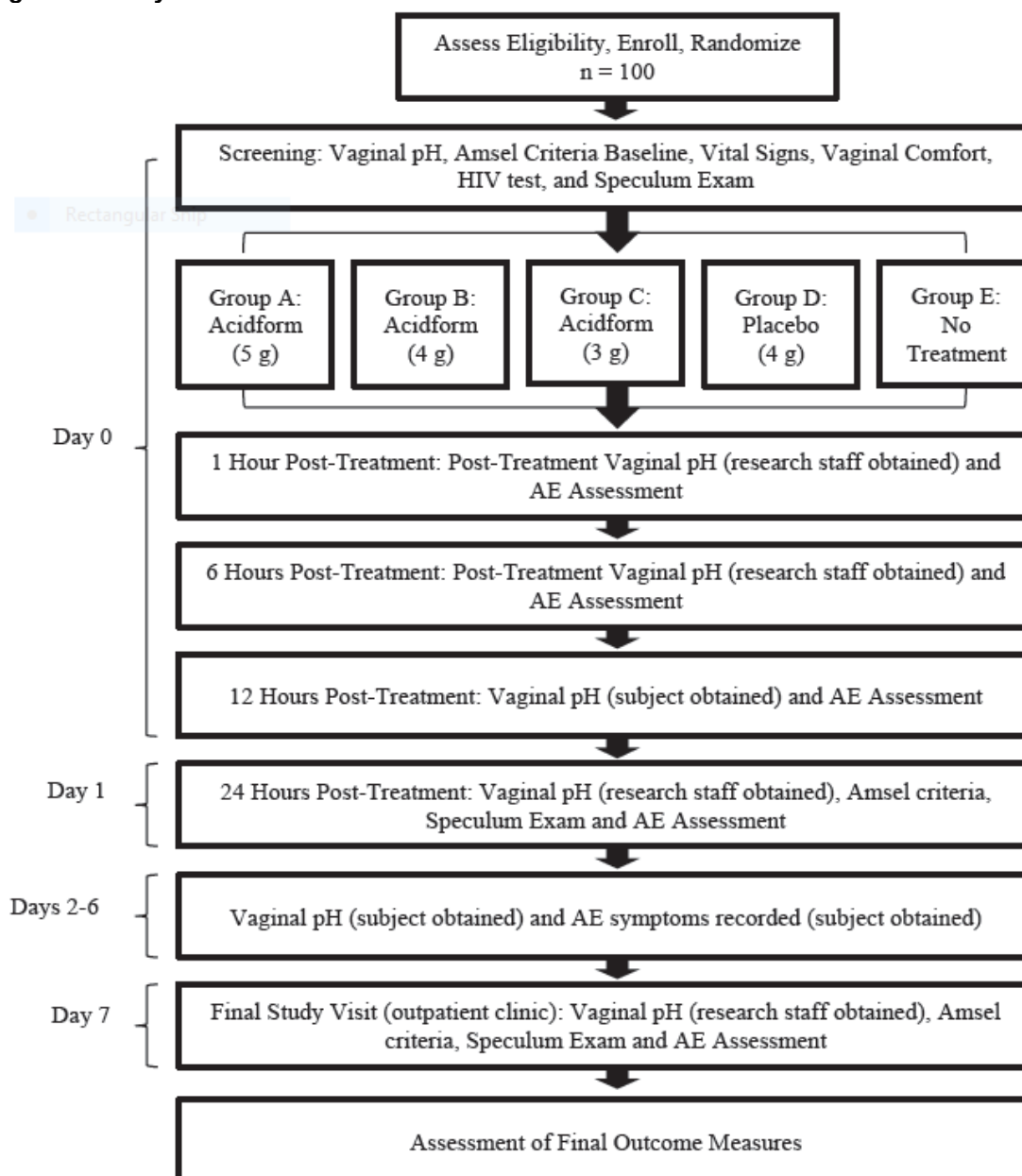
Table 29. Demographics and Baseline Characteristics (ITT Population)

Subject Characteristic	PHEXXI (N = 1384) n (%)
Age (years)	
Mean (SD)	27.7 (4.5)
Median	28
Min, Max	18, 35
Race	
White	955 (69.0)
Black or African American	348 (25.1)
Asian	35 (2.5)
American Indian or Alaska Native	6 (0.4)
Native Hawaiian or Pacific Islander	2 (0.1)
Other	38 (2.7)
Ethnicity	
Hispanic or Latino origin	571 (41.3)
Not Hispanic or Latino origin	805 (58.2)
Not Reported	8 (0.6)
BMI at Screening (kg/m ²)	
Mean (SD)	28.8 (8.1)
Median	27.09
Min, Max	13.2, 110.5

Source: Table 14.1.6 in Study AMP002 clinical study report.

16.7. EVO-002 Study Schematic and Flow⁶

Figure 9. Study Schematic/Flow



⁶ NDA 208352. EVO-002 Study Report Body, eCTD SN: 0034.

16.8. AMP 002 Schedule of Assessments

Table 30. AMP002 Schedule of Assessments

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

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

- a. The time period between Visit 2 and Visit 3 will vary based subject's first on-study cycle as defined in Figure 1.
- b. Treatment will end after seven study cycles. The cycle at enrollment will be included as one of the seven study cycles only if the time from enrollment to the start of the next menstrual period was ≥ 21 days.
- c. Includes documentation of the start date of last menstrual period.
- d. Height, weight, and blood pressure will be measured at Screening. Only weight and blood pressure will be measured at subsequent visits.
- e. Central laboratory will analyze CBC with differential, chemistry panels, and perform HIV test and chlamydia and gonorrhea assessments at Screening. Urine microscopy and culture and Pap tests will be performed locally.
- f. Physical examination to include assessment of heart, lungs, and abdomen, and a breast examination at the discretion of the Investigator.
- g. Gynecological examination is to include a speculum and bimanual examination. Investigators will note the presence or absence of vulvar, vaginal, or cervical findings, including epithelial disruption, or areas of obvious erythema; these will be assessed as either not present, mild, moderate, or severe; the presence or absence of bleeding, petechiae, or sloughing will also be recorded (Section 5.4.3). Clinically significant changes from Baseline as judged by the Investigator are to be reported as AEs. If a woman experiences any significant gynecological symptoms, she should return to the clinical site as soon as possible for a gynecological examination. Wet mount and vaginal pH for monilia, BV, and trichomonas will be performed only for symptomatic women.
- h. Results from a Pap test performed at the screening clinical site ≤ 12 months prior to the Screening Visit may be used provided the report is available.
- i. Chlamydia and gonorrhea assessments to be performed at Visits 3, 4, and 5 only if the subject indicates that she has changed sexual partners or is symptomatic. If the subject reports that her partner has been diagnosed or is being treated, she should be assessed/treated as per clinical site standard.
- j. In addition to the urine culture at Screening and Visit 5, subjects will be instructed to contact the clinical site to schedule a dipstick urinalysis and possibly a urine culture any time they suspect they may have a UTI.
- k. If dipstick urinalysis is 1+ for analytes of blood, leukocyte esterase, protein or nitrites, the urine should be sent for urine culture and microscopic urinalysis.
- l. Only to be performed if the subject presents to the clinical site with urinary symptoms. Dipstick urinalysis should be performed at any visit where a subject presents to the center with urinary symptoms.
- m. A urine pregnancy test should be administered any time a subject misses her period or suspects pregnancy. If a subject reports a positive home pregnancy test, a serum β -hCG should be performed.
- n. Subjects will record in their eDiary dates/times of gel use, dates/times of sexual activity, vaginal bleeding, and use of back-up contraception (including reasons for back-up contraception, if applicable). Additionally, subjects will record gel-related genitourinary side effects (vaginal itching, burning, or pain) and assess them as mild, moderate, or severe; these side effects and non-menstrual cycle vaginal spotting/bleeding will be analyzed as AEs. At each visit, Amphora and eDiary compliance data will be reviewed and subjects assessed for re-education. Between visits, sites and subjects will receive alerts if a subject has missed eDiary entries. Sites will record documentation of contact with the subject around eDiary compliance.
- o. Provide instructions on how to use the study drug at Enrollment Visit.
- p. Between-visit telephone contact is to include assessment of AEs, concomitant medications, sexual activity, use of backup contraception, compliance with use of the study drug and eDiary, need for an unscheduled visit, and confirmation of contact information.
- q. Includes confirmation of subject contact information. At the Enrollment Visit and each subsequent study visit/contact, the subject should be reminded to not have intercourse, use the study drug, or place anything in the vagina within 24 hours of the next scheduled visit to the clinical site.
- r. Perform Enrollment Visit upon verification that all eligibility criteria have been met.
- s. At Visit 4, the clinical site staff is to discuss post-treatment contraception with the subject, which would be started at completion of Cycle 7.
- t. The final visit to the clinical site will take place 14-30 days after the seventh study cycle or after the end of treatment if the subject discontinues treatment prematurely.

Source: NDA 208352, AMP002 Protocol and/or Amendment, Table 1, p13-14, eCTD SN: 0034.

16.9. Adjudicated Pregnancies

Table 31. Adjudicated Pregnancies

Subject ID Number	Date of Enrollment	Date of last product use	LMP	Estimated Date of Conception	On/Off Treatment Per Applicant	On/Off Treatment Per Medical Officer
(b) (6)	4-Oct-2017	14-May-2018	21-Apr-2018	6-May-2018	Not on-treatment+	On-treatment
	26-Oct-2017	21-Jun-2018	8-Jun-2018	18-Jun-2018	Not on-treatment+	On-treatment
	28-Nov-2017	20-Jun-2018	12-Jul-2018	27-Jul-2018	Not on-treatment+	On-treatment
	16-Oct-2017	9-Mar-2018	1-Mar-2018	18-Mar-2018	Not on treatment+	On-treatment
	14-Dec-2017	12-Jan-2018	30-Dec-2018	13-Jan-2018	Not pregnant+**	On-treatment
	9-Aug-2017	15-Oct-2017	22-Sep-2017	11-Oct-2017	On-treatment	On-treatment
	23-Aug-2017	9-Dec-2017	12-Oct-2017	30-Oct-2017	On-treatment	On-treatment
	25-Aug-2017	29-Dec-2017	25-Nov-2017	10-Dec-2017	On-treatment	On-treatment
	29-Aug-2017	28-Sep-2017	24-Aug-2017	1-Sep-2017	On-treatment	On-treatment
	30-Aug-2017	29-Jan-2018	11-Jan-2018	3-Dec-2017	On-treatment	On-treatment
	20-Nov-2017	25-Nov-2017	17-Nov-2017	1-Dec-2017	On-treatment	On-treatment
	13-Sep-2017	5-Feb-2018	4-Jan-2018	22-Jan-2018	On-treatment	On-treatment
	20-Sep-2017	19-Nov-2017	20-Oct-2017	11-Nov-2017	On-treatment	On-treatment
	25-Sep-2017	29-Sep-2017	30-Nov-2017	10-Dec-2017	On-treatment	On-treatment
	28-Sep-2017	9-Nov-2017	6-Oct-2017	1-Nov-2017	On-treatment	On-treatment
	29-Sep-2017	26-Jan-2018	28-Dec-2017	11-Jan-2018	On-treatment	On-treatment
	2-Oct-2017	28-Oct-2017	5-Oct-2017	18-Oct-2017	On-treatment	On-treatment
	3-Oct-2017	14-Feb-2018	20-Jan-2018	12-Feb-2018	On-treatment	On-treatment
	6-Oct-2017	17-Oct-2017	18-Sep-2017	9-Oct-2017	On-treatment	On-treatment
	9-Oct-2017	22-Feb-2018	20-Jan-2018	3-Feb-2018	On-treatment	On-treatment
	11-Oct-2017	14-Jan-2018	1-Dec-2017	4-Jan-2018	On-treatment	On-treatment
	12-Jan-2017	9-Mar-2018	21-Feb-2018	9-Mar-2018	On-treatment	On-treatment
	19-Oct-2017	13-Apr-2018	14-Mar-2018	28-Mar-2018	On-treatment	On-treatment
	19-Oct-2017	22-Apr-2018	14-Apr-2018	28-Apr-2018	On-treatment	On-treatment
	20-Oct-2017	30-Apr-2018	5-Apr-2018	11-Apr-2018	On-treatment	On-treatment

NDA/BLA Multi-disciplinary Review and Evaluation NDA 208352
Lactic acid, citric acid, and potassium bitartrate (PHEXXI)

Subject ID Number (b) (6)	Date of Enrollment	Date of last product use	LMP	Estimated Date of Conception	On/Off Treatment Per Applicant	On/Off Treatment Per Medical Officer
	20-Oct-2017	20-Feb-2018	30-Jan-2018	13-Feb-2018	On-treatment	On-treatment
	23-Oct-2017	31-Dec-2017	20-Dec-2017	4-Jan-2018	On-treatment	On-treatment
	23-Oct-2017	11-Feb-2018	2-Jan-2018	16-Jan-2018	On-treatment	On-treatment
	24-Oct-2017	4-Feb-2018	7-Jan-2018	15-Jan-2018	On-treatment	On-treatment
	27-Oct-2017	4-Feb-2018	14-Jan-2018	28-Jan-2018	On-treatment	On-treatment
	30-Oct-2017	8-Jun-2018	26-Apr-2018	24-May-2018	On-treatment	On-treatment
	1-Nov-2017	15-Feb-2018	11-Jan-2018	27-Jan-2018	On-treatment	On-treatment
	1-Nov-2017	24-Feb-2018	22-Jan-2018	9-Feb-2018	On-treatment	On-treatment
	1-Nov-2017	20-Dec-2017	1-Dec-2017	13-Dec-2017	On-treatment	On-treatment
	8-Nov-2017	7-Mar-2018	7-Dec-2017	21-Dec-2017	On-treatment	On-treatment
	8-Nov-2017	10-Jan-2018	24-Nov-2017	7-Feb-2018	On-treatment	On-treatment
	8-Nov-2017	4-Dec-2017	12-Nov-2017	5-Dec-2017	On-treatment	On-treatment
	8-Nov-2017	17-Mar-2018	19-Feb-2018	5-Mar-2018	On-treatment	On-treatment
	9-Nov-2017	6-Jan-2018	1-Dec-2017	20-Dec-2017	On-treatment	On-treatment
	13-Nov-2017	13-Jan-2018	18-Dec-2017	2-Jan-2018	On-treatment	On-treatment
	13-Nov-2017	6-Dec-2017	5-Nov-2017	19-Nov-2017	On-treatment	On-treatment
	14-Nov-2017	3-Feb-2018	5-Jan-2018	20-Jan-2018	On-treatment	On-treatment
	15-Nov-2017	3-Mar-2018	2-Feb-2018	16-Feb-2018	On-treatment	On-treatment
	15-Nov-2017	18-Dec-2017	17-Nov-2017	4-Dec-2017	On-treatment	On-treatment
	15-Nov-2017	5-Dec-2017	20-Nov-2017	2-Dec-2017	On-treatment	On-treatment
	16-Nov-2017	5-May-2018	5-Apr-2018	5-May-2018	On-treatment	On-treatment
	17-Nov-2017	1-Apr-2018	28-Feb-2018	11-Mar-2018	On-treatment	On-treatment
	20-Nov-2017	18-Dec-2017	2-Dec-2017	22-Nov-2017	On-treatment	On-treatment
	27-Nov-2017	9-May-2018	15-Apr-2018	3-May-2018	On-treatment	On-treatment
	27-Nov-2017	17-Jan-2018	24-Dec-2017	3-Jan-2018	On-treatment	On-treatment
	28-Nov-2017	10-Jan-2018	9-Dec-2017	19-Dec-2017	On-treatment	On-treatment
	29-Nov-2017	8-Apr-2018	Uncertain	26-Mar-2018	On-treatment	On-treatment

NDA/BLA Multi-disciplinary Review and Evaluation NDA 208352
Lactic acid, citric acid, and potassium bitartrate (PHEXXI)

Subject ID Number	Date of Enrollment	Date of last product use	LMP	Estimated Date of Conception	On/Off Treatment Per Applicant	On/Off Treatment Per Medical Officer
(b) (6)	29-Nov-2017	14-Feb-2018	29-Dec-2017	4-Jan-2018	On-treatment	On-treatment
	4-Dec-2017	21-Dec-2017	3-Dec-2017	17-Dec-2017	On-treatment	On-treatment
	5-Dec-2017	5-Jul-2018	6-Jun-2018	23-Jun-2018	On-treatment	On-treatment
	5-Dec-2017	4-Jan-2018	23-Nov-2017	7-Dec-2017	On-treatment	On-treatment
	8-Dec-2017	12-Jan-2018	17-Dec-2017	24-Dec-2017	On-treatment	On-treatment
	8-Dec-2017	17-Feb-2018	23-Jan-2018	4-Feb-2018	On-treatment	On-treatment
	12-Dec-2017	25-Apr-2018	29-Mar-2018	12-Apr-2018	On-treatment	On-treatment
	13-Dec-2017	27-Jan-2018	23-Dec-2017	20-Jan-2018	On-treatment	On-treatment
	15-Dec-2017	14-Jun-2018	6-May-2018	20-May-2018	On-treatment	On-treatment
	15-Dec-2017	2-May-2018	7-May-2018	23-Apr-2018	On-treatment	On-treatment
	20-Dec-2017	12-Jun-2018	8-May-2018	23-May-2018	On-treatment	On-treatment
	21-Dec-2017	30-Mar-2018	17-Mar-2018	1-Apr-2018	On-treatment	On-treatment
	27-Dec-2017	4-Jun-2018	21-Apr-2018	7-May-2018	On-treatment	On-treatment
	27-Dec-2017	31-Jan-2018	20-Jan-2018	20-Jan-2018	On-treatment	On-treatment
	2-Jan-2018	22-Jan-2018	21-Dec-2017	7-Jan-2018	On-treatment	On-treatment
	3-Jan-2018	6-Jan-2018	23-Apr-2018	14-May-2018	On-treatment	On-treatment
	3-Jan-2018	9-Feb-2018	6-Jan-2018	20-Jan-2018	On-treatment	On-treatment
	3-Jan-2018	21-Feb-2018	23-Jan-2018	5-Feb-2018	On-treatment	On-treatment
	4-Jan-2018	16-Feb-2018	25-Jan-2018	8-Feb-2018	On-treatment	On-treatment
	5-Jan-2018	15-Jul-2018	8-Jul-2018	7-Jun-2018	On-treatment	On-treatment
	9-Jan-2018	19-Mar-2018	24-Jan-2018	26-Feb-2018	On-treatment	On-treatment
	9-Jan-2018	28-Mar-2018	18-Feb-2018	9-Mar-2018	On-treatment	On-treatment
	10-Jan-2018	11-Apr-2018	12-Mar-2018	26-Mar-2018	On-treatment	On-treatment
	10-Jan-2018	17-Jun-2018	20-May-2018	4-Jun-2018	On-treatment	On-treatment
	12-Jan-2018	30-May-2018	27-Apr-2018	10-May-2018	On-treatment	On-treatment
	16-Jan-2018	26-Apr-2018	24-Mar-2018	8-Apr-2018	On-treatment	On-treatment
	17-Jan-2018	17-Mar-2018	13-Feb-2018	11-Mar-2018	On-treatment	On-treatment

