Clinical Study Protocol with Revision 01

A Randomized, Double-Blind, Placebo-Controlled, Parallel Design, Multiple-Site Study to Evaluate the Therapeutic Equivalence of Estradiol Vaginal Cream USP, 0.01% (Teva Pharmaceuticals, USA) to Estrace® Estradiol Vaginal Cream, USP, 0.01% (Warner Chilcott) in the Treatment of Atrophic Vaginitis

Study Number 71436001

NCT03294538

Protocol with Revision 1 Approval Date: 18 April 2016

1.0 TITLE PAGE

Drug Product	Estradiol Vaginal Cream USP, 0.01%
Design	Randomized Double-Blind, Placebo-Controlled Parallel Design
Population	Up to 660 post-menopausal females aged 30-75 years inclusive
Sponsor	Teva Pharmaceuticals, USA
Protocol Number	71436001
[redacted] **Study Number**	71436001
Protocol Date	02-11-2015 (Rev 0) 04-18-2016 Revision 1

[redacted]

2.0 KEY STUDY PERSONNEL AND FACILITIES

Sponsor:	Teva Pharmaceuticals, USA
	[redacted]
CRO:	[redacted]
Sponsor's Representative:	[redacted]
CRO representative	[redacted]
Medical Monitor:	[redacted]
Biostatistician:	[redacted]

SIGNATURE PAGE

We, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study. The study will be performed according to this protocol and all applicable FDA regulations.

[redacted] Date

[redacted] Date

[redacted] Date

[redacted] Date

PRINCIPAL INVESTIGATOR'S SIGNATURE

I _____, agree to conduct protocol 71436001 Rev. 0 in accordance with FDA regulations, ICH guidelines and Good Clinical Practice. I understand that no deviations from the protocol may be made without the prior permission of the Sponsor (Teva Pharmaceuticals, USA) or [redacted] the company managing the study.

_____ _____

Principal Investigator Date

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4.0 SYNOPSIS

Protocol Number	71436001
Title	A Randomized, Double-Blind, Placebo-Controlled, Parallel Design, Multiple-Site Study to Evaluate the Therapeutic Equivalence of Estradiol Vaginal Cream USP, 0.01% (Teva Pharmaceuticals, USA) to Estrace® Cream (estradiol vaginal cream, USP, 0.01%; Warner Chilcott) in the Treatment of Atrophic Vaginitis
Objectives	1. Evaluate the therapeutic equivalence of the Test formulation, Estradiol Vaginal Cream USP, 0.01% (Teva Pharmaceuticals, USA) to the marketed product, Estrace® Cream (estradiol vaginal cream, USP, 0.01%; Warner Chilcott) in patients with atrophic vaginitis. 2. Demonstrate the superiority of the Test and Reference (active) treatments over Placebo (vehicle) cream in patients with atrophic vaginitis. 3. Compare the safety of Test, Reference and Placebo treatments in patients with atrophic vaginitis.
Sponsor	Teva Pharmaceuticals, USA
Study Products	• Test: Estradiol Vaginal Cream, USP, 0.01% (Teva Pharmaceuticals, USA) • Reference: Estrace® Cream (estradiol vaginal cream, USP, 0.01%; Warner Chilcott) • Placebo: Placebo cream (Teva Pharmaceuticals, USA) Study products will be supplied in tubes, with a calibrated plastic applicator for dose (2g) administration.
Route of Administration	Topical (Vaginal)
Treatment Randomization	2:2:1 (Test: Reference: Placebo)
Patient Population	Up to 660 healthy post-menopausal females aged 30-75 years inclusive with symptoms of vulvar and vaginal atrophy and no contraindication to estrogen therapy.
Study Design	Randomized, Double-Blind, Placebo-Controlled, Parallel Design
Study Conduct	Patients will administer study medication once daily for 7 days. Patients will visit the clinical center for a total of 3 scheduled visits: 1. Visit 1/Screening (Day -14 to Day -1) 2. Visit 2/Randomization (Day 1)