NDA/BLA Multi-disciplinary Review and Evaluation NDA 208352
Lactic acid, citric acid, and potassium bitartrate (PHEXXI)

Subject ID Number	Date of Enrollment	Date of last product use	LMP	Estimated Date of Conception	On/Off Treatment Per Applicant	On/Off Treatment Per Medical Officer
(b) (6)	18-Jan-2018	30-Mar-2018	2-Mar-2018	15-Mar-2018	On-treatment	On-treatment
	19-Jan-2018	30-Mar-2018	1-Mar-2018	16-Mar-2018	On-treatment	On-treatment
	20-Jan-2018	26-Jul-2018	9-Jul-2018	17-Jul-2018	On-treatment	On-treatment
	25-Jan-2018	19-Feb-2018	12-Jan-2018	29-Jan-2018	On-treatment	On-treatment
	25-Jan-2018	16-Feb-2018	13-Jan-2018	26-Jan-2018	On-treatment	On-treatment
	25-Jan-2018	19-Feb-2018	14-Jan-2018	20-Feb-2018	On-treatment	On-treatment
	29-Jan-2018	27-Feb-2018	17-Jan-2018	1-Feb-2018	On-treatment	On-treatment
	29-Jan-2018	25-Jun-2018	22-May-2018	7-Jul-2018	On-treatment	On-treatment
	29-Jan-2018	26-Feb-2018	21-Aug-2018	8-Aug-2018	On-treatment	On-treatment
	30-Jan-2018	27-Mar-2018	20-Feb-2018	27-Mar-2018	On-treatment	On-treatment
	1-Feb-2018	11-Apr-2018	12-Mar-2018	26-Mar-2018	On-treatment	On-treatment
	1-Feb-2018	14-Apr-2018	1-Mar-2018	21-Mar-2018	On-treatment	On-treatment
	1-Feb-2018	24-Jul-2018	17-Jun-2018	28-Jun-2018	On-treatment	On-treatment
	1-Feb-2018	21-Jan-2018	11-Jun-2018	22-Jun-2018	On-treatment	On-treatment
	1-Feb-2018	23-Feb-2018	9-Feb-2018	18-Feb-2018	On-treatment	On-treatment
	2-Feb-2018	4-Mar-2018	2-Feb-2018	15-Feb-2018	On-treatment	On-treatment
	2-Feb-2018	20-Mar-2018	22-Mar-2018	4-Apr-2018	On-treatment	On-treatment
	5-Feb-2018	3-May-2018	6-Apr-2018	13-May-2018	On-treatment	On-treatment
	18-Oct-2017	15-Nov-2017	23-Oct-2017	6-Nov-2017	On-treatment	On-treatment
	23-Oct-2017	11-May-2018	12-May-2018	31-May-2018	On-treatment	On-treatment
	27-Dec-2017	5-Mar-2018	28-Jan-2018	14-Feb-2018	On-treatment	On-treatment
	19-Jan-2018	13-Jun-2018	14-May-2018	28-May-2018	On-treatment	On-treatment
	24-Jan-2018	2-Apr-2018	7-Mar-2018	21-Mar-2018	On-treatment	On-treatment
	29-Jan-2018	15-Feb-2018	30-Jan-2018	15-Feb-2018	On-treatment	On-treatment
	8-Jun-2018	24-Jun-2018	8-Jun-2018	23-Jun-2018	On-treatment*	On-treatment
	16-Jan-2018	30-Aug-2018	24-Sep-2018	1-Jul-2018	On-treatment*	On-treatment
	10-Jan-2018	13-Apr-2018	27-Feb-2018	13-Mar-2018	On-treatment*	On-treatment

NDA/BLA Multi-disciplinary Review and Evaluation NDA 208352
Lactic acid, citric acid, and potassium bitartrate (PHEXXI)

Subject ID Number	Date of Enrollment	Date of last product use	LMP	Estimated Date of Conception	On/Off Treatment Per Applicant	On/Off Treatment Per Medical Officer
(b) (6)	7-Nov-2017	7-Dec-2017	15-Dec-2017	28-Dec-2017	Not on-treatment	Not on-treatment
	29-Jan-2018	8-Feb-2018	8-Jan-2018	23-Jan-2018	Not on-treatment	Not on-treatment
	13-Sep-2017	21-Jan-2018	5-Feb-2018	22-Feb-2018	Not on-treatment	Not on-treatment
	21-Sep-2017	27-Sep-2017	4-Sep-2017	18-Sep-2017	Not on-treatment	Not on-treatment
	13-Nov-2017	10-Jan-2018	7-Feb-2018	22-Feb-2018	Not on-treatment	Not on-treatment
	29-Nov-2017	1-Aug-2018	29-Jun-2018	14-Aug-2018	Not on-treatment	Not on-treatment
	3-Jan-2018	24-Jan-2018	12-Dec-2017	26-Dec-2017	Not on-treatment	Not on-treatment
	5-Jan-2018	22-Jan-2018	17-Dec-2017	31-Dec-2017	Not on-treatment	Not on-treatment
	30-Jan-2018	2-Sep-2018	8-Sep-2018	22-Sep-2018	Not on-treatment	Not on-treatment
	25-Oct-2017	14-Jun-2018	15-Jun-2018	1-Jul-2018	Not on-treatment	Not on-treatment
	3-Feb-2018	25-Aug-2018	31-Aug-2018	n/a	Non-pregnant	Non-pregnant

+indicates pregnancies adjudicated as "On-treatment" by the Review Division; there was non-agreement between the Review Division and the Applicant.

*Indicates pregnancies that were adjudicated by the Pregnancy Review Committee as "insufficient information to adjudicate." Per the agreed upon Statistical Analysis Plan, these pregnancies are to be counted as "On-treatment."

**Indicates a pregnancy that was identified by positive pregnancy test in an Emergency Department per subject report. The Applicant identified this subject as "Not pregnant." The Review Division considers this pregnancy "On-treatment." This pregnancy has been included in the primary efficacy analysis.

Source: NDA 208352. AMP002 ADTTE, AMP002 ADTTE2, AMP002 Narratives, eCTD SN: 0034; AMP002 Applicant Response to Information Request received May 4, 2020, eCTD SN: 0049.

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/s/

GERALD D WILLETT
05/21/2020 05:33:18 PM

AUDREY L GASSMAN
05/22/2020 08:30:33 AM

Statistical Memorandum

NDA/BLA #: NDA 208352 Complete Response Resubmission
EDR \\Cdsesub1\evsprod\NDA208352\0034
Applicant: Evofem, Inc.
Drug Name: Amphora Vaginal Gel
Indications: Prevention of Pregnancy
Dates: Receive date: November 25, 2019
PDUFA date: May 25, 2020
Biometrics Division: Division of Biometrics 4
Statistical Reviewer: Weiya Zhang, Ph.D., DB 4
Concurring Reviewer: Mahbood Sobhan, Ph.D., Acting Statistical Team Leader, DB 3
Medical Division: Division of Bone, Reproductive and Urologic Products (DBRUP)
Clinical Team: Anandi Kotak, M.D., Medical Reviewer, DBRUP
Gerald Willett, M.D., Medical Reviewer Team Leader, DBRUP
Project Manager: Jennifer Dao, DBRUP

Evofem submitted the NDA 208352 Complete Response Resubmission on November 25, 2019. The original NDA was submitted on July 2, 2015. A complete response letter was issued on April 28, 2016. The major deficiency issues included marked disparities in pregnancy, discontinuation, loss to follow-up, and adverse event reporting rates between the US and Russian cohorts in the study, and inaccurate definition for on-treatment pregnancies and evaluable cycles used for the efficacy analysis. To address these deficiencies, Evofem conducted a six-month, single-arm, open-label study AMP002 to evaluate the pregnancy rate in women using Amphora. The following information requests pertaining the study AMP002 were sent to the applicant on January 24, 2020.

1. You stated in study AMP002 protocol Section 5.6 that subjects would keep a daily electronic Diary to record coital information, study drug use information, use of concomitant medications, including other vaginal products and other contraceptives, menses, and sign and symptoms data for subject or as presorted to her by her partner.
 - a. Please submit a copy of this electronic diary and the CRF page for this electronic diary, or indicate its location if submitted.
 - b. Clarify the source CRF pages (and associated annotations) for the information listed in the electronic Diary in the protocol Section 5.6 if this electronic Diary was not used during the study.
2. In the clinical study report for AMP002 Section 11.4.2.2, you stated that a new menses eCRF was added to collect the start date of menses during the study and these were used to define these were used to define the start of each cycle used in the efficacy analysis.

- a. Please clarify the reason that a new menses eCRF page was added during trial.
 - b. Provide a copy of this new CRF page.
 - c. Provide the annotation for this new eCRF page.
3. Clarify the source data for listing 16.2.5.1.
4. Your data definition file is not adequate to understand the study data. (a) For example, in the RP domain, the values for RPTTESTCD could be LMPDAT, LMPDAT, MADT1 – MADAT9, etc. it is not clear the source of these dates. Please provide details. (b) In the ADTTE dataset, the derivation for AVAL values for PARAMCD of PREG1 to PREG6 is not clear. Please provide the conception date and its source CRF page and derivation of AVAL values for PARAMCD of PREG1 to PREG6.
5. Submit the software programs used for the primary analyses and sensitivity analyses for the primary and secondary efficacy endpoints in study AMP002.
6. In the Section 4.7.2.1 of study AMP002 statistical analysis plan, one of the criteria to determine the evaluable cycles is “Cycles must start on or before date of last study product use +7 days.” Provide details on how this criterion was used to determine the evaluable cycles and whether this sentence indicates that you took the cycle end date as date of last study product use + 7 days.

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/s/

WEIYA ZHANG
02/03/2020 03:19:57 PM
Memo to complete response resubmission

MAHBOOB SOBHAN
02/03/2020 03:30:40 PM



Memorandum

**PHARMACOLOGY/TOXICOLOGY
MEMO**

Date:	April 1, 2019
IND or NDA #	NDA 208352; SDN 33, eCTD 0032; 3-8-2019
Sponsor:	Evoform Biosciences
Drug/Indication:	Amphora Vaginal Gel; Prevention of Pregnancy
Reviewer:	Kimberly Hatfield, PhD

Background:

Amphora is a non-hormonal, acid-buffering vaginal gel (pH 3.5) comprised of lactic acid (1.8%), citric acid (1%) and potassium bitartrate (0.4%), that is proposed for use in preventing pregnancy. The gel is provided in (b) (4) applicators pre-filled with 5 g Amphora gel (dose amount = 5 g). One applicator of the product is to be used immediately before or at any time up to 1 hour before each episode of vaginal intercourse.

The applicant, Evoform, first submitted this NDA on July 2, 2015 as a 505(b)(2) application, and received a Complete Response Letter on April 28, 2016. Approvability issues were noted by the applicant as including clinical efficacy analysis, drug substance manufacturing facility and select combination product deficiencies. The initial NDA pharmacology/toxicology review was conducted by Dr. Deepa Rao and was submitted 4/12/2016. Pharmacology/toxicology recommended approval 'based on the long history of use, common nature of the active ingredients, the lack of novel excipients, and lack of significant adverse events in nonclinical studies.'

The applicant has submitted a Type B Post-action meeting request to discuss questions related to the resubmission of NDA 208352, currently proposed for May/June 2019.

Summary of nonclinical data:

The applicant does not ask any specific nonclinical questions.

The applicant provides draft responses to their CR letter list of deficiencies. There were no CR letter deficiencies/comments provided by pharm/tox in the CR letter.

Outstanding Nonclinical Issue:

There are no outstanding nonclinical issues. Pharm/tox does not have any comments at this time for the applicant. Approvability of the resubmission will be dependent on review of any new data or information in the application.

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KIMBERLY P HATFIELD
05/02/2019 01:33:32 PM

MUKESH SUMMAN
05/03/2019 03:31:56 PM

Deputy Division Director Summary Review

Date	April 28, 2016
From	Audrey Gassman, MD
NDA #	208352
Applicant name	Evofem, Inc.
Date of submission	June 30, 2015
Date of submission receipt	July 2, 2015
PDUFA goal date	May 2, 2016
Proprietary name/established name	Amphora gel/lactic acid, citric acid, and potassium bitartrate gel
Dosage form/strengths/regimen	Vaginal gel/1.76% lactic acid, 1.0% citric acid and 0.4% potassium bitartrate in each 5 gram dose/supplied as 5 gram dose in pre-filled (b) (4) applicator used no earlier than 1 hour before each episode of vaginal intercourse
Proposed indication	Use for prevention of pregnancy
Action	Complete Response

Material reviewed/consulted	Names of discipline reviewers
Project Regulatory Manager/Chief Project Regulatory Manager	Charlene Williamson/Jennifer Mercier
CDTL	Lisa Soule, MD
Medical Officer Reviewer	Regina Zopf, MD
Statistical Review Team	Kate Dwyer PhD/Mahboob Sobhan PhD
Pharmacology/toxicology Review	Deepa Rao, DVM, PhD Kim Hatfield, PhD
Clinical Pharmacology Review	Myong Jin Kim
OPQ (CMC) Review Leads Drug Substance Drug Product Process Facility Biopharmaceutics	Mark Seggel, PhD Debasis Ghosh Sarah Ibrahim Kelly Forney-Stevens Tony Wilson Vidula Kolhatkar
Product Quality Microbiology	Yarery Smith
DMEPA	Danielle Harris, PharmD, BCPS/Denise Baugh, PharmD, BCPS
OPDP	Carrie Newcomer, PharmD
DMPP	Shawna Hutchins, MPH, BSN, RN Marcia Williams PhD LaShawn Griffiths, RN, MSHS-PH, BSN
OSI	Roy Blay, PhD Janice Pohlman, MD, MPH Kassa Ayalew MD, MPH
CDRH Biomedical Engineer	Veronica Price
CDRH Combination Product Lead	Lt Viky Verna
CDRH Division of Manufacturing and Quality Review	Jamie Kamon-Brancazio

OND=Office of New Drugs

CDTL=Cross-Discipline Team Leader

CMC = Chemistry, Manufacturing and Controls

OPQ = Office of Product Quality

OPDP= Office of Prescription Drug Promotion

DMPP=Division of Medical Policy Programs

DMEPA=Division of Medication Error Prevention and Analysis

OSI=Office of Scientific Investigations

CDRH= Center for Devices and Radiologic Health

1. Introduction
2. Background
3. CMC
4. Nonclinical Pharmacology/Toxicology
5. Clinical Pharmacology
6. Clinical Microbiology
7. Efficacy/Statistics
8. Safety
9. Advisory Committee Meeting
10. Pediatrics
11. Other Relevant Regulatory Issues
12. Labeling
13. Decision/Action/Risk Benefit Assessment

1. Introduction

The Applicant, Evofem, Inc., submitted an NDA 208352 on June 30, 2015 and received on July 2, 2015, to obtain marketing approval for a new prescription non-hormonal contraceptive gel that will be applied vaginally. The proposed indication for this contraceptive gel is prevention of pregnancy. For the purposes of this review, this new contraceptive gel will be referred to by the proposed tradename, Amphora.

This contraceptive gel contains lactic acid, citric acid and potassium bitartrate in a 5 gram single pre-filled applicator. The gel in each applicator contains approximately 88 mg lactic acid, 50 mg citric acid, and 20 mg potassium bitartrate. The gel is applied vaginally with the applicator each time before each act of vaginal intercourse. The gel will be available in two configurations: as individual pre-filled applicators with heat-sealed overwraps and (b) (4).

The proposed mechanism of action of Amphora gel is that it buffers the vaginal pH to remain acidic when semen is introduced. Normally, the presence of ejaculate increases the pH of the vagina which allows spermatozoa to survive. The presence of acidifying gel has been demonstrated in vitro to immobilize and/or kill spermatozoa. This mechanism of action prompted the Applicant to propose Amphora Gel for use as a spermicide, preventing conception.

Although there are no FDA-approved spermicidal gels, spermicide products have been developed and marketed under an over-the-counter (OTC) monograph process. The majority of these OTC products have the active ingredient nonoxonyl-9 (N-9). Formulations with N-9 include gels, creams, foam, suppositories and film. These products can be used alone, with a mechanical diaphragm or as back-up contraception when an immediate contraceptive product is needed. The mechanism of action for these N-9 products as contraceptive products are similar to Amphora gel as the product either mechanically blocks sperm from entering the reproductive tract.

Comment: Amphora gel is regulated as a combination drug-device product as the delivery system, an applicator, is considered a device. CDRH was consulted to evaluate the functionality of the applicator. CDRH's consult review is summarized in section 11 of this memo entitled, "Other Relevant Regulatory Issues".

The Sponsor was asked for a rationale for seeking approval of this product as prescription-only all other currently available spermicides in the US are over the counter (OTC). The Sponsor stated that spermicides have low utilization rates and that women are not particularly aware of/knowledgeable about this option. The Sponsor determined that the optimal path of introduction for this novel product to increase awareness would be through prescription that would involve an interaction with a healthcare provider.

Two previous OTC spermicide products have been evaluated through the NDA process for safety and efficacy: the Today Sponge (NDA 018683) and Delfen vaginal aerosol (NDA 014249). Both of these approved products have N-9 as the active ingredient. The Amphora gel product would be the first prescription spermicide product without N-9. My review summarizes the findings of efficacy and safety of Amphora gel and discusses benefit-balance of Amphora gel and my overall recommended regulatory action for this application.

2. Background

Amphora gel was originally developed under the name Acidform gel by the Program for the Topical Prevention of Conception and Disease (TOPCAD) (Chicago, IL) at Rush University, a university-based, not-for-profit organization. The original IND sponsor, the Contraceptive Research and Development group (CONRAD) initiated discussions of Amphora gel for the indication of prevention of pregnancy with the Division of Reproductive and Urologic Products (now, the Division of Bone, Reproductive, and Urologic Products) in 2002. At the time of opening the IND (IND 64623), the sponsor had conducted a phase 1 clinical trial overseas and nonclinical studies (a 10-day rabbit irritation study and two nonclinical studies with a prototype formulation). The sponsor proposed two phase 1 studies: a 14-day safety trial in women (A02-074) and a 7-day safety study in men (A02-076) to evaluate local tolerance. Both study protocols were reviewed and determined to be safe to proceed.

Acidform gel was subsequently cleared as a 510k device (K033776) in June 2004 under the tradename Instead Vaginal Lubricant. However, Acidform gel was never marketed as a lubricant in any country. Acidform gel was then licensed to the Applicant (Evofem) for commercialization as a spermicidal gel (tradename Amphora gel).

The Applicant initiated development of Amphora gel as a vaginal spermicide under IND 109,300. The formulation of Amphora gel is identical to that of Acidform gel studied by CONRAD under IND 64,623 (IND withdrawn in 2004) and also to that of Instead Intimate Lubricant (510K approved under K033776). The Applicant has received authorization from the original sponsor (CONRAD) to cross-reference the preclinical, manufacturing and clinical information from their withdrawn IND.

On October 18, 2010, the Division met with the Applicant for a Type B Pre-IND meeting to discuss development for Amphora gel as a contraceptive product. Responses were provided to the Applicant on issues related to Chemistry, Manufacturing and Controls (CMC), nonclinical and compatibility issues with condoms and diaphragms. The Division agreed that a single, pivotal, randomized non-inferiority trial with a comparator arm of an approved spermicide gel (with the active ingredient nonoxynol-9) would be acceptable. In addition, preliminary clinical advice was provided on the design and conduct of a phase 3 trial. At that meeting, the Applicant agreed to demonstrate an acceptable non-inferiority margin and to provide 5,000 cycles of exposure data to Amphora with 200 subjects completing a full year of treatment.

The Applicant submitted a complete phase 3 trial protocol for Trial AMP001 in February 2011. The Applicant supported their proposed phase 3 program with information from multiple previously completed clinical studies of Amphora. The submitted clinical studies included information from a phase 2 study that had been completed in South Africa. This South African study evaluated the safety and feasibility of Amphora compared to KY Jelly over a 6 month timeframe. The phase 3 protocol and supportive information was reviewed and determined to be safe to proceed. An Advice letter containing guidance on clinical, statistical and CMC issues was sent on August 2, 2011. This guidance included:

- At least 50% of data should be obtained from subjects at North American study sites
- Pregnancies that have an estimated date of conception (EDC) up to 7 days after the last recorded use of spermicide gel should be considered as on-treatment
- All pregnancies should be reported, regardless of whether or not they are believed to have occurred on-treatment, as the Division will independently make this determination in addition to the Sponsor's categorization

The Sponsor responded to some of the comments related to the protocol and a proposed non-inferiority margin and submitted Amendment 1 and 2 in February and July of 2012, respectively.

Comment: The Applicant did not submit a Statistical Analysis Plan for AMP001 for review by the FDA statistical team.

On December 9, 2014, a pre-NDA meeting was held with the Applicant to discuss the adequacy of the CMC, non-clinical and clinical development program. At this meeting, key issues related to stability of the product, the clinical results and the content and format of the NDA were discussed. At that meeting, the Applicant was also informed that they needed to perform a comprehensive use-related risk analysis to identify user-related risks associated with the proposed product as the applicator was considered a device. Additional comments from the Center for Devices and Radiologic Health (CDRH) on applicator stability, additional nonclinical testing of the applicator and additional requests for information that would be necessary for approval were sent on February 4, 2015.

The NDA application for Amphora gel was submitted on June 30, 2015 and received on July 2, 2015. After review of the clinical and statistical data, on March 23, 2016, DBRUP issued a “Deficiencies Preclude Discussion” letter notifying the applicant that significant deficiencies had been identified that preclude discussion of labeling and PMC/PMRs at this time. These deficiencies were related to conduct and analysis of the clinical Trial AMP001 (refer to 02/26/16 Memorandum to File). Additional discussions of efficacy and safety issues identified in this application are discussed in Section 7 and 8 of this review.

3. CMC - OPQ

Amphora gel is a drug product-device that consists of an acid-buffering gel with three active ingredients: lactic acid, citric acid, and potassium bitartrate. These agents act to maintain the low pH of the vagina. Inactive ingredients include two natural polymer thickeners (alginic acid and xanthan gum), a humectant (glycerin), a preservative (benzoic acid), and water. The device component is the (b) (4) applicator which will be supplied in two configurations for commercialization. The Applicant is proposing to market two configurations. The first configuration is as individual heat-sealed overwraps as single doses. (b) (4)

The three active drug substances in Amphora are USP/NF grade and the concentration of each substance is well within the limits used in other pharmaceutical products. The inactive ingredients alginic acid and xanthan gum were added to improve viscosity of the product. Glycerin provides lubrication to improve ease of application. Benzoic acid was added to provide an antimicrobial preservative in the product. The Applicant also provided information on product design, commercial formulation, dosage form, compatibility, specifications and overall control strategy of the drug product. The review teams evaluated these aspects of the drug substance and drug product as well as information on the container closure and stability of the drug product.

The Drug Process team identified eight deficiencies that will require additional information on the following: fill adjustments, release data for bulk drug product batches, compatibility of drug product with manufacturing equipment, information on bulk homogeneity and viscosity, adding an in-process control (b) (4)

As Amphora gel’s activity does not depend on release of active pharmaceutical ingredients in the drug product but on the overall buffering ability of the product, no Biopharmaceutics review was necessary for this application.

Comment: The formulation of Amphora gel has not changed since initial testing of the product by the original sponsor (CONRAD) in the 1990’s.

After review of the CMC information, the overall assessments by the OPQ review teams at the time of the first Quality Assessment review (overall recommendation dated April 11, 2016) included the following comments:

- Drug Substance – “From a standpoint of CMC (Drug Substance), the NDA is recommended for approval.”
- Drug Product – “This NDA is recommended for Approval from the Drug Product perspective.”
- Process – “Inadequate per process review – minor deficiencies (see deficiencies above).”
- Biopharmaceutics – “There are no biopharmaceutics data to review in this application.”
- Environmental Assessment – “The claimed categorical exclusion is sufficient to support approval of this NDA.”

The first Quality Assessment review included a brief summary of the CDRH-ODE review of the device components (pre-filled applicator and disposable applicator). A CDRH ODE review was necessary as the inclusion of applicators with Amphora gel reclassified the product as a Combination Product. The OPQ technical lead stated that the CDRH-ODE reviewer had identified deficiencies related to the characterization of these components (e.g., mechanical function and stability; biocompatibility). In addition, at the time of the first OPQ review, the OPQ technical lead stated that a recommendation regarding manufacturing facility CGMP status from the CDRH Facilities review team within the Office of Process and Facility was pending. The OPQ technical lead reported that a review addendum from CDRH Office of Process and Facilities would be filed when a final recommendation regarding facility acceptability was issued.

After assessing all of the outstanding deficiencies available at the time of the first OPQ Quality Assessment, the OPQ technical lead concluded in his April 11, 2016, review that, “In current form, this new drug application is not ready for approval.”

On April 25, 2016, Tony Wilson from the Office of Process and Facilities (OPF) summarized the final inspection results for this NDA and stated that, “...The inspection found significant quality and cGMP deficiencies. Therefore, this facility is not acceptable for the operations proposed in this NDA. OPF hence has issued an overall Withhold recommendation for this application...”

The OPQ technical lead added an addendum to the April 25, 2016 review and stated that, “A Complete Response for Evofem Inc.’s NDA 208352, Amphora (lactic acid, citric acid, and potassium bitartrate) Vaginal Gel, is recommended from the OPQ perspective, and in accordance with 21 CFR 314.125(b)(1), 21 CFR 314.125(b)(8) and 21 CFR 314.125(b)(13).”

No postmarketing commitments or requirements were recommended by the OPQ review teams.

Comments:

- *The Applicant will be informed that resolution of the deficiencies identified during inspection of the (b) (4) manufacturing facility will be required prior to Approval of Amphora gel.*

- *In addition, the Applicant will be informed of the deficiencies identified by the Center for Devices and Radiologic Health reviewer related to the applicators for use with Amphora gel (refer to section 11 for additional details).*

4. Nonclinical Pharmacology/Toxicology

There are no novel drug substances in Amphora gel. All of the active ingredients are common in food and/or endogenous pH buffering agents that are Generally Recognized As Safe (GRAS) with significant information on use as inactive ingredients in other FDA-approved products. No specific toxicokinetic studies were conducted as the product is not systemically absorbed. The nonclinical toxicology studies evaluated local tolerance.

No new nonclinical studies were submitted with the NDA. Three nonclinical studies that evaluated local tolerance (vaginal irritation) were previously evaluated under IND 64623, which the Applicant has obtained appropriate cross-reference from the previous sponsor. These nonclinical studies did not identify any concerning findings with Amphora gel. In addition, two toxicology studies conducted under 510(k) #033776 (Instead Vaginal Lubricant) were also submitted. These two studies were a penile and rectal irritation study, respectively. No concerning findings were identified in these studies.

After review of the submitted materials from the Applicant, the Pharmacology/Toxicology reviewer concluded in their April 12, 2016, review 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 nonclinical studies, Amphora gel appears to be reasonably safe for approval.”

Comment: I concur that the only outstanding issue for the Pharmacology/Toxicology team is labeling.

5. Clinical Pharmacology

No pharmacokinetic or clinical studies to evaluate systemic exposure were required as the efficacy of Amphora gel is solely dependent on local activity and not on absorption or metabolism of the active drug substances (lactic acid, citric acid, and potassium bitartrate) from the dosage form. In addition, no dedicated drug-drug interaction studies were conducted. The clinical pharmacology team concurred with the Applicant concluded that there was no clinical pharmacology studies that required review.

The Clinical Pharmacology CDTL, Dr. Myong Jin Kim, confirmed that no Clinical Pharmacology review was required in her review dated April 22, 2016, and stated that, “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.”

No postmarketing commitments or requirements were recommended by the Clinical Pharmacology review team.

Comment: During the review, the clinical review team identified that an in vitro study submitted to evaluate the interaction of Amphora gel with other commonly used vaginal products (Protocol EFM-COOO 1-GMP00 16.00) was conducted room temperature (25°C. This study did not identify any shifts in the pH of Amphora gel at room temperature, but the Applicant did not justify why testing at 25°C is relevant to clinical use. The Applicant will be asked to submit a justification for the applicability of these results and additional data on the interaction with commonly used vaginal preparations may be necessary.

6. Clinical Microbiology

Amphora gel is a non-sterile formulation for topical vaginal administration. As Amphora gel contains benzoic acid as an antimicrobial preservative, a clinical microbiologic review was requested by OPQ. The Applicant evaluated aerobic microbial count, total yeasts and mold count and tests for absence of indicator organisms including *Candida albicans*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*.

A review by the Product Quality Microbiology group was performed to evaluate the sterility and microbial attributes of the product. The Microbiology reviewer assessed the container closure system and microbial limits for the two commercial formulations as well as the microbial limits testing of stability batches. After her review, she provided her findings in the OPQ Quality Assessment Review on December 15, 2015, and stated that, “No microbiology deficiencies were identified based upon the information provided.”

No postmarketing requirements or postmarketing commitments related to product quality microbiology were recommended.

Comment: I concur with the Clinical Microbiology reviewer that from a quality microbiology standpoint, there are no outstanding issues.

7. Efficacy/Statistics

Contraceptive efficacy data for Amphora gel was obtained from one multicenter, open-label, randomized, comparator phase 3 clinical trial, Trial AMP001, entitled, “A Multicenter, Open-Label, Randomized Study of the Contraceptive Efficacy and Safety of Amphora™ Gel Compared to Conceptrol® Vaginal Gel.” The trial was conducted at the 62 study sites (49 in the US and 13 in Russia). The objective of the trial was to determine the contraceptive efficacy of Amphora gel compared to Conceptrol® Vaginal Gel containing N-9 as the active ingredient (hereafter referred to as N-9 gel) over 7 menstrual cycles (referred to as 7 cycles hereafter). Women treated with Amphora gel could continue using the product for up to 13 cycles in an open-label safety extension study.

Key entry criteria for Trial AMP001 included women ages 18-45 years who had a single male sex partner who had a regular normal cyclic menses of 21 to 40 days. Key exclusion criteria included allergy or sensitivity to spermicides or products containing N-9, three or more urinary tract infections (UTIs) in the year prior to screening, have a UTI or symptomatic bacterial or yeast vaginitis at entry, have a history of recurrent vaginal infections or disorders, or be pregnant, lactating or breastfeeding. In addition, women with an abnormal PAP with malignant cells could not participate and women with an abnormal PAP with evidence of disease including atypical glandular cells (AGUS) or high grade squamous intraepithelial lesion (HSIL) could not participate unless a colposcopy and/or treatment showed no evidence of disease. Notably, there were no exclusion criteria based on parity, weight or body mass index (BMI).

There were 5 scheduled study visits: screening (Visit 1), and two follow-up visits (Visits 3 and 7) at the end of the efficacy portion of the trial. Clinical evaluations, laboratory assessments and collection of adverse events and tolerance questionnaires were conducted at these visits. The treatment duration of evaluable cycles in the final protocol was 7 treatment cycles. On the 7th visit, those using Amphora gel that did not become pregnant were asked to participate in the safety extension study.

Women who met the enrollment criteria were randomized to receive single-use applicators of either:

- Amphora gel, 5 g doses containing citric acid, potassium bitartrate, and lactic acid or;
- N-9 (Conceptrol) gel containing 100 mg of N-9 (4% concentration) in 2.5 mL of gel.

Women were provided pregnancy kits, coital diaries, and test product and given instructions on how to use them. A total of 3,389 women were enrolled. A total of 3,324 subjects were randomized 1:1 to either Amphora gel or the comparator N-9 gel. All women who were randomized between the ages of 18 and 35 were designated the ITT population. Of the 3,324 women in the ITT population, 2,683 women were enrolled at US sites and 641 women at Russian sites.

Efficacy analysis for this study was based on a modified intent to treat population (MITT-FDA). This population consisted of subjects in the ITT population who were between ages 18 and 35 years who received at least one dose of study medication over the 7-cycle treatment period. In addition, these subjects had diaries that indicated they had a least one episode of coitus on Amphora gel or N-9 gel, did not use backup or emergency contraception and there was one report of pregnancy status. A total of 5,223 subjects were screened for the study, with 1,695 women who received Amphora gel and 1,694 women who received an N-9 gel. An overview of the disposition of subjects is provided in Table 1 below:

Table 1: Subject disposition by study arm and country*

	US Amphora gel N(%)	US N-9 gel N(%)	Russia Amphora gel N(%)	Russia N-9 gel N(%)
ITT	1,341	1,341	324	317
MITT-FDA	971	999	323	316
Completed 7-cycle (efficacy phase)	355 (37%)	401 (40%)	310 (96%)	307 (97%)
Pregnancy	136 (14%)	119 (12%)	9(3%)	4(1%)
Premature Discontinuation	480 (49%)	479(48%)	4(1%)	5(2%)
Reasons for discontinuation				
Loss to follow-up	180	165	0	0
Withdrew consent	101	114	1	0
Protocol violation	103	112	1	3
Not sexually active	22	15	2	0
Adverse event	18	19	0	0
Investigator/sponsor decision	17	19	0	0
No longer primary method	10	7	0	0
Other	29	28	0	2

*Source: Adapted from Table 12 of the clinical review dated April 26, 2016.

Comment: I concur with the CDTL's comment in her April 27, 2016 review that, "The loss of one-quarter of the ITT population from the efficacy population is very high and likely reflects poor study conduct or poor subject compliance with study instructions."

Subject disposition was similar when comparing treatment arms within each country, but significantly different when comparing US and Russian sites. US participants had a significantly higher discontinuation rate, pregnancy rate and lower completion rate as compared to Russian subjects. In addition, significant demographic differences were also identified as well. Among US participants, 54% were white, 35% black and 30% were Hispanic or Latino. In Russia, almost 100% were white. Finally, mean BMI in US subjects was greater than 29 kg/m as compared to 22 in Russian subjects. (For additional demographic data and differences, refer to Tables 3 and 4 of the Statistical Review dated April 18, 2016).

The clinical and statistical review teams evaluated these differences in demographics, baseline characteristics and discontinuation rates between the US and Russian sites. After review, the statistical reviewer stated that, "In the early review phase of this NDA, we also identified the cumulative pregnancy rates of the US and Russian population is dramatically different. In addition to pregnancy rates, these populations were also differed with regards to discontinuation rate, weight, and BMI. The concerns were communicated to the sponsor in the 74-Day Filing Review Issues letter. Although the Applicant provided response to these review issues, however, we believed that the Applicant did not provide adequate justification for the discrepancy in US versus Russian data to indicate that the Russian data is generalizable to the US population."

In her review dated April 26, 2016, the clinical reviewer concurred with the statistical reviewer that the Applicant had failed to justify the generalizability of the Russian data to the US population and stated, "...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."

For the purposes of efficacy determination, the clinical and statistical reviewers both concluded that the Russian data was not generalizable and therefore, could not be relied upon for the purposes of the efficacy analysis and drug approval.

Comment: Identified discrepancies between the data collected at US and Russia sites were not limited to the demographic and discontinuation rates. As examples identified by the clinical reviewer, intercourse rates occurred less than twice per cycle in 17% from both treatment arms from cycles at US sites as compared to 10% from both treatment arms from cycles in Russia as well as large differences in the number of protocol deviations at US sites as compared to Russian sites. These discrepancies further support the lack of generalizability of the data from Russian sites when compared to US sites and application of the findings to the population in the US that would be likely to use this product.

The clinical and statistical review team identified additional issues with the Applicant's efficacy database including inappropriate use of cycles from the extension phase of the phase 3 Trial AMP001. These cycles from the safety extension were being used to replace non-evaluable cycles in the phase 3 trial. Non-evaluable cycles were defined as cycles with no diary data, no intercourse, use of back-up or emergency contraception or alternative contraception and cycles of abnormal length (which are likely non-ovulatory cycles with no chance of conception). The clinical and statistical reviewers agreed that all of these cycles needed to be removed from the efficacy database.