	3. Visit 3/End of Study (Day 8 + 1)
Inclusion Criteria	1. Signed Informed Consent that meets all criteria of current FDA regulations. 2. Females aged 30-75 years inclusive who are postmenopausal, defined as follows: a. At least 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH level of > 40mIU/ml. b. At least 6 weeks post-surgical bilateral oophrectomy, with or without hysterectomy c. Hysterectomy without oophorectomy if of age that investigator believes would have naturally reached 12 months of spontaneous amenorrhea if uterus had remained intact.. 3. Have ≤5% superficial cells on vaginal smear cytology. 4. Vaginal pH > 5.0. 5. At least one of the following patient self-assessed moderate to severe symptoms of vulvar and vaginal atrophy (VVA) from the following list that is identified by the patient as being most bothersome to her: a. Vaginal Dryness b. Vaginal and/or Vulvar Irritation/Itching c. Dysuria d. Vaginal Pain associated with sexual activity e. Vaginal Bleeding associated with sexual activity* *provided that patient is currently sexually active and plant to remain so throughout study. 6. "Normal" Screening mammogram completed within 9 months before screening in all patients > 40 years old. 7. Normal clinical breast examination at the Screening Visit. 8. Documented papanicolaou (PAP) smear conducted within the previous 12 months with no findings that the Investigator believes would contraindicate the use of topical vaginal estradiol. 9. Patients with an intact uterus should have vaginal ultrasonography results to confirm an inactive endometrial lining, defined as endometrial thickness less than 4 mm.

Exclusion Criteria	1. Females younger than 30 years of age or older than 75 years of age. 2. Patients with a serum FSH level of ≤ 40mIU/ml at screening. 3. Greater than 5% superficial cells on vaginal cytology. 4. Vaginal pH ≤ 5. 5. Significant history or current evidence of chronic infectious disease, system disorder, organ disorder or other medical condition that in the Investigator's opinion would place the study patient at undue risk by participation or could jeopardize the integrity of the study evaluations. 6. Patients with an intact uterus should have vaginal ultrasonography results to confirm an inactive endometrial lining. Patients with an endometrial thickness 4 mm and greater should be excluded. 7. Documented PAP smear conducted within the previous 12 months with findings that the Investigator believes would contraindicate the use of topical vaginal estradiol. 8. Patients with known concurrent vaginal infections including but not limited to: Candida albicans, Trichomonas vaginalis, Chlamydia trachomatis, Neisseria gonorrhea or Gardnerella vaginalis. 9. Patients with active vaginal herpes simplex infection or have had an outbreak within 30 days of the first dosing day. 10. Patients with known, suspected or current history of carcinoma of the breast. All patients over the age of 40 must have had a mammogram performed within 9 months of the study start and all patients will have a physical breast exam performed at screening. 11. Patients with known, suspected or current history of hormone dependent tumor. 12. Patients with baseline systolic blood pressure of > 150 mm Hg and/or diastolic pressure > 90 mm Hg. 13. Any patient with undiagnosed vaginal bleeding or significant risk factors for endometrial cancer. 14. Any history of estrogen-dependent neoplasia (e.g., endometrial cancer). 15. History of acute thrombophlebitis or thromboembolic disorder. 16. Any current or recent (within the previous 6 months) genital bleeding of unknown etiology. 17. Any prescription treatment or over-the-counter or natural remedies for vaginal dryness/irritation within 28 days of screening. Products used for

	lubrication during sexual intercourse within 7 days of screening. 18. Patients whose fasting triglyceride levels are greater than 350 mg/dL. 19. Any patient with a history of radiation therapy or recent (within previous 6 weeks) surgical therapy to the vaginal or cervical areas. 20. Any known or suspected allergies that in the Investigator's opinion would compromise the safety of the patient. 21. Patients who have used vaginal hormonal products (rings, creams, gels) within the 28 days before screening. 22. Any patient who has used transdermal estrogen and/or progestin therapy within the 28 days before screening. 23. Patients who have used oral estrogen and/or progestin therapy or intrauterine progestin therapy within the 56 days before screening. 24. Patients who have used progestin implants or estrogen alone injectable drug therapy within the 3 months before the screening. 25. Patients who have used estrogen pellet therapy or progestin injectable drug therapy within the 6 months before screening. 26. Patients who, in the opinion of the Investigator, would be non-compliant with the requirements of the study protocol. 27. Patients who are unable or unwilling to give informed consent. 28. Receipt of any drug as part of a research study within 30 days before screening. 29. Patients who have participated in this study previously.
Efficacy Endpoints	**<u>Primary Efficacy Endpoint</u>** The primary efficacy endpoint is the proportion of patients in the Per Protocol (PP) population that are identified as "Responders" at the end of the treatment period evaluated on Day 8 + 1. A responder is defined as a patient with at least a 25% reduction from baseline in the sum of % basal/parabasal + % intermediate cells on vaginal cytology AND vaginal pH < 5.0 with a change from baseline vaginal pH of at least 0.5. **<u>Secondary Efficacy Endpoint</u>** The secondary efficacy endpoint is the proportion of patients in the PP population that are identified as "Treatment Success" at the end of the treatment period evaluated on Day 8 + 1. A "Treatment Success" is defined as a score of 0 or 1 at Day 8 + 1 for the symptom identified at baseline as the most bothersome. This evaluation is to