In her review dated April 15, 2015, the statistical reviewer summarized the statistical issues with Trial AMP001 as follows:

1. "On-treatment pregnancy was not clearly defined. Per FDA, 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.
2. Primary endpoint is based on 6-month (183 days) cumulative pregnancy rate instead of 7-cycles (196 days) cumulative pregnancy rate as per Division's requirement in estimating 7-cycles cumulative pregnancy rate.
3. Regional heterogeneity in efficacy. Although the Division communicated this concern to the Applicant at the early review phase of this NDA, the Applicant has not provided adequate justification for the discrepancy in US versus Russian data to indicate that the Russian data are generalizable to the US population. There are extensive differences in demographic, discontinuation rate, and efficacy outcomes

- among US and Russian populations. Therefore, this reviewer concludes that the Russian data is not applicable to the US populations.
4. Use of cycles from the extension study window to replace non-evaluable cycles in the 7-cycle study that resulted in biased efficacy in favor of Amphora™ Gel. The CRF did not identify the subject's cycle number at the time of entering the extension study and the extension start date was a calculated post-hoc. Also the diary dataset did not flag the cycles collected in the extension part of the study. For the 7-cycle analysis, the "compressed cycle" was used by adding subsequent cycles to replace non-evaluable cycles up to cycle 17.
 5. Lengths of many cycles included in the original efficacy analysis fall outside of 21 to 40 days (expected normal menstrual cycle in a reproductive woman)."

Comment: I concur with the statistical reviewer that the Russian data was substantially discrepant compared to the US data and therefore not acceptable for the purposes of use for approval in the US. I also agree that use of cycles from the safety extension study to replace non-evaluable cycles during the 7-cycle study was not acceptable as this potentially biased the efficacy in favor of Amphora gel. In addition, non-evaluable cycles that have an abnormal length (outside of the 21-40 day timeframe) should be removed as it is unlikely pregnancy would occur in these cycles.

Efficacy Analysis: During a December 9, 2014 pre-NDA meeting, the Division reiterated that on-treatment pregnancies were any conception within 7 days of gel product use. The statistical reviewer noted that on-treatment pregnancy was not clearly defined in the dataset. The Division requested the Applicant use a standard definition for an on treatment pregnancy of 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. The Applicant revised the analysis using the Division's recommended definition of on-treatment pregnancies and created the dataset MITT7, which the FDA statistical and clinical reviewer used as the primary analysis population for Trial AMP001.

The MITT7 dataset was the primary efficacy dataset to calculate the incidence of pregnancy as assessed by cumulative percentage of typical-use 6 month pregnancies (183 days) using evaluable cycles. The primary analysis was a Kaplan-Meier estimation of six-month cumulative pregnancy probability in the MITT7 population by treatment group. The non-inferiority testing for the primary efficacy analysis tested a 95% confidence interval for the difference between treatment groups (Amphora gel versus the comparator N-9 gel). Non-inferiority between the two products would be demonstrated if the upper bound of the 95% confidence interval (CI) was $\leq 5.5\%$.

The statistical reviewer analyzed evaluable cycles from the US data using a 7-cycle (196 days) cumulative pregnancy rate using the MITT7 dataset. As previously mentioned above, the Russian data was not included in the final primary efficacy analysis because of the significant heterogeneity identified between the US and Russian data. The cumulative pregnancy rate for the US sites using the Kaplan-Meier estimation is outlined in Table 2:

Table 2: Cumulative Pregnancy Rate using dataset MITT7 in the US population*

	Amphora gel	N-9 Gel
Subjects at risk of pregnancy	971	999
On-treatment pregnancies	98	87
7-cycle cumulative pregnancy rate (196 days)	18.0%	14.1%
Treatment difference	3.9% (-1.1%, 8.9%)	
Evaluable cycles	3,232	3,229

*Adapted from Table 7 of the Statistical Review dated April 16, 2016.

Based on this analysis, the statistical reviewer concluded that Trial AMP001 demonstrated a non-inferiority margin with an upper bound of the 95% confidence interval that exceeded the pre-specified margin of 5.5%. Sensitivity analyses performed by the statistical reviewer also showed that the upper bound of the 95% CI exceeded the non-inferiority margin (Refer to Tables 9 and 10 in the Statistical review dated April 16, 2016. The statistical reviewer stated that, “The final results showed that there was substantial reduction in the evaluable cycle number (less than half of the pre-specified 7,000 cycles) in the primary efficacy analysis. Further, we confirm that the treatment difference in the US population is 3.9% with the upper bound of the 95% confidence interval more than 5.5%. Therefore, the study failed to demonstrate that Amphora™ Gel is non-inferior to Conceptrol® (N-9) Vaginal Gel.”

As the upper bound of the 95% CI exceeded the non-inferiority margin in the US population, the clinical and statistical reviewers concluded that Trial AMP001 failed to demonstrate that Amphora gel is non-inferior to the comparator N-9 vaginal gel.

In addition, the CDTL also noted an additional deficiency as follows, “The Applicant did not address the Division’s request to provide data on the timing of gel application relative to intercourse and to provide a sensitivity analysis stratified by time of application. Rather, the Applicant provided an analysis that looked at “dosing deviations;” however, the nature of these deviations was not described. Presumably they could have included either a prolonged interval between application and intercourse, or failure to repeat dosing before a subsequent act of intercourse.”

Comment: I concur with the CDTL that the lack of information on the acceptable timeframe required between gel application and intercourse is a significant concern. Without efficacy data on time intervals between application and intercourse, it is not possible to label what the appropriate timeframe should be. The Applicant will need to address this issue with additional clinical data.

Efficacy Summary:

The efficacy database for Amphora gel was reviewed by the clinical and statistical review teams. Both the statistical and clinical review teams determined that significant discrepancies between US and Russian data led to the conclusion that the data from Russia was not generalizable to the US population and therefore, only the US data was

included in primary analysis calculations. After removal of the Russian data, data from the extension cycles, and data from non-evaluable cycles, the primary analysis of the corrected dataset (MITT7) failed to meet the pre-specified non-inferiority margin and therefore, failed to demonstrate efficacy of Amphora Gel.

The statistical reviewer concluded the following, “Based on the corrected datasets, the results did not demonstrate that Amphora™ Gel was non-inferior to Conceptrol® Vaginal Gel in the US. From a statistical perspective, the information and data submitted by the Applicant with one controlled study do not provide evidence regarding the effectiveness of Amphora™ Gel, a nonhormonal vaginal contraceptive gel, indicated for use in the prevention of pregnancy in adults 18 years of age and older.”

The CDTL stated the following conclusions as her overall assessment of efficacy in her review dated April 27, 2016 that, “The contraceptive efficacy study conducted by the Applicant did not provide evidence of an acceptable level of efficacy for Amphora gel in the prevention of pregnancy. Based on the re-analysis deemed appropriate by the Division, the pre-specified non-inferiority margin was exceeded, suggesting that Amphora gel does not adequately preserve the treatment effect of N-9 spermicidal gel.”

I agree with the clinical and statistical review teams that efficacy was not established for Amphora gel and a new clinical trial will be necessary. In addition, I concur with the CDTL that the Applicant will need to provide data regarding the timing of gel application relative to intercourse to ensure that the study results are generalizable to actual use.

8. Safety

The clinical review team focused primarily on the safety database from the phase 3 Trial AMP001. The study enrolled healthy, sexually active women, 18 to 45 years of age, at risk of pregnancy who desired contraception with a single male sex partner. Women were randomized to receive Amphora gel or N-9 gel during the first 7 cycles of treatment. Women who were treated with Amphora gel and completed 7 cycles of treatment were eligible to receive up to 13 cycles of treatment in an extension study.

The safety database for Amphora gel is derived from phase 3 Trial AMP001 and consists of a total of 2,935 women, of which 1,458 women were treated for up to 7 cycles with Amphora gel and 1,477 were treated with N-9 gel. A total of 341 women who were treated with Amphora entered the safety extension phase for up to 13 total cycles. Additional safety data was collected in subsets of women who had colposcopies and women who had cultures for yeast and bacterial infections.

The clinical reviewer also evaluated supportive safety data from 10 submitted published studies for Acidform Gel that were conducted in the US and overseas. Nine (9) of the studies investigated the safety of the product following vaginal administration of the product for the purpose of reversible contraception, in some studies with the concomitant use of a female diaphragm. In these studies, the clinical reviewer identified 298 women

and 24 men who were exposed to the gel product (See clinical review, page 77 dated April 26, 2016).

Comment: The clinical reviewer evaluated the safety database from AMP001 reported with Amphora alone and also compared to N-9 gel. The other published studies were reviewed separately and a brief summary of the clinical reviewer's findings are outlined below.

Primary safety cohort (phase 3 Trial AMP001):

In the phase 3 Trial AMP001, a total of 1,458 women who were generally healthy, 18 to 45 years of age who requested intrauterine contraception were enrolled. The safety population for AMP001 included 1,135 women from US sites and 324 women from Russian sites. The Division and the Applicant had agreed that 5,000 cycles of safety data was necessary with at least half from US sites. As there were disparities when comparing data from Russian and US sites, only the data from the US was used in the safety analyses. In the completed trial, a total of 4,074 were obtained from US sites. Since the Division and the Applicant had agreed that 5,000 cycles were necessary, the clinical review team concluded that Trial AMP001 provided insufficient exposure in terms of cycle to Amphora for the purposes of complete safety analyses.

Comment: I concur with the CDTL that the overall safety database was inadequate in terms of total evaluable cycles to characterize the safety profile of Amphora gel for the proposed indication. As there were identified disparities between US and Russian safety data (as demonstrated by the reporting of only 1 SAE in Russia as compared to 29 SAEs in US sites) raises significant concerns of underreporting of adverse events at Russian sites and the non-generalizability of findings from the Russia data to a US population. Based on these concerns, the clinical review team focused their evaluation on the safety data obtained solely from US sites.

Deaths and Non-fatal Serious Adverse Events:

Deaths: No deaths were reported in the development program for Amphora gel.

Non-fatal Serious Adverse Events (SAEs): The clinical reviewer identified a total of 30 subjects reported an SAE. Of those subjects, 11 of 1,135 subjects treated with Amphora gel (0.8%) and 19 of 1,160 subjects treated with N-9 gel (1.3%) had an SAE. The most frequently occurring SAE was ectopic pregnancy, reported in 1 subject treated with Amphora gel (0.1%) and 3 subjects treated with N-9 gel.

Of the 30 subjects, the clinical reviewer identified two that were associated with use of Amphora gel. These two cases included one report of pyelonephritis (Subject (b) (6)) and one report of an anal abscess (Subject (b) (6)). After review of the SAE reports, the clinical reviewer concluded in her review dated April 26, 2016 that, "There was an extremely low rate of SAEs in all arms."

Comment: I concur with the clinical reviewer that the incidence of SAEs with Amphora gel was uncommon. Given the reduced number of cycles in women from US sites, it is unclear whether the SAEs in these two subjects represent a clinical difference or trend in an increased rate of serious infections between Amphora and the comparator N-9 gel. This potential difference will need to be evaluated in a follow-up clinical trial.

Discontinuations due to Adverse Events:

The clinical reviewer identified a total of 29 women who discontinued Amphora for an adverse event and 30 women who discontinued N-9 because of an adverse event and stated in her April 26, 2016 review that, “The total number of women who discontinued due to an AE was similar across treatment arms.”

The CDTL noted in her review dated April 27, 2016, that, “Overall, the types and frequency of AEs that led to premature discontinuation are consistent with those expected with a spermicide, and do not differ markedly between treatment arms.”

Comment: I concur that there were no significant safety issues or trends identified in the women who prematurely discontinued in the Amphora gel treatment group from Trial AMP001 because of an adverse event.

Common Adverse Events (AEs) in less than or equal to 2% of Subjects)

The most common adverse events reported in Trial AMP001 were yeast vaginitis, urinary tract infection (UTI), vulvovaginal discomfort and vulvovaginitis. The AEs were reported equally between treatment arms in the US (although the same events were reported in significantly lower rates in women at Russian sites). The clinical reviewer evaluated the most commonly reported AEs that were possibly drug-related. A synopsis of the results from US sites from her table is presented in Table 3 below:

Table 3: Common Adverse Events by Treatment Arm ($\geq 2\%$)*

Adverse Event	US Amphora gel (N=1,135)	US N-9 Gel (N=1,160)
Yeast vaginitis	14.6%	17.9%
Urinary tract infection	13.6%	20.3%
Vulvovaginitis	14.1%	17.3%
Vulvovaginal discomfort	8.2%	11.1%
Vaginal discharge	3.2%	4.0%
Urinary discomfort	1.6%	3.8%

*Source: Adapted from Table 25 of the clinical review dated April 26, 2016.

The clinical reviewer noted the following regarding the adverse events, “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.”

In evaluating the vulvovaginal symptoms, the clinical reviewer evaluated a discomfort questionnaire that evaluated symptoms of genitourinary discomfort after cycles 1, 3, 7 for both Amphora gel and N-9 gel as well as after cycles 10 and 13 in the extension study of Amphora gel. The clinical reviewer stated in her April 2016 review that in US participants, roughly one-third of women in both treatment arms (35.9% in the Amphora gel group and 33.9% in the N-9 gel group) reported some level of discomfort (Refer to the clinical review dated April 26, 2016, Table 26, page 86).

After review of the clinical adverse events, the clinical reviewer provided the following conclusions in her April 26, 2016 review regarding the safety data, “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.”

In her April 27, 2016 review, the CDTL agreed with the clinical reviewer’s assessment of the adverse events and stated that, “Overall, the rate and types of AEs are not unexpected for spermicidal gels.” The CDTL also concurred with the clinical reviewer that the failure of the Applicant to report AEs shortly after gel use likely resulted in under-reporting of genitourinary symptoms.

Comment: I agree with the clinical reviewer and CDTL that the safety database for AMP001 likely represents an under-reporting of symptoms of genitourinary discomfort, especially given the high rates of discontinuation, lack of collection of early adverse events and discomfort as identified when evaluating the Applicant’s discomfort questionnaire. In designing a new clinical trial, all symptoms that are reported from use of the product should be collected and reported.

Other Safety Evaluations:

1. Vital signs/laboratory testing (hematology/chemistry): The clinical reviewer evaluated changes in vital signs and laboratory values in Trial AMP001. She identified the following issue, “There were a large proportion of subjects that had no changes from baseline to end of treatment in systolic and diastolic blood pressure. The Applicant was queried about this lack of change in baseline and replied that,

“...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)).” Data integrity was also assessed by the Office of Scientific Investigation, who found no evidence of irregularities. The clinical reviewer evaluated the Applicant’s response regarding the lack of changes in blood pressure and concluded in her April 2016 review that, “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”.

No other safety signals or trends in reported vital signs or laboratory tests were reported by the clinical reviewer or CDTL.

Comment: Although there was initial concern from the clinical reviewer related to the lack of change in blood pressure readings at the Russian sites, after further evaluation by OSI and Applicant’s response, no data integrity issue was identified.

2. Partner tolerability was addressed through submission of a published study conducted under IND 109,300. This study evaluated 36 men for gel use over 7 days. All adverse events with Amphora gel were reported as mild and were related to topical application (tingling and dryness). After review of this published study, the clinical reviewer concluded in her April 26, 2016 review that, “The product safety and tolerability profile in male users is acceptable; however, the data are limited.”
3. Colposcopy was performed on a planned subset of women (74 subjects treated with Amphora gel and 70 in the N-9 group). Colposcopies were performed with investigators blinded to treatment assignment. Colposcopy was performed at baseline, after Cycles 1, 3, 7 and 10 and 13 in the extension subset. After review of the colposcopy data, the clinical reviewer concluded that, “Approximately two-thirds of participants observed in the colposcopy study did not have any lesions. Amphora appears no more or less irritating to the cervicovaginal area than N-9 gel”.
4. Quantitative cultures for bacterial and yeast vaginitis were obtained in a subset of 79 women treated with Amphora gel and 79 treated with N-9 gel. The results were evaluated by the clinical reviewer. She concluded in her April 26, 2016 review that, “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.”
5. Condom compatibility studies were requested by the CDRH review, Mechanical testing results were submitted to evaluate condoms and female diaphragms in the presence of Amphora gel. The Applicant also submitted published literature on the use of Amphora gel with use of a diaphragm as compared to placebo gel. The CDRH

reviewer evaluated the data and concluded in her review (refer to consult dated March 21, 2016, that:

- a. Condom compatibility: “CDRH accepts a <10% difference as supporting compatibility; therefore, the data provided supports the compatibility of the gel with polyisoprene condoms.”
- b. Diaphragm compatibility: “...The data provided supports the compatibility of the gel with vaginal diaphragms.”

The clinical reviewer concurred with the CDRH reviewer and stated in her April 26, 2016 review that, “Use of condoms and diaphragms is compatible with Amphora gel.”

- A 4-month safety update was submitted by the Applicant on September 2, 2015. No new relevant literature was identified by the Applicant. As safety outcome data was not collected on a large proportion of participants due to loss to follow-up, the safety update contained limited follow-up pregnancy and infant outcomes and included only follow-up on 66% of live births to Amphora exposed women. After evaluation, the clinical reviewer concluded in her April 26, 2016 review that, “The safety information gathered over this reporting period (during the 4-month safety update) from participants who participated in AMP001 does not raise any new safety signals.” In her review dated April 27, 2016, the CDTL concurred that, “...no new safety signals were identified in the Safety Update.”

Comments:

- *The CDTL evaluated the clinical reviewer’s submission-specific safety issues and concurred with her findings. I also concur with the clinical reviewer and CDTL that there were no significant safety signals or trends identified from the vital sign and laboratory data from Trial AMP001, subset safety studies from AMP001 or from review of the external publications submitted to support partner tolerability. In addition, no concerns were raised by the CDRH and clinical reviewers regarding condom or diaphragm integrity that would require additional safety data.*
- *Of note, as Amphora gel has not been marketed as a spermicide or as a lubricant in any country to date, no postmarketing safety data was available for review this cycle.*

Safety Summary:

The clinical reviewer determined that the safety database for Amphora gel did not identify a significant safety issue that would preclude approval. The clinical review summarized her conclusions regarding the safety of Amphora gel in her review dated April 26, 2016 and stated, “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.”

The Cross-Discipline Team Leader (CDTL) concurred with the primary Medical Officer's assessment of the inadequacy of the overall safety database for Amphora gel in her CDTL review dated April 26, 2016 and stated that, "The overall safety findings for Amphora gel are reassuring, as would be expected for a nonsystemic and non-hormonal contraceptive method. The major concerns limiting the interpretability of the safety data are:

- The Applicant's decision not to consider as AEs any reports of mild genitourinary symptoms associated with product use that lasted no more than one hour.
- The discrepancies in the reporting of AEs between the US and the Russian populations."

The CDTL also commented on the safety data from Russian sites as follows, "As with the efficacy data, the much lower reporting rates for AEs noted in the Russian population raises questions about the generalizability of Russian data to the US target population. With the Division's decision not to rely upon Russian data in support of either efficacy or safety, the Applicant did not obtain the requested number of cycles of exposure to Amphora gel, making the safety assessment inadequate".

No postmarketing requirements or postmarketing commitments related to safety were recommended by the CDTL.

I concur with the CDTL that the safety database for Amphora gel from AMP001 is inadequate to support approval. I agree with the CDTL that Trial AMP001 had an inadequate collection of data immediately post-use, a high discontinuation rate and the significant discrepancy between the US and Russian safety data that precluded use of Russian data in the safety assessment. Based on these considerations, the Applicant needs to provide additional safety data and provide a complete safety profile for Amphora.

9. Advisory Committee Meeting

Spermicides to prevent pregnancy have been used in the United States for many years. No unique efficacy or safety issues were identified in this application that required expert input. Therefore, no Advisory Committee advice was necessary to make a regulatory determination on this application.

10. Pediatrics

On December 22, 2015, the Applicant requested a waiver of pediatric studies required by the Pediatric Research Equity Act (PREA). Although the submission contained a rationale for the waiver, it was found incomplete as it did not contain the required initial pediatric study plan (iPSP). The Sponsor was contacted by phone on January 22, 2015, and informed that their submission was incomplete. The Applicant then submitted their iPSP on January 30, 2015 with a request for a full waiver of pediatric studies.

The Division reviewed the iPSP in consultation with the Pediatric Review Committee (PeRC) and provided advice to the Applicant on the iPSP. The advice included:

- Requesting a partial waiver for pediatric males and premenarchal females as they are not at risk of pregnancy
- Providing justification as to why extrapolation of data from adult women to postmenarchal adolescents would support dosing, efficacy and safety in this population if women under 18 were not going to be enrolled in the phase 3 trial

The Applicant then revised their iPSP and resubmitted it on May 11, 2015. The Applicant's revised iPSP included a request for a partial waiver for pediatric males and premenarchal females as well as a justification for extrapolation of dosing, efficacy and safety data from adult women to adolescents. On June 9, 2015, the Applicant received an advice letter to confirm agreement with the May 2015 iPSP partial waiver and justification for extrapolation to adolescent females. In addition, the Applicant was informed that there were no further comments on the Applicant's iPSP. .

11. Other Relevant Regulatory Issues

Division of Medical Policy Programs (DMPP):

DMPP was consulted by the Division on September 19, 2015, to review the proposed instructions for use. As the Division is issuing a complete response for this application, the DMPP review team placed a memo in DARRTS on February 17, 2016. The memo stated that they will not provide labeling recommendations or comments during this review cycle.

Office of Prescription Drug Promotion (OPDP):

OPDP was consulted by the Division on September 19, 2015 to review the proposed package insert, instructions for use and carton/container labeling. As the Division is issuing a complete response for this application, the OPDP reviewer placed a memo in DARRTS on April 4, 2016. The memo stated that they will not provide labeling recommendations or comments during this review cycle.

Office of Scientific Investigations (OSI):

OSI conducted inspections of five clinical sites that participated in the phase 3 Trial AMP001 (Drs. Andruczyk, Yang, Hernandez, Prokofyeva and Tarasova) submitted in support of this NDA. The Clinical Inspection Summary did identify some deviations from regulations at Dr. Andruczyk's site and issued a Form FDA 483, but concluded that the data generated by all clinical sites and submitted by the Applicant appeared adequate in support of the respective indication (See OSI Clinical Inspection Summary dated April 7, 2016).

Division of Medication Error Prevention and Analysis (DMEPA):

The DMEPA review team was consulted to review the container label, carton labeling, instruction for use and prescribing information from a medication error perspective. In

their review dated December 10, 2015, the DMEPA reviewer noted that there were areas of the prescribing information that could be revised for clarity. In addition, the DMEPA team also identified container and carton labeling that were vulnerable to confusion and recommended revised text and insertion of a barcode to the immediate container. After the decision was made to provide a Complete Response to the Applicant, the Division and DMEPA agreed that these comments will be provided to the Applicant in the next review cycle.

The DMEPA review team also assessed the proposed tradename “Amphora” and found it acceptable. (See DMEPA review dated August 24, 2015)

Financial Disclosure:

The clinical reviewer did not identify any issues of serious concern related to financial disclosures for this application. She stated that, "There were no reportable financial disclosures among investigators in this application; therefore, disclosed financial interests should not affect approvability of this product. (See clinical review dated April 26, 2016).

CDRH consult review:

The Center for Devices and Radiologic Health (CDRH) Obstetric and Gynecologic Devices Branch was consulted because the product is a combination product as it will be marketed with two product specific applicators. Specifically, CDRH was consulted to evaluate the:

- Functionality of the applicators
- Condom/diaphragm compatibility
- Assessment of the need for inspections related to the device (applicators)

The CDRH reviewer identified deficiencies in the characterization of the applicator components. After review of the applicators, the CDRH reviewer provided her comments in a review dated March 21, 2016 and stated that, "Based on my review of the information provided in these documents, the firm has not provided sufficient information on the applicators proposed for use with the Amphora® gel. The firm should address the noted outstanding issues related to the device description, bench testing, biocompatibility and shelf life."

The CDRH reviewer also evaluated the condom and diaphragm compatibility studies. The reviewer determined that the Applicant had provided adequate information and an overview of her findings are provided in section 8 of this review.

A separate consult was submitted to the CDRH Office of Compliance (CDRH-OC). This consult was initiated by OPQ to (1) evaluate the applicant's compliance with Quality System Requirements and to (2) determine if any 'medical device' inspections were required. In the CDRH-OC review dated March 31, 2016, the reviewer stated that, "The application for NDA-208352 for Amphora gel is approvable from the perspective of the applicable Quality System Requirements." No inspections were recommended by the CDRH-OC reviewer.

Comment: These deficiencies will be sent to the Applicant. The Applicant will need to respond to all of the outstanding component deficiencies identified by the CDRH reviewer in their Complete Response.

12. Labeling

Clinical and statistical deficiencies outlined above in sections 7 and 8 above precluded labeling negotiations.

13. Decision/Action/Risk Benefit Assessment

Decision:

I agree with the Cross-Discipline Team Leader, Medical Officer, and Statistical review teams that this supplemental efficacy application should receive a Complete Response action detailing the deficiencies identified by the clinical, statistical, OPQ and CDRH review teams.

Risk Benefit Assessment:

One phase 3 Trial AMP001 was submitted to support approval of Amphora gel for prevention of pregnancy along with 10 publications that provided supportive safety information. During the review cycle, there were major issues identified in the analysis including: 1) large discrepancies between data from the US and data from Russia, 2) no clear definition of on-treatment pregnancies, 3) no rules for excluding cycles based on no diary data, use of back up, alternative contraception or when no intercourse occurred 4) removal of cycles from the safety extension trial where Amphora gel alone was used and 5) use of cycles that had abnormal duration and unlikely to be ovulatory cycles where pregnancy would occur.

When all of the non-evaluable and abnormal cycles along with the discrepant data from Russia were removed, the efficacy analysis failed to meet the pre-specified non-inferiority threshold. In addition, the Applicant has not provided data on the timing of gel application relative to intercourse which is necessary for efficacy of the product.

From a safety perspective, removal of the data from Russia from Trial AMP001 led to an inadequate database that did not reach the 5,000 cycle threshold required for analysis. In addition, I concur with the clinical reviewer and CDTL that after removal of the data from Russian sites, lack of capture of adverse events immediately after gel application and the high rate of discontinuation resulted in underreporting of adverse events and therefore the safety profile for Amphora gel is inadequate. A new safety database is necessary to capture all early adverse events.

The following deficiencies with respect to the device (applicators) were also identified:

- The manufacturing facility, (b) (4) will require satisfactory resolution of manufacturing deficiencies prior to approval of Amphora gel
- Outstanding device component, biocompatibility, bench testing and device stability issues related to the applicator for proposed use with Amphora gel as identified by the CDRH reviewer will need to be resolved prior to approval of Amphora gel.

Based on the outstanding efficacy, safety, manufacturing and device related deficiencies; I do not believe the risk-benefit assessment of Amphora gel is satisfactory for approval this review cycle.

Post-Marketing Requirement/Commitment and Risk Evaluation and Mitigation Strategies (REMS):

- No Risk Evaluation and Mitigation Strategies (REMS) program was recommended by any of the review teams during the review cycle for this supplemental application.
- No other postmarketing requirements or commitments were recommended by the review teams during this review cycle for this supplemental application.

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/s/

AUDREY L GASSMAN
04/28/2016

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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Table of Abbreviations

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

Evoform, 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 Evoform 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
- Evoform 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 [REDACTED] (b) (4)
[REDACTED]
- 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

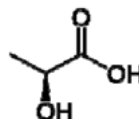
4.1 Chemistry Manufacturing and Controls

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:

C₃H₆O₃

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)

(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 (b) (4), 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)	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
05-19-11 to 04-23-14			1,694		
		Conceptrol	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:

- ***Evoform 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. Evoform agreed to this recommendation.***
- ***In the Type B end-of-phase 2 (EOP2) meeting held on October 13, 2013, DBRUP advised Evoform 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 $\geq$ four times in the past year or $\geq$ 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 vaginalis*, and H₂O₂- 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 H₂O₂-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 Population	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 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 all cycles 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

Reviewer's Comments:

- ***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.

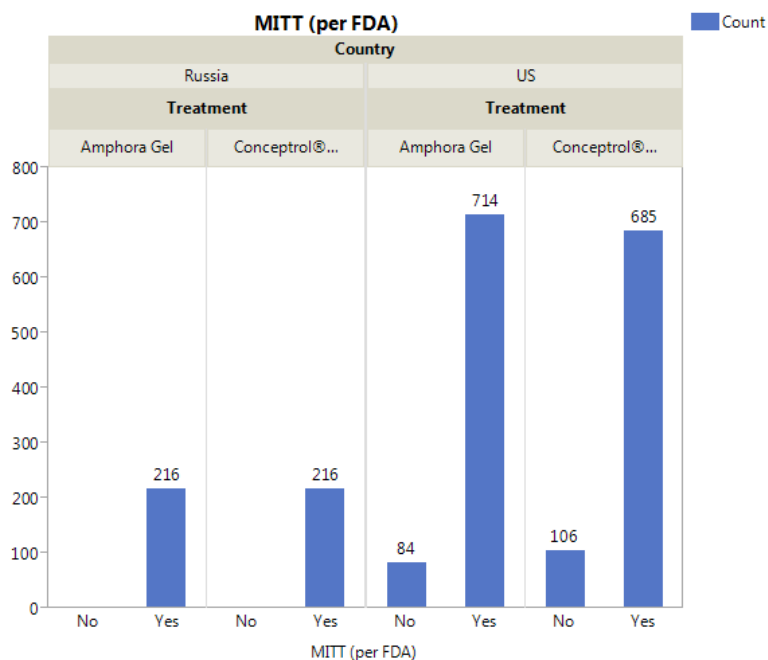
Table 9: Specific Protocol Deviations by Treatment Arm

	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		Description	
A	Additional act of intercourse within 1 hour after application and extra study product not applied.	E	Inserted study product after intercourse started.
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.	F	Lubricant used with study product during act of intercourse.
C	Original act delayed or additional act of intercourse more than 2 hours after application and extra study product not applied.	G	Other:
D	Less than one full applicator of study product used for each act of intercourse.	For Research ONLY: Cycle #: _____ # of Acts: _____ Date Reviewed: _____ Initials: _____	

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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 ≥ 175	406 (42)	401 (40)		18 (6)	16 (5)
BMI (kg/m²)					
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 ≥ 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:

“Evoform 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, Evoform 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

Analysis Population	US			Russia			ALL
	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 $\leq$ Estimated date of conception $\leq$ 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 $\leq$ Estimated date of conception $\leq$ (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.

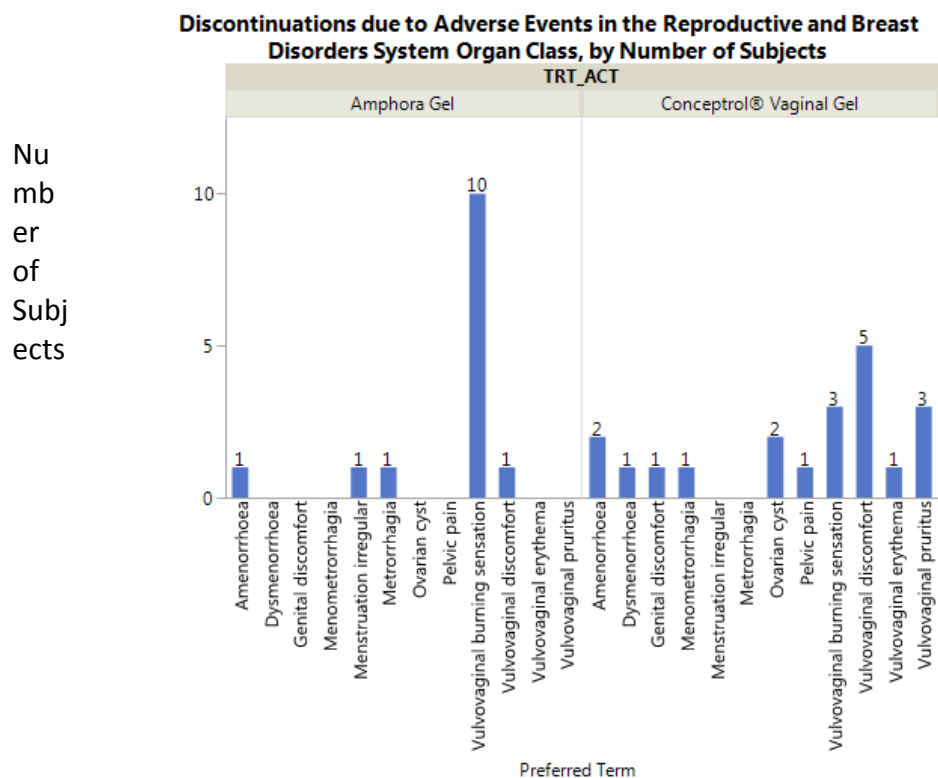
There were no deaths.

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	Madagascar	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 $\geq 2\%$ of the ATD population (by country) are shown in Table 25.

Table 25: AMP001: All AEs $\geq 2\%$ 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.

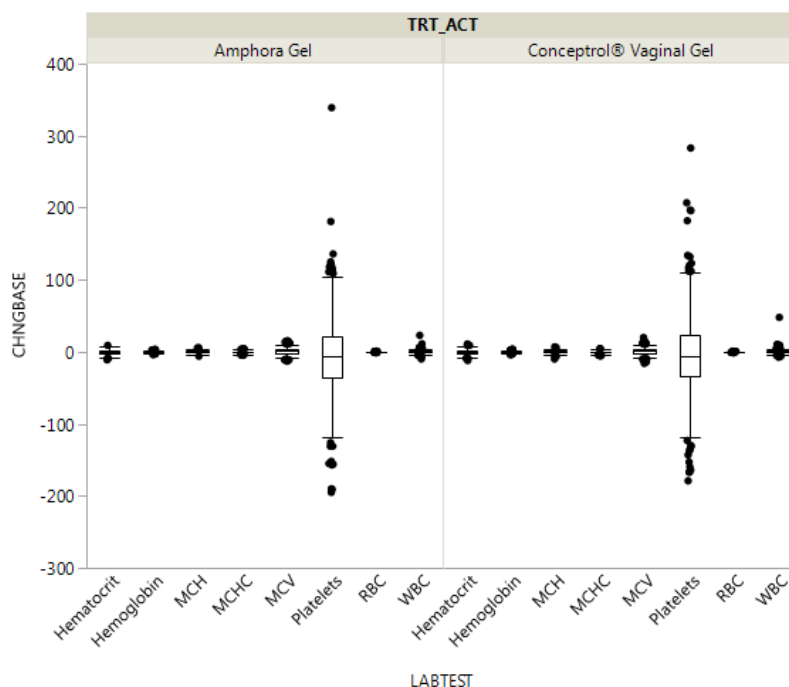
Reviewer's Comments:

- *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	50 (69.4)	44 (66.7)	94 (68.1)
1-2	13 (18.1)	12 (18.2)	25 (18.1)
3-4	6 (8.3)	5 (7.6)	11 (8.0)
5-6	2 (2.8)	5 (7.6)	7 (5.1)
7-8	1 (1.4)	0	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 H₂O₂+ Lactobacillus, H₂O₂– Lactobacillus, H₂O₂ 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 pediatric 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.

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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.

CLINICAL PHARMACOLOGY MEMORANDUM

NDA 208352	Submission Date: 07/02/2015
Brand Name	Amphora Gel
Generic Name	Lactic Acid, Citric Acid, Potassium Bitartrate
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Bone, Reproductive, and Urologic Products
Sponsor	Evoform, Inc.
Submission Type	Original NDA
Dosing Route / Regimen	Vaginal gel, 5 g gel used no earlier than 1 hour before sexual intercourse
Indication	Prevention of pregnancy

The Applicant submit a New Drug Application (NDA) for Amphora gel™ (88 mg lactic acid, 50 mg citric acid, 20 mg potassium bitartrate in a 5 g dose), an non-hormonal contraceptive spermicidal gel, for the prevention of pregnancy. It is proposed that Amphora gel exerts its contraception efficacy by maintaining the acidic vaginal environment in the presence of semen and immobilizing the sperm.

In support of this NDA, the Applicant conducted a single pivotal Phase 3 study (AMP001) evaluating the contraceptive efficacy and safety of Amphora gel in preventing pregnancy in adult females over 18 years of age compared to Conceptrol® Vaginal Gel. In addition, the Applicant provided the published literature references to demonstrate the spermicidal effect after treatment with Amphora gel 0–30 minutes and 8–10 hours prior to coitus.