	be based on patient self-assessed symptoms of vulvar and vaginal atrophy on a scale of 0 to 3 where 0 = none and 3 = severe. Refer to Appendix B for rating scales.
Safety Parameters	Adverse events will be classified using standard MedDRA terminology and summarized by treatment group. Summary tables comparing the type, incidence, severity and Investigator's opinion of relationship to the study drug will be prepared by treatment group. Signs and symptoms of atrophic vaginitis will not be considered adverse events, unless in the Investigator's opinion, they have increased in frequency and/or severity to such an extent that the Investigator/patient considers that it is in the patient's best interest to be dropped from continued participation in the study and given alternative therapy for their atrophic vaginitis. . If sufficient data exist, adverse event frequencies will be compared between treatments using Fisher's exact test or a similar test. Concomitant medication use during the randomized treatment period will be tabulated by patient. Adverse events reported during the study will be tabulated in a summary table listing the type, incidence, severity and Investigator's opinion to drug relationship.
Evaluation of Therapeutic Equivalence and Superiority	**<u>Therapeutic Equivalence</u>:** Therapeutic equivalence of the Test product to the Reference product based on the primary endpoint will be evaluated in the PP population after the end of treatment on Day 8 + 1. If the 90% confidence interval (calculated using Yates' continuity correction) for the absolute difference between the proportion of patients considered as "Responders" (at least a 25% reduction from baseline in the sum of % basal/parabasal + % intermediate cells on vaginal cytology AND vaginal pH < 5.0 with a change from baseline vaginal pH of at least 0.5) in the Test and Reference groups is contained within the range [-20%, +20%] then bioequivalence of the Test product to the Reference product will be considered to have been demonstrated for the primary endpoint. Therapeutic equivalence of the Test product to the Reference product based on the secondary endpoint will be evaluated in the PP population after the end of treatment on Day 8 + 1. Secondary analysis will compare the proportion of patients considered to be a "Treatment Success" for their most bothersome symptom. A "Treatment Success" is defined as a score of 0 or 1 at Day 8 for the symptom identified at baseline as the most bothersome). If the 90% confidence interval (calculated using Yates' continuity correction) for the absolute difference between the proportion of patients considered as "Treatment Success" in the Test and Reference groups is contained within the

	range [-20%, +20%] then bioequivalence of the Test product to the Reference product will be considered to have been demonstrated for the secondary endpoint. To declare therapeutic equivalence of the Test product to the Reference product, bioequivalence must be demonstrated for only the primary endpoint. Bioequivalence testing of the secondary endpoint will be conducted for supportive information. **Superiority:** Superiority of the Test and Reference products against the Placebo for primary and secondary endpoints will be tested at the 5% significance level ($p < 0.05$; using two-sided, continuity-corrected Z-test) in the modified Intent-to-Treat (mITT) population using last observation carried forward. The superiority of Test and Reference treatments over the Placebo will be evaluated identically in separate Z-Test analyses.
Sample Size Determination	The primary statistical analysis of interest is the proportion of patients in the Per Protocol (PP) population that are identified as "Responders" at the end of the treatment period evaluated on Day 8 + 1. [redacted], a sample size of 224 patients per active group in the PP population [redacted] (i.e., the 90% confidence interval (Yates' continuity-corrected) of the absolute difference between the Test and Reference "Responder" rate rates is within a defined equivalence range [-20%, +20%]). [redacted]. Using a 2:1 (active: placebo) randomization scheme, and assuming the conversion rate from mITT to PP will be about 90%, 250 patients in each of active groups and 125 patients in the placebo group of the mITT population [redacted]. [redacted] To allow for about 5% of patients who may drop out from the study or are otherwise non-evaluable, up to 660 patients may be randomized to obtain 625 patients in the mITT population (i.e., 250 in each active group and 125 in the Placebo group).