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.

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/s/

MYONG JIN KIM
04/22/2016



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: 208352/000

Drug Name: Amphora™ Gel

Indication(s): Prevention of Pregnancy

Applicant: Evofem, Inc.

Date(s): Submitted: 06/30/2015
Received: 07/02/2015
PDUFA: 05/02/2016

Review Priority: Standard

Biometrics Division: Division of Biometrics III

Statistical Reviewer: Kate Dwyer, Ph.D.

Concurring Reviewers: Mahboob Sobhan, Ph.D.

Medical Division: Division of Bone, Reproductive and Urologic Products, HFD-580

Clinical Team: Regina Zopf, MD, MPH, Clinical Reviewer
Lisa Soule, MD, Clinical Team leader

Project Manager: Charlene Williamson

Keywords: NDA review, non-inferiority, Kaplan-Meier product limit

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1 EXECUTIVE SUMMARY

The information and data in this application do not support the efficacy of Amphora™ Gel for use in the prevention of pregnancy in adults 18 years of age and older. This conclusion is based on a single multinational Phase 3 study APM001.

APM001 was a multicenter, open-label, randomized, controlled, Phase III study of repeated use of Amphora™ Gel compared to Conceptrol® Vaginal Gel as the method of contraception over seven cycles of use. In addition, Amphora™ Gel subjects continued the study for up to 13 cycles of treatment upon completion of the first seven cycles of treatment. The primary efficacy objective was to demonstrate that the 6-month (7-cycles) cumulative pregnancy rate in Amphora™ Gel treated women is not inferior to Conceptrol® Vaginal Gel treated women. To demonstrate non-inferiority, the upper bound of the 95% confidence interval for the treatment difference must be less than or equal to 5.5%.

The Applicant's analysis showed that the difference in pregnancy rate (Amphora™ minus Conceptrol®) was 0.5% (95% CI: -2.2%, 3.2%). Based on the upper bound of 3.2%, which was less than 5.5%, the Applicant concluded that Amphora™ Gel was not inferior to Conceptrol® Vaginal Gel.

However, this reviewer identified two major data and analysis issues: (i) inappropriate use of cycles (including cycles from the extension part of the study to replace non-evaluable cycles in the 7-cycle non-inferiority analysis and cycles that were out of the normal range)); and (ii) effect of regional (US vs Russia) differences in efficacy that have resulted in biased estimates. Cycles are considered non-evaluable if there are no diary data, no intercourse, or use of back-up or emergency contraception.

Following Division's advice, the Applicant resubmitted the analysis data and efficacy results. To address the above issues, the final efficacy analysis is based on revised cycle definition and US data only.

The final results showed that there was substantial reduction in the evaluable cycle number (less than half of the pre-specified 7,000 cycles) in the primary efficacy analysis. Further, we confirm that the treatment difference in the US population is 3.9% with the upper bound of the 95% confidence interval more than 5.5%. Therefore, the study failed to demonstrate that Amphora™ Gel is non-inferior to Conceptrol® Vaginal Gel.

From a statistical perspective, the information and data submitted by the Applicant do not provide evidence regarding the effectiveness of Amphora™ Gel, a non-hormonal vaginal contraceptive gel, indicated for use in the prevention of pregnancy in adults 18 years of age and older.

2 INTRODUCTION

2.1 Overview

The Applicant, Evofem Inc., seeks approval of Amphora™ Gel a non-hormonal vaginal contraceptive gel indicated for use in the prevention of pregnancy in adults 18 years of age and older.

According to the Applicant, Amphora™ Gel is an acid-buffering gel containing three active ingredients, 88 mg (1.76%) lactic acid, 50 mg (1.00%) citric acid, and 20 mg (0.40%) potassium bitartrate, in a 5 g dose (equivalent to 5 mL), which acidify the vaginal environment, immobilizing spermatozoa and thereby making Amphora™ gel spermicidal.

The Applicant has submitted one phase 3 clinical study (AMP001 CSR) conducted in the United States and Russia entitled “A Multicenter, Open-Label, Randomized Study of the Contraceptive Efficacy and Safety of Amphora™ Gel Compared to Conceptrol® Vaginal Gel,” to evaluate the contraceptive efficacy and safety of Amphora™ Gel in preventing pregnancy in adult females 18 to 45 years of age. Table 1 presents a brief summary the study addressed in this review.

Table 1: List of all studies included in analysis

Study	Phase and Design	Treatment Period	# of Subjects per Arm	Study Population
AMP001	Phase 3, open-label, Randomized, multicenter, active-controlled	7 cycles with a subset in Amphora™ group extend to 13 cycles	Amphora™: 1,695 Conceptrol®: 1,694	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

Source: Reviewer’s summary based on study reports.

2.2 Data Sources

The study data, reports and additional information for these studies were submitted electronically. The submitted SAS data sets for all studies were complete and well documented. These items are located in the Electronic Document Room at [\\Cdsub1\EVSPROD\NDA208352](#) under the submissions dated 07/06/2015, 10/30/2015, 03/10/2016, and 03/17/2016.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There were several data and analysis quality issues noted by the reviewer in the original submission dated 07/06/2015, which are summarized as follows:

- 1) On-treatment pregnancy was not clearly defined.

Per FDA, 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.

- 2) Primary endpoint is based on 6-month (183 days) cumulative pregnancy rate instead of 196 days as per Division's requirement in estimating 7-cycles cumulative pregnancy rate.
- 3) Use of cycles from the extension study window to replace non-evaluable cycles in the 7-cycle study that resulted in biased efficacy in favor of Amphora™ Gel.
- 4) The CRF did not identify the subject's cycle number at the time of entering the extension study and the extension start date was calculated post-hoc. Also the diary dataset did not flag the cycles collected in the extension part of the study. For the 7-cycle analysis, the "compressed cycle" was used by adding subsequent cycles to replace non-evaluable cycles up to cycle 17.
- 5) Integrity of the Russian data is questionable due to the following reasons:
 - a. A pregnancy rate was far less than US data and also far below what was expected with use of a spermicide gel.
 - b. Discontinuation rate was far lower than the US region and also lower than what would be expected for a clinical trial.

Although the Division communicated this concern to the Applicant at the early review phase of this NDA, the Applicant has not provided adequate justification for the discrepancy in US versus Russian data to indicate that the Russian data are generalizable to the US population. There are extensive differences in demographic, discontinuation rate, and efficacy outcomes among US and Russian populations. Therefore, this reviewer concludes that the Russian data is not applicable to the US populations.

To address the above issues, the Division asked the Applicant to clarify and update the related datasets to reflect that the subject's study duration in the 7-cycle analysis window is Cycle 1-7 only and no more than 196 days from the enrollment date. The impact of the cycle length issue is further discussed while Applicant's efficacy results are discussed and reviewed in section 3.2.4 and 3.2.5.

3.2 Evaluation of Efficacy

The efficacy evaluation of Amphora™ Gel is based on study AMP001.

3.2.1 Study Design

APM001 was a multicenter, open-label, randomized, controlled, Phase III study of repeated use of Amphora™ Gel compared to Conceptrol® Vaginal Gel as the method of contraception over seven cycles of use. In addition, there is an opportunity for Amphora™ Gel subjects to continue with study treatment for up to 13 cycles of treatment upon completion of the first seven cycles of treatment.

Healthy, sexually active women at risk of pregnancy who desired contraception, aged 18 to 45 years, with a single male sex partner, of which both partners were at low risk for HIV and sexually transmitted

disease (STD) infection. *Subjects were required to have regular, normal, cyclic menses with a usual length of 21 to 40 days.* Subjects were willing to engage in at least two acts of heterosexual vaginal intercourse each cycle and used the study product as the only method of contraception over the course of the study with the exception of emergency contraception (EC), when indicated. Subjects were capable of using the study product properly, recording a daily diary of coital information, product use information and sign and symptom data for both the subject and her partner. In a subset group, women aged 36 to 45 were enrolled to determine the effect of age on contraceptive efficacy; these women were required to meet all other eligibility criteria.

A summary of study assessments and procedures and the time points at which they were to be made during the study is presented in Table 2.

Table 2: Schedule of Assessments

Procedures	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							
Eligibility (Inclusion/Exclusion)	X	X						
Medical/Gyn History	X							
Demographics	X							
Randomization		X						
Prior 6 month History of contraceptive use	X							
Pre-Trial Medications	X	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 Study Drug		X	X	X		X	X	X
Drug Return and Accountability			X	X		X	X	X
Dispense Home Pregnancy Test Kit		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 ^T	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

Source: Table 9-1 in AMP001 study report.

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 2 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 Emergency Contraception during the study. Participants were instructed check a pregnancy test 2 weeks after the admission visit.

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 only in Amphora™ Gel group were invited to participate in a 13 cycle extension trial. If they chose not to participate an exit visit was to be performed.

Simulation methods were used to evaluate the likelihood of various sample sizes providing enough information to test the primary hypothesis (one-sided Type I error of 0.025). The simulations assumed the following:

- 31% of cycles have backup contraceptive use and are excluded from analysis
- 6.5-12% of subjects fail to provide at least one diary for evaluation
- Exponential hazard for:
 - Pregnancy rate first 6 months: 13-15%
 - Pregnancy rate last 6 months: 6%
 - Dropout rate for month 1: 10%;
 - Dropout rate for months 2-6: 38%;
 - Dropout rate for months 7-12: 16.5%

With 2,600 subjects aged 18 through 35 years (inclusive) randomized in a 1:1 ratio to use either Amphora™ or Conceptrol®, the power was 80-88% and it was estimated that 7,000 cycles of Amphora™ Gel use would be recorded. In addition, it was assumed that 40-55% of the Amphora™ Gel group who completed 7 cycles of use would continue into the 13 cycle-extension with Amphora™ Gel. When women aged 36 through 45 years old (inclusive) at entry were included, it was anticipated 209-289 subjects would complete one year (13 cycles) of use.

However, during a review of incoming data revealed that in trial planning, the Applicant found out that the number of missing diaries and the number and timing of early discontinuations was underestimated. The 500 additional subjects were enrolled from sites in the United States and Russia; thus, the total estimated sample size for the study increased to 3,300. There were 62 clinical research sites (49 from the United States and 13 from Russia) that participated in the trial.

3.2.2 Statistical Methodologies

3.2.2.1 Analysis Populations

The following analysis populations were pre-specified in the protocol:

Intent-To-Treat (ITT): 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): ITT subjects whose diaries indicated they had at least one episode of coitus while using the assigned study product (also referred as “Typical-Use”), between 18 to 35 years of age (inclusive) at enrollment, had at least 1 cycle without any backup contraception or EC, and for whom there was at least one report of pregnancy status. Cycles in which backup contraception or EC was used were removed and the remaining cycles were compressed to provide contiguous cycles.

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

MITT7: In the pre-NDA meeting held on December 09, 2014, the Division reiterated that on-treatment pregnancy is defined as any conceptions that occur within 7 days after the last use of the Gel. Therefore, the Applicant defined a new analysis population (MITT7) using the corrected definition of on-treatment pregnancy. The only difference between the MITT and MITT7 population is the on-treatment pregnancy definition.

During the early review of this NDA including the SAS coding, we noted that the on-treatment pregnancy was not clearly defined. The Applicant was requested to provide a clear definition of on-treatment pregnancies as well as updated analysis results.

In order to address the FDA requests, the Applicant has created another analysis population FDA MITT7 using the following FDA recommended on-treatment pregnancy definition:

- 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.

3.2.2.2 Primary Efficacy Endpoint and Analysis

The Primary efficacy endpoint is the cumulative probability of typical-use 6-month (183 days) of Amphora™ Gel compared to Conceptrol® Vaginal Gel. MITT population is the primary efficacy population. Typical-Use referred to subjects whose diaries indicated they had at least one episode of coitus while using the assigned study product.

The primary hypothesis to be tested is whether subjects administered Amphora™ Gel has a six-month cumulative pregnancy probability that is not inferior to that of subjects using Conceptrol® Vaginal Gel. Using Blackwelder's approach for non-inferiority testing, the null and alternative hypotheses are expressed as:

$$\begin{array}{ll} \text{Ho: } \pi_A > \pi_C + 0.055 \\ \text{VS } & \text{H}_A: \pi_A \leq \pi_C + 0.055 \end{array}$$

Where π_A and π_C represent the six-month cumulative pregnancy probabilities for Amphora™ Gel and Conceptrol® Vaginal Gel, respectively.

Kaplan-Meier methods were used to estimate the six-month cumulative pregnancy probability of women in the MITT population by treatment group. Any pregnancies that occurred prior to

randomization or post-discontinuation from the study were excluded. 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 treatment differences. If the upper bound for the confidence interval of the difference was < 5.5 , then the null hypothesis would be rejected.

Reviewer's Comment

During the pre-NDA meeting held on December 09, 2014, the Division pointed out that the Statistical Analysis Plan (SAP) for study AMP0001 had not been submitted for review, but the Applicant did not follow through in submitting the final SAP prior to NDA submission.

Although this was a seven cycle study, the primary endpoint which the Applicant pre-specified was the cumulative probability of typical-use 6-month (183 days). In the 74-Day Filling Review Issues letter dated September 11, 2015, the Division advised the Applicant the pregnancy rates for contraceptive products are typically based on 7-cycle (196 day) trial period, 28 day per cycle.

In the early review phase of this NDA, we also identified the cumulative pregnancy rates of the US and Russian population is dramatically different. In addition to pregnancy rates, these populations were also differed with regards to discontinuation rate, weight, and BMI. The concerns were communicated to the sponsor in the 74-Day Filling Review Issues letter. Although the Applicant provided response to these review issues, however, we believed that the Applicant did not provide adequate justification for the discrepancy in US versus Russian data to indicate that the Russian data is generalizable to the US population.

Therefore from this point on, all the analyses are presented separately by region, US versus Russia. The primary analyses are based on FDA MITT7 population. The primary endpoint would be 7-cycles (196 days) cumulative pregnancy rate.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Details of subject disposition in study AMP001 are summarized in Table 3. Discrepancies in subject disposition were similar by arm but, were significantly different by country. US participants in each arm discontinued the trial at a rate of approximately 47% for reasons other than pregnancy or adverse event, while over 96% of Russian participants completed the study and much less likely to experience pregnancy compared to US participants. According to the clinical reviewer, the pregnancy rates in Russian sites were also much lower than in previously published spermicide trials evaluating efficacy of spermicide gels and not comparable to the US population.

The low completion rate in the trial and the number of premature discontinuations in the US population is problematic as it yields poor quality trial data.

Table 3: Subject Disposition

	US				Russia			
	Amphora Gel™ n (%)		Conceptrol® n (%)		Amphora Gel™ n (%)		Conceptrol® n (%)	
Enroll	1,371		1,376		324		318	
Age 18 - 35	1,256		1,289		324		318	
ITT	1,341		1,342		324		317	
ATD	1,135		1,160		324		316	
FDA MITT7	971	100%	999	100%	323	100%	316	100%
Completed Treatment	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%

Source: Reviewer's analysis.

Because the large discrepancy between the number of subjects in the Intent to Treat (ITT) population and FDA-MITT7, the demographics and baseline characteristics of the treatment groups are summarized in Table 4 by region using FDA-MITT7 population. Overall, the demographic and baseline characteristics appear to be balanced across treatment groups but differed significantly across regions for race, ethnicity, body weight and BMI.

The majorities of subjects in U.S. were white (54%), followed by black (35%) and other races, among which 30% were Hispanic or Latino. In Russia region 100% of subjects were white and only one subject was Hispanic or Latino.

The mean BMI in U.S. subjects was greater than 29 kg/m², while the mean BMI in Russia subjects was 22 kg/m². Almost all of the subjects with BMI 30 kg/m² or greater were from U.S. region (40% US region, 3% Russia). Also over 40% of the U.S. subjects weighted greater than 175 kg and only less than 6% of the Russian subjects weighted greater than 175kg.

Table 4: Demographics and Baseline Characteristics (FDA-MITT7 Population)

Demographic and Baseline	US		Russia	
	Amphora™	Conceptrol®	Amphora™	Conceptrol®
	N=971 n (%)	N=999 n (%)	N=324 n (%)	N=316 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)	322 (100)	316 (100)
Not Hispanic or Latino	679 (70)	710 (71)	1 (0)	0 (0)
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 ≥ 175	406 (42)	401 (40)	18 (6)	16 (5)
BMI (kg/m²)				
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 ≥ 30	399 (41)	391 (39)	10 (3)	8 (3)

Source: Reviewer's analysis.

3.2.4 Applicant's Original Efficacy Results and Conclusions

The primary efficacy endpoint was the cumulative percentage of typical-use 6-month (183 days) pregnancy. The Applicant's primary analysis was conducted using Kaplan-Meier methods to estimate the six-month cumulative pregnancy probability of women in the MITT population by treatment group. The non-inferiority hypothesis was tested by calculating a 95% confidence interval for the difference. If the upper bound for the confidence interval of the difference was < 5.5, then the null hypothesis would be rejected.

The results based on the pre-specified analysis are summarized in Table 5. The results showed that the difference in pregnancy percentages (Amphora™ minus Conceptrol®) was 0.5% (95% CI: -2.2%, 3.2%). The Applicant thus concluded that since the upper bound of the 95% CI for the difference in pregnancy percentages was less than the non-inferiority margin of 5.5%, Amphora™ Gel was not inferior to Conceptrol® Vaginal Gel.

Table 5: Six-Month (183 Day) Cumulative Pregnancy Percentages (MITT Population)

Six-Month Pregnancy Percentage	Amphora™ (N=1,292)	Conceptrol® (N=1,314)	Difference ²
Number of Subjects at Risk of Pregnancy at the Time of Randomization ¹	1,259	1,281	
Number of Pregnancies on or before Day 183	111	100	
Six-Month (183 days) Cumulative Pregnancy Percentage	10.5%	10.0%	0.5%
95% CI for Pregnancy Percentage	(8.6%, 12.3%)	(8.1%, 11.9%)	(-2.2%, 3.2%)

¹Excludes MITT subjects who had a pregnancy detected after being randomized but the pregnancy was determined to have started before the randomization date. Subjects with no cycles without backup or EC are excluded unless they became pregnant while on study.

²Difference = Amphora™ – Conceptrol®. If the upper bound of the confidence interval at 6 months is ≤ 5.5%, we conclude non-inferiority
Source: Table 11-4 in AMP001 study report.

During the review of this NDA, we found two major review issues which would significantly impact the efficacy results besides the region differences. First, because the Applicant did not collect information in the CRF to identify the subject's cycle number at the time of entering the extension study as pointed out in section 3.1, cycles from the extension study window were used to replace non-evaluable cycles in the 7-cycle analysis. Second, lengths of many cycles included in the original primary efficacy analysis fall outside normal range of 21 to 42 days.

In a teleconference on February 10, 2016, the Applicant acknowledged that cycles observed in the Amphora™ arm in the extension part of the study (beyond Cycle 7) were used to supplement the 7 cycle non-inferiority analysis. As showed in Table 6, most of the cycles beyond cycle 7 were only collected in Amphora™ Gel treatment arm and not in active comparator Conceptrol® treatment arm. Therefore, using cycles occurring in the extension study did bias the non-inferiority test in favor of Amphora™ Gel.

Table 6: Cycle Distribution (FDA-MITT7 Population)

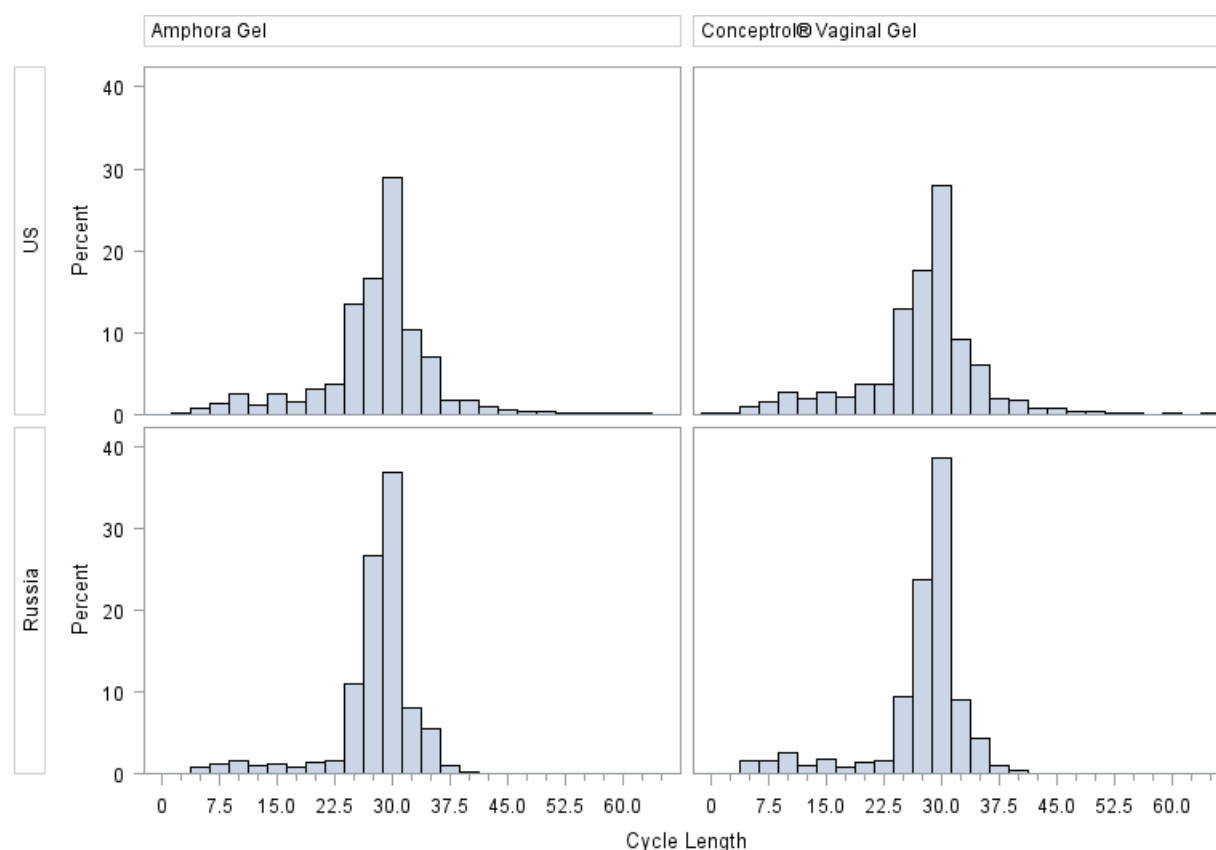
Diary Cycle	US		Russia	
	Amphora™	Conceptrol®	Amphora™	Conceptrol®
Cycle 0	936	965	297	288
Cycle 1	945	979	322	313
Cycle 2	887	912	319	311
Cycle 3	788	808	318	311
Cycle 4	711	718	316	309
Cycle 5	619	612	315	309
Cycle 6	566	576	314	307
Cycle 7	536	543	313	307
Cycle 8	430	421	311	303
Cycle 9	248	105	135	31
Cycle 10	194	22	111	9
Cycle 11	180	9	105	1
Cycle 12	168	4	103	
Cycle 13	160	2	103	
Cycle 14	143	1	100	
Cycle 15	28		19	
Cycle 16	10		1	
Cycle 17	4			

Source: Reviewer's analysis.

Although the subjects entered the study were required to have regular, normal, cyclic menses with a usual length of 21 to 40 days, as depicted in Figures 1, lengths of many of the cycles included in the original efficacy analysis fall outside of 21 to 42 days which is also physiologically expected length for ovulatory cycles. The Division believed that these cycles should not be counted as evaluable cycles.

Furthermore, regional heterogeneity (unexpectedly favorable efficacy in Russia) has impacted the overall point estimate in favor Amphora™ Gel.

Figure 1: Distribution of Cycle Length (FDA-MITT7 Population)



Note: Means of cycle length around 28 days and median 29 days with STD of 13 and 6 in the US and Russia, respectively; Range of the cycle length was 1 – 468 days and 1 to 69 days in US and Russia region, respectively.

Source: Reviewer's analysis.

3.2.5 Final Efficacy Results and Conclusions

After the discussion on February 10, 2016, a finalized Information Request (IR) was sent to the Applicant on February 26, 2016. In the IR, the Division clearly defined that the cycles to be included in the 7 cycle analysis are Cycles 1-7, through a maximum of 196 days. Efficacy analysis should begin on Day 1 of menses of Cycle 1. Also the diary 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, in accord with your entry criteria, the typical cycle length should be ≥ 21 days and ≤ 42 days. Cycles outside these limits should be excluded from analysis.

Per Division's request, the Applicant addressed all the data issues and provided revised datasets and final efficacy results in the submission dated 03/01/2016, 03/10/2016 and 03/17/2016. This reviewer confirmed these results. The summary of primary efficacy results using evaluable cycles (exclude cycles that are ≤ 21 days or ≥ 42 days in length) is summarized in Table 7. As showed in Table 7, the upper bounds of the

95% confidence intervals for the difference in 7-cycles cumulative pregnancy rates were 8.9% in the US population (exceeding the non-inferiority margin of 5.5%), demonstrating that Amphora Gel™ was not as effective as Conceptrol® Vaginal Gel. As previously mentioned in this review, Russian data was not included in the final primary efficacy analysis due to large discrepancies in regards to demographics, discontinuation rates and cumulative pregnancy percentages.

Further note that there were only 3,232 evaluable cycles in Amphora™ Gel treatment arm in the FDA-MITT7 population which is less than half of the pre-specified 7,000 cycles in the primary efficacy analysis, thus no valid conclusion can be drawn from these limited available data. This was also considerably less than the 5,000 that was recommended for the evaluation of efficacy and safety by the Division.

Table 7: Cumulative Pregnancy Rate by Region, FDA MITT7 Population

	US		Russia	
	Amphora™	Conceptrol®	Amphora™	Conceptrol®
FDA-MITT7	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

*Exclude cycles that are ≤ 21 days or ≥ 42 days in length

Source: Table 14.2.41 in study report and Reviewer's analysis.

Results of sensitivity analysis using all cycles (including cycles that are ≤ 21 days or ≥ 42 days in length) (Table 8) and Applicant's pre-specified primary endpoint of 6-month (183 days) cumulative pregnancy rate for evaluable cycles and all cycles (Table 9 and Table 10; APPENDIX) showed that the upper bounds of the 95% confidence intervals exceeding the non-inferiority margin of 5.5% in the U.S. population.

Table 8: Cumulative Pregnancy Rate by Region (All Cycles), FDA-MITT7 population

	US		Russia	
	Amphora™	Conceptrol®	Amphora™	Conceptrol®
FDA-MITT7	971	999	323	316
# Subjects at Risk of Pregnancy at the Time of Enrollment	849	895	320	310
Number of On-treatment Pregnancies	98	87	6	4
7-Cycles Cumulative Pregnancy Rate (196 days)	16.8%	13.8%	2.1%	1.3%
7-Cycles 95% CI	(13.3%, 20.2%)	(10.9%, 16.7%)	(0.4%, 3.7%)	(0.0%, 2.6%)
Treatment Differences	3.0% (-1.5%, 7.5%)		0.2% (-1.6%, 2.1%)	
Number of All Cycles*	4,572	4,722	2,186	2,129

* Include cycles that are ≤ 21 days or ≥ 42 days in length

Source: Table 14.2.43 in study report and Reviewer's analysis.

Failure to demonstrate non-inferiority of Amphora Gel™ to Conceptrol® Vaginal Gel in the U.S. population did not warrant further subgroup analyses.

3.3 Evaluation of Safety

Refer to the clinical reviewer's report for evaluation of safety data.

4 SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

During the review of the original NDA submission, we have noted the following data definition and statistical issues with regards to efficacy analysis.

1. On-treatment pregnancy was not clearly defined.
Per FDA, 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.
2. Primary endpoint is based on 6-month (183 days) cumulative pregnancy rate instead of 7-cycles (196 days) cumulative pregnancy rate as per Division's requirement in estimating 7-cycles cumulative pregnancy rate.
3. Regional heterogeneity in efficacy.

Although the Division communicated this concern to the Applicant at the early review phase of this NDA, the Applicant has not provided adequate justification for the discrepancy in US versus Russian data to indicate that the Russian data are generalizable to the US population. There are extensive differences in demographic, discontinuation rate, and efficacy outcomes among US and Russian populations. Therefore, this reviewer concludes that the Russian data is not applicable to the US populations.

4. Use of cycles from the extension study window to replace non-evaluable cycles in the 7-cycle study that resulted in biased efficacy in favor of Amphora™ Gel.

The CRF did not identify the subject's cycle number at the time of entering the extension study and the extension start date was a calculated post-hoc. Also the diary dataset did not flag the cycles collected in the extension part of the study. For the 7-cycle analysis, the "compressed cycle" was used by adding subsequent cycles to replace non-evaluable cycles up to cycle 17.

5. Lengths of many cycles included in the original efficacy analysis fall outside of 21 to 40 days.

4.2 Conclusions and Recommendations

Based on the corrected datasets, the results did not demonstrate that Amphora™ Gel was non-inferior to Conceptrol® Vaginal Gel in the US. From a statistical perspective, the information and data submitted by the Applicant with one controlled study do not provide evidence regarding the effectiveness of Amphora™ Gel, a non-hormonal vaginal contraceptive gel, indicated for use in the prevention of pregnancy in adults 18 years of age and older.

APPENDIX

Sensitivity Analyses

Table 9: Six-Month (183 days) Cumulative Pregnancy Rate by Region, FDA-MITT7 Population

	US		Russia	
	Amphora™	Conceptrol®	Amphora™	Conceptrol®
FDA-MITT7	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

*Exclude cycles that are ≤ 21 days or ≥ 42 days in length

Source: Table 14.2.41 in study report and Reviewer's analysis.

Table 10: Six-Month (183 days) Cumulative Pregnancy Rate by Region, FDA-MITT7 Population

	US		Russia	
	Amphora™	Conceptrol®	Amphora™	Conceptrol®
FDA-MITT7	971	999	323	316
# Subjects at Risk of Pregnancy at the Time of Enrollment	849	895	320	310
Number of On-treatment Pregnancies	96	87	4	4
Six-Month Cumulative Pregnancy Rate (183 days)	15.7%	13.8%	1.3%	1.3%
Six-Month 95% CI	(12.5%, 18.9%)	(10.9%, 16.7%)	(0.0%, 2.5%)	(0.0%, 2.6%)
Treatment Differences	1.9% (-2.4%, 6.2%)		-0.1% (-1.8%, 1.7%)	
Number of All Cycles*	4,572	4,722	2,186	2,129

* Include cycles that are ≤ 21 days or ≥ 42 days in length

Source: Table 14.2.43 in study report and Reviewer's analysis.

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/s/

KATE L DWYER
04/15/2016

MAHBOOB SOBHAN
04/15/2016

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 208352
Supporting document/s:	Supporting Document Number 1
Applicant's letter date:	06/30/2015
CDER stamp date:	07/02/2015
Product:	Amphora™ Gel
Indication:	Non-hormonal vaginal contraceptive gel for use in preventing pregnancy
Applicant:	Evoform, Inc.
Review Division:	Division of Bone, Reproductive, and Urology Products
Reviewer:	Deepa B. Rao, D.V.M., Ph.D.
Supervisor/Team Leader:	Lynnda Reid, Ph.D.
Division Director:	Hylton Joffe, M.D., M.M.Sc.
Project Manager:	Zeta-Mae Williamson

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 208352 are owned by Evoform, Inc., or are data for which Evoform, Inc., has obtained a written right of reference.

Any information or data necessary for approval of NDA 208352 that Evoform, Inc., does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 208352.

Abbreviation	Definition
ADME	Absorption, Distribution, Metabolism, Excretion
CFR	Code of Federal Regulations
CDRH	Center for Devices and Radiological Health
CMC	Chemistry Manufacturing Controls
GRAS	Generally Recognized As Safe
NDA	New Drug Application
SCOGS	Select Committee on GRAS Substances

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1 Executive Summary

1.1 Introduction

This 505(b)(2) application is submitted by Evofem, Inc. for their non-hormonal vaginal contraceptive gel product (Amphora™ Gel). Evofem, Inc is seeking approval for the use of Amphora™ Gel in the prevention of pregnancy in adult women aged ≥ 18 years. Amphora™ Gel is an acid-buffered gel (pH = 3.5) containing three active ingredients, namely, lactic acid (88 mg, 1.76%), citric acid (50 mg, 1%), and potassium bitartrate (20 mg, 0.4%) in a 5 g dose (equivalent to 5mL). There are no novel drug substances in Amphora™ Gel, and, all of the components are inactive ingredients in other FDA-approved products, are listed as Generally Recognized As Safe (GRAS) substances, or are within acceptable limits for use as excipients in other FDA-approved vaginal or topical products. The mechanism of action is based on buffering the vaginal acidic environment to maintain the pH below 5 even in the presence of semen. Evofem, Inc., is not relying on a listed drug in this 505(b)(2) application, but rather, on Evofem-conducted clinical and nonclinical studies, as well as published literature.

1.2 Brief Discussion of Nonclinical Findings

The sponsor has right of reference to IND 64623 for nonclinical information in support of Amphora™ Gel. Nonclinical toxicology studies were conducted to evaluate local tolerance in the vagina and submitted for review under IND 64623.

There are no novel drug substances in Amphora™ Gel. From a safety perspective, there is no “active” drug component for the proposed drug product. All stated active ingredients (lactic acid, citric acid, and potassium bitartrate) are common in food and/or endogenous pH buffering agents that are GRAS-listed substances with long histories of use as inactive ingredients in other FDA-approved products (including vaginal products). All excipients are also either GRAS-listed, or are common ingredients that exist in other FDA-approved drug products at acceptable levels and routes of administration.

No specific pharmacokinetic/ADME/toxicokinetic studies were conducted, or were considered to be necessary (per FDA agreement at the 9 December 2014 pre-NDA meeting). Systemic absorption of Amphora™ Gel active ingredients is considered to be unlikely based on the chemical characteristics of the product (that are designed to retain the formulation within the local vaginal environment). Systemic absorption is not required for efficacy since Amphora™ Gel acts by buffering the local vaginal environment to maintain an acidic pH even in the presence of semen.

Nonclinical toxicology studies conducted under IND 64623 evaluating local tolerance with Amphora™ Gel did not reveal any relevant safety concerns. 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.

1.3 Recommendations

1.3.1 Approvability

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 nonclinical studies, Amphora™ Gel appears to be reasonably safe for approval.

1.3.3 Labeling

Labeling will be addressed in an addendum review.

2 Drug Information

2.1 Drug

CAS Registry Number :

Anhydrous Citric acid: 77-92-9

L-Lactic acid: 79-33-4

Monopotassium tartrate (Cream of tartar, Potassium bitartrate): 868-14-4

Generic Name

Amphora™ Gel (previously Acidform Gel)

Code Name

None

Chemical Name

Citric acid: 2-Hydroxypropane-1,2,3-tricarboxylic Acid

L-Lactic acid: 2-Hydroxypropanoic acid

Monopotassium tartrate: Potassium; (2R, 3R) - 2,3,4-trihydroxy-4-oxobutanoate

Molecular Formula/Molecular Weight

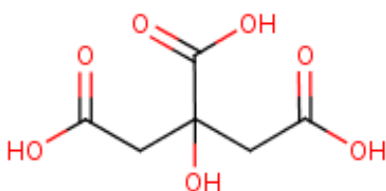
Citric acid: C₆H₈O₇ / 192.124 g/mol

L-Lactic acid: C₃H₆O₃ / 90.08 g/mol

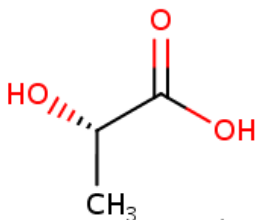
Monopotassium tartrate: KC₄H₅O₆ / 188.177 g/mol

Structure or Biochemical Description

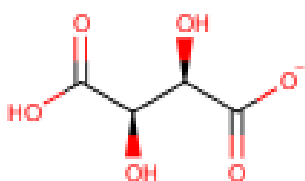
Citric Acid



L-Lactic Acid



Monopotassium tartrate



Pharmacologic Class: Spermicide / Non-hormonal vaginal contraceptive

2.2 Relevant INDs, NDAs, BLAs and DMFs

1) IND 64623:

Product Name: Acidform Gel

Sponsor: CONRAD

Indication: Vaginal Contraceptive

Status: Withdrawn (12/17/2009; not due to safety concerns)

2) IND 109300:

Product Name: Acidform Gel

Sponsor: Evofem, Inc

Indication: Spermicidal Contraceptive

Status: Active (03/20/2011)

3) # K033776 [510(k) clearance from CDRH]

Device Name: Instead Intimate Lubricant

Predicate Device:

- a. K982673 – The Just Between Us™ lubricant by Key West Fragrance & Cosmetic Factor
- b. K983216 – CVS Personal Lubricant by San-Mar Laboratories

Sponsor: Instead, Inc

Indication: “Instead Intimate Lubricant is intended to enhance the comfort and ease of intimate activity and is compatible with latex and polyurethane condoms”

Status: Cleared as “Substantially Equivalent” to predicate device

2.3 Drug Formulation

Amphora™ Gel (referred to as Acidform Gel in historical documentation and literature references) is an acid-buffered gel (pH= 3.5) containing three small organic acids/acid salts acting as buffering agents (lactic acid, citric acid, potassium bitartrate), a humectant (glycerin), two thickeners or gelling agents (alginic acid and xanthan gum), a preservative (benzoic acid), and water (see Table 1 below).