5.0 STUDY SCHEMATIC

	Visit 1 Screening (Day -14 to Day-1)	**Visit 2** Randomization (Day 1)	**Visit 3** End of Study (Day 8 + 1) or Early Termination
Informed Consent	X		
Demographics	X		
Medical History	X	X	
Inclusion/Exclusion Criteria Review	X	X	
Vital Signs	X	X	X
Rating of Symptoms	X	X	X
Physical Exam Including Pelvic Exam	X		X
Breast Exam	X		X
Vaginal Cytology and pH	X		X
PAP*	X		
Serum FSH, Fasting Triglycerides	X		
Mammogram**	X		
Vaginal Ultrasound***	X		
Dispense/Collect Study Medication		X	X
Dispense, Collect, Review Patient Diary		X	X
Adverse Events			X
Concomitant Medications	X	X	X

** Patients who do not have documentation of a PAP smear completed within the last 12 months.*

***Patients over the age of 40 who do not have documentation of a mammogram completed within the 9 months before screening will have a mammogram as part of the screening evaluations.*

****Patients with an intact uterus will have a vaginal ultrasound as part of the screening evaluations*

6.0 LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Term
AE	Adverse Event
ANDA	Abbreviated New Drug Application
C	Celsius
CRF	Case Report Form
CRO	Clinical Research Organization
eCTD	electronic Common Technical Document
F	Fahrenheit
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
g	gram
GCP	Good Clinical Practices
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
ml	milliliter
NDA	New Drug Application
OHRP	Office of Human Rights Protection
OTC	Over-the-Counter
PAP	Papanicolaou
PP	Per Protocol
SAE	Serious Adverse Event
SAP	Statistical Analytical Plan
SAS	Statistical Analysis Software
USA	United States of America
USP	United States Pharmacopeia

7.0 INTRODUCTION

7.1 Disease Being Treated

Female menopause is generally characterized by various signs and symptoms associated with the age-related decline in reproductive hormone levels. There are many indications associated with the reduction in circulating estrogen levels, one of the most common being atrophic changes in the vaginal mucosa.[1] Up to 40% of postmenopausal women have symptoms of atrophic vaginitis. Despite the prevalence of this condition, only 20-25% of symptomatic women seek medical help. Therefore, this condition presents a significant opportunity for improving the quality of life of a large patient population.[2-4]

Vaginal atrophy, also called atrophic vaginitis, is thinning, drying and inflammation of the vaginal walls due to a long-term and significant decline in circulating estrogen levels (~18 pg/ml) in the body.[2] Menopause has been shown to be the leading cause of this condition. However, in non-menopausal women, atrophic vaginitis can result from interruption of ovarian estrogen production by radiation therapy, chemotherapy, oophorectomy or immunologic disorders. Various medications can also cause or contribute to vaginal atrophy, including tamoxifen, danazol (Danocrine®), medroxyprogesterone acetate, leuprolide (Lupron®), and nafarelin acetate (Synarel®).[2]

Symptoms of atrophic vaginitis include vaginal dryness, burning, irritation and leukorrhoea. A cytologic examination of a vaginal smear is typically used to confirm atrophy. Patients with positive diagnosis exhibit a decreased proportion (< 5%) of superficial (mature, protective) cells, compared to 30-60% in healthy pre-menopausal females. There is also a corresponding increase in intermediate and basal/parabasal (immature, fragile) cells. Moreover, patients also exhibit an increase in vaginal pH from a usually acidic (pH 3.5-4.0) to neutral (pH 6.0-8.0). This environment is more favorable for the growth of vaginal infections, which potentially exacerbate symptoms of atrophic vaginitis.[2,4]

7.2 Availability and Efficacy of Already Approved Therapies

Over the Counter (OTC) vaginal moisturizers and water-based lubricants are considered the first line of therapy for atrophic vaginitis. For the more advanced and chronic cases, topical (vaginal) or oral estrogen therapy is often considered. There are a number of prescribed estrogen replacement therapies, approved by the Food and Drug Administration (FDA) for the treatment of atrophic vaginitis, including oral tablets (Estrace®, Femtrace®), transdermal patches (Vivelle-Dot®), transvaginal rings (Estring®), vaginal tablets (Vagifem®) and vaginal creams (Estrace® Premarin®).[1,2]