Table 1: Qualitative and Quantitative Composition of Amphora™ Gel

Component	Function	Composition (% w/w)	Quantity per 5 g Dose (mg)
Lactic acid, USP	Drug substance	1.76	88
Citric acid, USP	Drug substance	1.00	50
Potassium bitartrate, USP	Drug substance	0.40	20
Glycerin, USP	Humectant	(b) (4)	
Alginic acid, NF	Gelling agent		
Xanthan gum, NF	Gelling agent		
Sodium hydroxide, NF	pH adjustment		
Benzoic acid, USP	Preservative		
Purified water, USP	Solvent		
Total:		100.0	5,000

2.4 Comments on Novel Excipients

There are no novel drug substances in Amphora™ Gel. All excipients are either GRAS-listed, or are common ingredients that exist in other FDA-approved drug products at acceptable levels and routes of administration.

Some potential for concern regarding alginic acid was raised during CMC review of the IND. Nonclinical review indicates that alginic acid is below the maximum oral dose in the FDA Inactive Ingredient Database ((b) (4) mg in Amphora™ Gel compared to the maximum oral dose of 400 mg in the inactive ingredient database), is a GRAS substance per CFR, is widely used in cosmetics and food, has no genotoxic properties, and that alginates are generally not absorbed. Based on this information, alginic acid was not considered to be of concern in the formulation for Amphora™ Gel.

2.5 Comments on Impurities/Degradants of Concern

Review of the submitted stability data suggests color change of Amphora™ Gel over time (refer to Quality Assessment review for further details regarding this issue).

2.6 Proposed Clinical Population and Dosing Regimen

The proposed patient population is adult women aged ≥ 18 years. Dosing is via a single applicator of Amphora™ Gel (5g, equivalent to 5 mL) that is directed to be used no earlier than one hour before each episode of vaginal intercourse. Another applicator of product is directed for use before each additional act of vaginal intercourse, even if intercourse occurs more than once in a day.

2.7 Regulatory Background

Amphora™ Gel was originally submitted in 2002 as Acidform Gel under IND 64623 by the group Contraceptive Research and Development (CONRAD). Acidform Gel, also referred to as Instead Vaginal Lubricant, received 510(k) clearance (as a device reviewed by CDRH) for use as a lubricant (#K033776) submitted by Instead®, Inc in 2004, but was not marketed. IND 64623 was withdrawn in 2010 based on administrative reasons related to the transfer of rights from CONRAD to Evofem, Inc (formerly Instead®, Inc), not for reasons of safety. CONRAD has authorized Evofem, Inc. to cross-reference IND 64623 for preclinical, manufacturing and clinical information. Evofem, Inc. submitted Amphora™ Gel for review under IND 109300 leading to this NDA 208352 with a right of reference to IND 64623 from CONRAD.

3 Studies Submitted

No nonclinical studies were submitted.

3.1 Studies Reviewed

Under IND 64623, three nonclinical studies were reviewed (Dr. Lynnda Reid, May 23, 2002). These include one 10-day vaginal irritation study in rats (preliminary non-GLP), and two vaginal irritation studies in rabbits (one preliminary non-GLP and one GLP). The 10-day GLP rabbit vaginal irritation study was conducted with Amphora™ Gel. The two non-GLP studies were conducted with the prototype formulations that are closely related to Amphora™ Gel, but these formulations also contain another spermicidal agent nonoxynol-9 (N-9).

Under 510(k) # K033776 to CDRH, two toxicology studies were submitted. These included a penile irritation study and a rectal irritation study in rabbits.

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

IND 64623 – Dr. Lynnda Reid (May 23, 2002)

IND 109300 – Dr. Kimberly Hatfield (March 16, 2011)

4 Pharmacology

The primary pharmacodynamic activity of Amphora™ Gel is the spermicidal effect due to buffering of the local pH of the vagina in the presence of semen. The introduction of sperm into the vagina causes a rise in pH to above 6.0 due to buffering activity of the ejaculate that neutralizes the normally acidic milieu of the vagina. The mechanism of action is based on the acidifying properties of Amphora™ Gel designed to maintain an acidic vaginal environment (pH = 3.5-4.5) in the presence of male ejaculate in the vagina. The use of an acid buffering gel as a contraceptive relies on the inability of spermatozoa to survive in acidic environments. Sperm motility was decreased with Amphora™ Gel.

The secondary pharmacodynamic activity is the cervical mucus penetration reduction/inhibition, bioadhesive strength, and viscosity-retaining properties of the Amphora™ Gel that was developed to form a protective, long-lasting layer of gel over the vagina/cervix surfaces.

Typical safety pharmacology studies were not conducted on the active ingredients in Amphora™ Gel. Systemic absorption is unlikely based on the chemical characteristics of the product (that are designed to retain the formulation within the local vaginal environment). The three active ingredients (lactic acid, citric acid, and potassium bitartrate) are common and/or endogenous pH buffering agents that are GRAS-listed substances with long history of use as inactive ingredients in other FDA-approved products (including vaginal administration products).

5 Pharmacokinetics/ADME/Toxicokinetics

Evoform has not conducted any pharmacokinetic/toxicokinetic studies on Amphora™ Gel to determine the systemic exposure of lactic acid, citric acid, and potassium bitartrate (per FDA agreement at the 9 December 2014 pre-NDA meeting). The decision was based on chemical characteristics of the formulation that render unlikely systemic absorption of the active ingredients in Amphora™ Gel, the lack of toxicity in the 10-day nonclinical studies with Amphora™ Gel, and the general nontoxic nature of the individual active ingredients (GRAS-listed substances). Calculated hypothetical estimates (based on 100% absorption of lactic acid and citric acid from a single dose of Amphora™ Gel) still do not exceed the upper limit of normal endogenous serum concentrations. All excipients are also either GRAS-listed, or are common ingredients that exist in other FDA-approved drug products at acceptable levels and routes of administration. Since the mechanism of action is based on buffering the local vaginal acidic environment to maintain the pH below 5 in the presence of semen, systemic absorption is not needed for efficacy.

6 General Toxicology

No acute or chronic nonclinical toxicology studies were conducted.

Three nonclinical studies were conducted and reviewed under IND 64623 to evaluate local toxicity of Amphora™ Gel in the vagina. These included one 10-day vaginal irritation study in rats (preliminary non-GLP), and two vaginal irritation studies in rabbits (one preliminary non-GLP and one GLP). The 10-day GLP rabbit vaginal irritation study was conducted with Amphora™ Gel. The two non-GLP studies were conducted with the prototype formulations that are closely related to Amphora™ Gel, but these formulations also contain the spermicidal agent N-9.

Two toxicology studies were submitted to CDRH under 510(k) # K033776. These included a penile irritation study and a rectal irritation study in rabbits. Amphora™ Gel was considered to be non-irritating to rabbit rectal and penile mucosa.

A summary of the 10-day rabbit vaginal studies are included in Section 10 under Special Toxicology Studies.

7 Genetic Toxicology

All active ingredients have been used in previously approved drug products as inactive ingredients and are not considered genotoxic.

8 Carcinogenicity

No carcinogenicity studies were conducted by Evofem, Inc. Based on published literature, information on carcinogenicity for each of the ingredients in Amphora™ Gel is addressed below. In summary, no treatment-related tumors were noted in carcinogenicity studies conducted with lactic acid and citric acid. For potassium bitartrate, no carcinogenicity studies are available.

Lactic Acid

The carcinogenicity of orally administered lactic acid has been evaluated in one rat study and one rabbit study.

Male and female Fischer 344 rats were fed diets containing the calcium salt of lactic acid at a concentration of 0, 2.5, or 5% for 2 years, calculated to provide a dose of 0, 2500, or 5000 mg/kg/day, respectively. There was no evidence of a significant dose-related increase in the incidence of tumors in any organ or tissue of treated animals [Joint FAO/WHO Expert Committee on Food Additives, 2014].

Female rabbits were dosed orally with 0.1 - 0.2 g/kg lactic acid in 100 -150 mL water twice daily for 5 months, and five female rabbits were dosed orally with 0.1 - 0.7 g/kg lactic acid in 50 - 100 mL water twice daily for 16 months (13 months actual treatment). No tumors were reported after 5 or 16 months, respectively [Cosmetic Ingredient Review Expert Panel, 1998].

Citric Acid

Rats dosed with 5% or 3% citric acid in a 2-year chronic oral feed study (approx. 1.2 and 2 g/kg/day) showed no evidence of carcinogenicity [United Nations Environment Programme, 2014].

Potassium Bitartrate

No evidence was found that potassium bitartrate is carcinogenic. It is not listed as a known or suspected carcinogen by the International Agency for Research on Cancer (IARC), the National Toxicology Program (NTP), or the California Environmental Protection Agency Office of Environmental Health Hazard Assessment (OEHHA, CA Prop 65) [International Agency for Research on Cancer, 2015; National Toxicology Program, 2014; State of California Environmental Protection Agency - Office of Environmental Health Hazard Assessment, 2015]. Potassium bitartrate is listed in the SCOGS GRAS database, and has been given a type 1 conclusion by the Committee [Select Committee on GRAS Substances, SCOGS-107]. It is also listed in the FDA Inactive Ingredients database for approved products, albeit by oral administration and at levels lower than those found in Amphora™ Gel (9.5-10 mg orally versus 20 mg in a single topical application of Amphora™ Gel) [U. S. Food and Drug Administration, 2015]. There are approximately 30 entries for tartaric acid in the FDA Inactive Ingredients database for a number of routes of administration, including oral, intravenous, intramuscular, subcutaneous, topical, and sublingual, and at a variety of dose levels up to 1.1 g (oral) [U. S. Food and Drug Administration, 2015].

9 Reproductive and Developmental Toxicology

All ingredients have been used individually in previously approved drug products as inactive ingredients and are not considered teratogenic. However, the proposed combination has not been tested.

10 Special Toxicology Studies

Three nonclinical studies were conducted and reviewed under IND 64623. These include one 10-day vaginal irritation study in rats (preliminary non-GLP), and two vaginal irritation studies in rabbits (one preliminary non-GLP and one GLP). The 10-day GLP rabbit vaginal irritation study was conducted with Amphora™ Gel. The two non-GLP studies were conducted with the prototype formulations that are closely related to Amphora™ Gel, but these formulations also contain the spermicidal agent N-9.

The following are reviews of these studies taken from Dr.Reid's review conducted under IND 64623.

Study title: 10-Day Rat Vaginal Irritation Study (Preliminary Non-GLP Study)

Summary findings: This study was performed at (b) (4) to evaluate vaginal irritation of ACIDFORM with 5 and 10% nonoxynol-9 compared to ACI-JEL® and sham controls in Charles River rats (n=5/group). Anterior, medial and posterior sections of the vagina were examined macro- and microscopically. Histopathology evaluations performed by (b) (4). Irritation was graded using the criteria of Eckstein, which scores for the presence and severity of epithelial ulceration, vascular congestion, leukocyte infiltration and edema.

The average composite irritation scores in rats were as follows:

	Score
Sham	0
ACI-JEL	3.0
ACIDFORM w/ 5% N-9	1.8
ACIDFORM w/ 10% N-9	2.4

Scoring: minimal 1-4; mild 5-8; moderate 9-11; marked 12-16

No other adverse effects were reported.

Study title: 10 Day Rabbit Vaginal Irritation Study (Preliminary Non-GLP Study)

Summary findings: This study was performed at (b) (4) to evaluate vaginal irritation of ACIDFORM with 5 and 10% nonoxynol-9 compared to ACIJEL® in New Zealand White rabbits (n=2-3/group). Anterior, medial and posterior sections of the vagina were examined macroscopically and histopathology evaluations performed by (b) (4). Irritation was graded using the criteria of Eckstein, which scores for the presence and severity of epithelial ulceration, vascular congestion, leukocyte infiltration and edema.

The average composite irritation scores were as follows:

	Score
ACI-JEL	4.8
ACIDFORM w/ 5% N-9	4.8
ACIDFORM w/ 10% N-9	7.0

Scoring: minimal 1-4; mild 5-8; moderate 9-11; marked 12-16

No other adverse effects were reported.

Study title: 10 Day Rabbit Vaginal Irritation Study (GLP Study)

Key study findings: mild irritation to vaginal epithelium

Study no: BSR Study 045-019, Vol. 1, page 331

Conducting laboratory and location (b) (4)

Date of study initiation: June 28, 1999

GLP compliance: yes

QA report: yes

Formulation/vehicle: ACIDFORM Gel with and without 2.5 and 5% nonoxynol-9

Methods (unique aspects): Test groups were as follows: untreated, sham (saline), ACIDFORM Gel, ACIDFORM with 2.5% nonoxyl-9, and ACIDFORM with 5% nonoxyl-9. Test materials were inserted into the vaginal cavity to a depth of ~15 cm using a French catheter. Material was slowly expelled as the catheter was removed from the vagina. Animals were sacrificed on day 11, ~24 hours after receiving the last dose.

Dosing:

Species/strain: New Zealand White Rabbits (b) (4)

#/sex/group or time point (main study): 10 females/treatment group; 6 females/control group

Age: ~6 months

Weight: 3.03-4.31 kg

Doses in administered units: 1 mL/dose

Route, form, volume, and infusion rate: vaginal insertion

Observations and times:

Clinical signs: daily

Body weights: daily

Gross pathology: The vagina was removed, cut longitudinally and observed for any signs of gross pathology.

Histopathology: Anterior, medial and posterior sections of the vagina were evaluated microscopically by (b) (4) using the criteria of Eckstein, which scores for the presence and severity of epithelial ulceration, vascular congestion, leukocyte infiltration and edema.

Results:

Mortality: none

Clinical signs: unremarkable

Body weights: Weight losses occurred in all groups: 1/6 untreated controls, 2/6 sham controls, 7/10 ACIDFORM, 7/10 ACIDFORM w/2.5% N-9, and 4/10 ACIDFORM w/5.0% N-9. Individual weight loss was less than 10% in all cases.

Gross pathology: unremarkable

Histopathology: Irritation scores were lowest in the anterior portion of the vagina, with comparable scores in the medial and posterior sections. Table 1 presents mean composite scores/group with the range of individual scores. Table 2 presents a breakdown of the incidence rate of minimal, mild, moderate or marked irritation in any portion of the vagina for each group. Irritation scoring is minimal 1-4; mild 5-8; moderate 9-11; marked 12-16.

Table 1:

	Composite Score	Range of Individual Scores
Untreated	0.8	0 - 3
Sham	3.7	2 - 11
ACIDFORM	5.3	4 - 14
ACIDFORM w/ 2.5% N-9	6.8	4 - 14
ACIDFORM w/ 5.0% N-9	8.6	4 - 14

Table 2:

n	Minimal (Scores 1-4)	Mild (Scores 5-8)	Moderate (Scores 9-11)	Marked (Scores 12-16)
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Untreated	6	3	0	0	0
Sham	6	3	2	1	0
ACIDFORM	10	3	5	1	1
ACIDFORM w/ 2.5% N-9	10	2	4	2	2
ACIDFORM w/ 5.0% N-9	10	1	3	0	6

Based on the mean composite findings, ACIDFORM is considered a mild vaginal irritant. ACIDFORM with nonoxyl-9 was generally more irritating and a dose-response relationship was evident between the 0, 2.5 and 5.0% ACIDFORM/nonoxyl-9 formulations.

No other adverse effects were reported.

11 Integrated Summary and Safety Evaluation

Evoform, Inc., is seeking a New Drug Application (NDA) approval for the use of Amphora™ Gel, a non-hormonal vaginal contraceptive gel product. The mechanism of action is based on the buffering activity of Amphora™ Gel in the vaginal environment to maintain an acidic pH in the presence of semen.

There are no novel drug substances in Amphora™ Gel. The ingredients of Amphora™ Gel include three active small organic acids/acid salts (lactic acid, citric acid, and potassium bitartrate), that are common and/or endogenous pH buffering agents that are GRAS-listed substances with long history of use as inactive ingredients in other FDA-approved products (including vaginal administration products). All excipients are also either GRAS-listed, or are common ingredients that exist in other FDA-approved drug products at acceptable levels and routes of administration.

No specific pharmacokinetic/ADME/toxicokinetic studies were conducted, or were considered to be necessary (per FDA agreement at the 9 December 2014 pre-NDA meeting). The three active ingredients (lactic acid, citric acid, and potassium bitartrate) are endogenous, commonly found in dietary ingredients, and are listed as GRAS substances. Ten day nonclinical studies in rats and rabbits with Amphora™ Gel did not reveal any relevant toxicity. Systemic absorption of Amphora™ Gel active ingredients is considered to be unlikely based on the viscosity of the product, and absorption is not required for efficacy since Amphora™ Gel acts by buffering the local vaginal environment to maintain an acidic pH even in the presence of semen.

Evoform, Inc., is not relying on a listed drug in this 505(b)(2) application, but rather, on Evoform-conducted clinical and nonclinical studies, as well as published literature. Nonclinical toxicology studies to evaluate local tolerance were completed in rats and rabbits under IND 64623. The sponsor has obtained the right of reference to IND 64623 for nonclinical information in support of Amphora™ Gel.

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.

From the nonclinical perspective, Amphora™ Gel appears to be reasonably safe for approval.

12 Appendix/Attachments

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/s/

DEEPA B RAO
04/12/2016

KIMBERLY P HATFIELD
04/12/2016
I concur.