Systemic (oral/transdermal patch) estrogen therapies have been shown to effectively treat symptoms of atrophic vaginitis, but bear undesirable side effects including increased risk of heart attacks, stroke, endometrial cancer and breast cancer.[5,6] Topical therapies (creams, transvaginal delivery systems) provide low doses of estrogen to the vaginal

mucosa to provide local relief for the symptoms of atrophic vaginitis, while reducing the unwanted side effects associated with systemic delivery systems.[7, 8]

Low dose, topical estrogen therapy is considered most appropriate and convenient for the treatment of vaginal symptoms associated with menopause, particularly when other symptoms including bone loss or vasomotor dysfunction do not need to be targeted.[8,9]

7.3 Scientific and Statistical Considerations

Estrogen therapy has been demonstrated to significantly increase the percentage of superficial cells in the vagina. This increase in the percentage of superficial cells along with a corresponding decrease in parabasal and intermediate cells has been demonstrated to be an accurate and reliable indicator of the status of estrogen levels in the vaginal wall, hence a measure of therapeutic efficacy of estradiol cream in the treatment of atrophic vaginitis. Cytologic assessment of cell samples from the lateral vaginal wall can be used to calculate the number/proportion of superficial, intermediate and parabasal cells. Elevated vaginal pH (pH > 5), monitored by a pH strip in the vaginal cavity, has also been shown to be a reliable indicator of vaginal atrophy. [2,5,7-10]

Clinical studies conducted as a part of the NDA (# 020216) for a similar product, Premarin® Vaginal Cream, 0.625 mg/g (Wyeth-Ayerst Laboratories) indicated that there was a significant increase (26%) in the number of superficial cells at Week 12 (once daily application), compared to baseline. There was also a 58% decrease in the number of parabasal cells, and a significant mean reduction in vaginal pH (-1.57) compared to baseline. Placebo response rates for were 1% and 7% for superficial cells and parabasal cells respectively, and -0.26 for vaginal pH.[11]

This study is designed per recommendations from two FDA draft guidances.[12,13] The FDA Draft Guidance for Estradiol 0.01% vaginal cream (September 2014) recommends a primary endpoint of the study as the proportion of patients in the per protocol (PP) population that are identified as responders at the end of the treatment period. A responder is to be defined as a patient with at least a 25% reduction from baseline in the sum of % basal/parabasal + % intermediate cells on vaginal cytology AND vaginal pH < 5.0 with a change from baseline vaginal pH of at least 0.5.[13] The study population is based on the FDA draft guidance for Industry, Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy (January 2003).[12]

7.4 Justification for use of Placebo

To confirm the sensitivity of a clinical endpoint study to differentiate between two possibly bio-inequivalent products (i.e., to prevent a false positive result of bioequivalence) OGD/FDA recommends that a placebo group be included in such studies.[14-16] In addition to the Test product demonstrating therapeutic equivalence to the Reference product, both the Test and Reference products should demonstrate statistically superior to the Placebo group.

Eligible patients will have a 20% chance of being randomized to Placebo (2:2:1 randomization scheme). There will be 132 patients randomized to the Placebo group, [redacted]

7.5 Risks and Benefits

The risks and benefits to patients enrolled in clinical research studies that include a placebo treatment group must be carefully considered based on three main criteria, namely: the disease being treated, the availability, efficacy and safety of already approved therapies, and the scientific and statistical requirements of the desired outcome of the research study. The Office of Human Rights Protection (OHRP), a Division of the USA Federal Government's Department of Health and Human Services, has issued a detailed guidebook to Institutional Review Boards (IRBs) that includes discussion on the use of placebos in clinical studies.[17]

Qualified patients have a 20% chance they may be randomized to Placebo. Randomized patients will be enrolled in the study for 8 + 1 days. Although the potential for any drug related side effects of significance occurring during the study are low, the risk is higher in the two active treatment groups than in the Placebo group.

All patients enrolled in this study will receive the benefit of free specialized medical care beyond standard medical treatment that would be expected through most health insurance plans. In addition, the patient will receive a stipend for participation to cover costs and expenses associated with trips to the medical facility.

8.0 STUDY OBJECTIVES

1. Evaluate the therapeutic equivalence of the Test formulation, Estradiol Vaginal Cream USP, 0.01% (Teva Pharmaceuticals, USA) to the marketed product, Estrace® Cream (estradiol vaginal cream, USP, 0.01%; Warner Chilcott) in patients with atrophic vaginitis.
2. Demonstrate the superiority of the Test and Reference (active) treatments over Placebo (vehicle) cream in patients with atrophic vaginitis.
3. Compare the safety of Test, Reference and Placebo treatments in patients with atrophic vaginitis.

9.0 INVESTIGATIONAL PLAN

9.1 Study Design and Plan Description

This randomized, double-blind, placebo-controlled, parallel group, multi-site study has been designed to evaluate the therapeutic efficacy and safety of a generic Estradiol Vaginal Cream USP, 0.01% (Teva Pharmaceuticals, USA) compared to the FDA Reference Listed Drug (RLD),

Estrace® Cream (estradiol vaginal cream, USP, 0.01%; Warner Chilcott) in patients with atrophic vaginitis. Additionally, both the Test and Reference products will be tested for superiority against a Placebo.

Following the 14-day screening period, patients who continue to meet the inclusion/exclusion criteria will be randomized in a 2:2:1 ratio (Test: Reference: Placebo) for 7 days of treatment. Up to 660 eligible postmenopausal female patients with atrophic vaginitis patients will be randomized, to obtain an mITT population with an estimated 250 patients in each of the active treatment groups and 125 in the Placebo treatment group.

Before any study-specific procedures are performed, all patients will read and sign the IRB-approved informed consent document.

To qualify for inclusion in the study, patients must be between the ages of 30-75 inclusive, postmenopausal with atrophic vaginitis assessed as moderate to severe using vaginal cytology, vaginal pH and patient-rated signs and symptoms. Patients cannot currently be undergoing treatment for atrophic vaginitis. Patients will only be eligible to participate in the study on one occasion and cannot have participated in another clinical research study within 30 days of being screened for this study.

At Visit 2 (Randomization), each qualified patient will be randomly assigned to one of the following treatment groups in a 2:2:1 ratio:

- **Test**: Estradiol Vaginal Cream, USP, 0.01% (Teva Pharmaceuticals, USA)
- **Reference**: Estrace® Cream (estradiol vaginal cream, USP, 0.01%; Warner Chilcott)
- **Placebo**: Placebo cream (Teva Pharmaceuticals, USA)

Study medication will be self-administered by the patient for 7 days according to the dosing instructions provided. Each patient will be required to dose once a day at approximately the same time of day for 7 consecutive days.

During the study patients will visit the research center for a total of 3 scheduled visits:

- Visit 1/Screening (Day -14 to Day -1)
- Visit 2/Randomization (Day 1)
- Visit 3/End of Study (Day 8+ 1)

Vaginal cytology and vaginal pH determination will be performed as a part of clinical evaluation at Visits 1 and 3. Visit 3 is to be scheduled on the day following the last day of dosing.

The primary efficacy endpoint is the proportion of patients in the per protocol (PP) population that are identified as “Responders” at the end of the treatment period evaluated on Day 8 + 1. A responder is defined as a patient with at least a 25% reduction from baseline in the sum of % basal/parabasal + % intermediate cells on vaginal cytology AND vaginal pH < 5.0 with a change from baseline vaginal pH of at least 0.5.

9.2 Selection of Study Design

This study has been designed based on the draft FDA Guidance for Industry; Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy (January 2003) and the Draft FDA Guidance on Estradiol Vaginal Cream (revised September 2014).[12,13] Statistical analyses of the clinical data will be based on recommendations in the FDA Guidances and any communications with OGD/FDA on how they would like such data analyzed. [12-16,18]

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

1. Signed Informed Consent that meets all criteria of current FDA regulations.
2. Females aged 30-75 years inclusive who are postmenopausal, defined as follows:
    a. At least 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH level of > 40mIU/ml.
    b. At least 6 weeks post-surgical bilateral oopohrectomy, with or without hysterectomy.
    c. Hysterectomy without oophorectomy if of age that investigator believes would have naturally reached 12 months of spontaneous amenorrhea if uterus had remained intact.
3. Have ≤ 5% superficial cells on vaginal smear cytology.
4. Vaginal pH > 5.0.
5. At least one of the following patient self-assessed moderate to severe symptoms of vulvar and vaginal atrophy (VVA) from the following list that is identified by the patient as being most bothersome to her:
    a. Vaginal Dryness
    b. Vaginal and/or Vulvar Irritation/Itching
    c. Dysuria
    d. Vaginal Pain associated with sexual activity
    e. Vaginal Bleeding associated with sexual activity*

    *provided that patient is currently sexually active and plant to remain so throughout study.
6. "Normal" Screening mammogram completed within 9 months before screening in all patients > 40 years old.
7. Normal clinical breast examination at the Screening Visit.

8. Documented papanicolaou (PAP) smear conducted within the previous 12 months with no findings that the Investigator believes would contraindicate the use of topical vaginal estradiol.
9. Patients with an intact uterus should have vaginal ultrasonography results to confirm an inactive endometrial lining, defined as endometrial thickness less than 4 mm.

9.3.2 Exclusion Criteria

1. Females younger than 30 years of age or older than 75 years of age.
2. Patients with a serum FSH level of ≤ 40mIU/ml at screening.
3. Greater than 5% superficial cells on vaginal cytology.
4. Vaginal pH ≤ 5
5. Significant history or current evidence of chronic infectious disease, system disorder, organ disorder or other medical condition that in the Investigator's opinion would place the study patient at undue risk by participation or could jeopardize the integrity of the study evaluations.
6. Patients with an intact uterus should have vaginal ultrasonography results to confirm an inactive endometrial lining. Patients with an endometrial thickness 4 mm and greater should be excluded.
7. Documented PAP smear conducted within the previous 12 months with findings that the Investigator believes would contraindicate the use of topical vaginal estradiol.
8. Patients with known concurrent vaginal infections including but not limited to: Candida albicans, Trichomonas vaginalis, Chlamydia trachomatis, Neisseria gonorrhea or Gardnerella vaginalis.
9. Patients with active vaginal herpes simplex infection or have had an outbreak within 30 days of the first dosing day.
10. Patients with known, suspected or current history of carcinoma of the breast. All patients over the age of 40 must have had a mammogram performed within 9 months of the study start and all patients will have a physical breast exam performed at screening.
11. Patients with known, suspected or current history of hormone dependent tumor.
12. Patients with baseline systolic blood pressure of > 150 mm Hg and/or diastolic pressure > 90 mm Hg.
13. Any patient with undiagnosed vaginal bleeding or significant risk factors for endometrial cancer.
14. Any history of estrogen-dependent neoplasia (e.g., endometrial cancer).
15. History of acute thrombophlebitis or thromboembolic disorder.

16. Any current or recent (within the previous 6 months) genital bleeding of unknown etiology.
17. Any prescription treatment or over-the-counter or natural remedies for vaginal dryness/irritation within 28 days of screening. Products used for lubrication during sexual intercourse within 7 days of screening.
18. Patients whose fasting triglyceride levels are greater than 350 mg/dL.
19. Any patient with a history of radiation therapy or recent (within previous 6 weeks) surgical therapy to the vaginal or cervical areas.
20. Any known or suspected allergies that in the Investigator's opinion would compromise the safety of the patient.
21. Patients who have used vaginal hormonal products (rings, creams, gels) within the 28 days before screening.
22. Any patient who has used transdermal estrogen and/or progestin therapy within the 28 days before screening.
23. Patients who have used oral estrogen and/or progestin therapy or intrauterine progestin therapy within the 56 days before screening.
24. Patients who have used progestin implants or estrogen alone injectable drug therapy within the 3 months before the screening.
25. Patients who have used estrogen pellet therapy or progestin injectable drug therapy within the 6 months before screening.
26. Patients who, in the opinion of the Investigator, would be non-compliant with the requirements of the study protocol.
27. Patients who are unable or unwilling to give informed consent.
28. Receipt of any drug as part of a research study within 30 days before screening.
29. Patients who have participated in this study previously.

9.3.3 Restrictions During the Study

Patients will be instructed to refrain from the following throughout the study:

- Any kind of estrogen, progesterone or androgen hormone replacement.
- Any other treatments, prescription, over-the-counter or natural products or natural methods, for the treatment of vaginal dryness/irritation including but not limited to vaginal lubricants, oils, creams, jellies, food products or saliva.
- Any vaginal drug products other than the study medication (e.g., vaginal antifungals).

9.3.4 Removal of Patients from the Study

Patients will be advised that they are free to withdraw from the study at any time for any reason or, if necessary, the Investigator may withdraw a patient from the study to protect the health of that patient. A patient may also be withdrawn for not complying with study procedures. The clinical report will include all reasons for early withdrawals.

All patients who are randomized and receive study medication will be included in the safety analysis comparing the Test/Reference/Placebo. If a randomized patient terminates from the study early, all efforts will be made to complete the end of study procedures. Patients who are not randomized and thus do not receive study drug, do not need end of study procedures performed. In case of early termination the Investigator shall fully document the reason for early termination. Reasons for early termination may include the following:

- Patient withdrew consent.
- Significant adverse event that led the Investigator or patient to withdraw for safety reasons.
- Non-compliance with protocol requirements (e.g., use of restricted medication, not following dosing procedures, failure to make scheduled study visits in a timely fashion).
- Pregnancy.
- Significant worsening of atrophic vaginitis such that the Investigator and/or patient believe it is in the best interest of the patient to withdraw from the study and be provided alternative treatment.
- Participant enrolls in another clinical trial, or is found to have previously enrolled in this study.

9.4 Treatments

9.4.1 Treatments Administration

Patients will be provided with verbal and written instructions on how to administer the study medication. Patients will be required to self-administer 2 grams of study medication once daily at approximately the same time of the day, for 7 consecutive days. The patients last dose should occur the day before visit 3. The patient should not dose on the day of visit 3.

Patients will gently squeeze the cream out of the tube and into the applicator until the required amount (2 g) is filled based on the calibrated markings on the applicator. The applicator is then to be unscrewed from the tube and cap replaced on the tube. To deliver medication, patients are to lie on back and insert the applicator into the vagina and deliver the dose by pressing down on the plunger. The applicator is to be cleaned with mild soap and warm water after each application.

9.4.2 Identity of Investigational Product

The following products will be used in this study:

- **Test**: Estradiol Vaginal Cream, USP, 0.01% (Teva Pharmaceuticals, USA)
- **Reference**: Estrace® Cream (estradiol vaginal cream, USP, 0.01%; Warner Chilcott)
- **Placebo**: Placebo cream (Teva Pharmaceuticals, USA)

All randomized study product will be blinded and packaged in sealed boxes. Each box of Reference product will contain a tube containing 42.5 g of study product (cream) and a calibrated plastic applicator for dose (2 g) administration, and each box of Test product will contain a tube containing 44 g of study product (cream) and a calibrated plastic applicator for dose (2 g) administration. Each tube will be identified by a label bearing the Sponsor name, protocol number, randomization number, treatment duration and a statement that the study medication is for Investigational Use Only. A corresponding label including the same randomization number will be attached to the patient's source document.

The study staff will dispense the study medication box only to those patients identified by the Investigator. The study staff will instruct the patients on the use and return of study drug. The patient will be instructed not to discuss the appearance of the study medication tube with any study personnel conducting the study visits i.e., the Investigator(s) or the Study Coordinator(s).

[redacted]

The study medication will be shipped to each Investigator's site from a centralized pharmacy. The Principal Investigator at each site is responsible for ensuring that all study medications are stored in a locked, secure location, with access limited to the Investigator and his/her designee(s). An accurate inventory of the study medication will be maintained in accordance with federal regulations. [redacted]

Once the site has been notified that they may do so, all unused study medication and empty or partially used tubes of study medication may be returned to the Sponsor or designee.

Storage Conditions: Study medication is to be stored in a secure, locked location, at room temperature, protected from temperatures in excess of 40ºC (104ºF).

9.4.3 Method of Assigning Patients to Treatment Groups

The study drug will be randomized, packaged and blinded by an independent packaging company. Randomization will be pre-planned according to a computer-generated randomization schedule. [redacted] Each patient will be provided with one patient kit, containing 1 tube of study medication.

Each patient will receive a screening number at Visit 1, which will be recorded in the patient's CRF. At Visit 2, eligible patients will receive a randomization number (based on treatment assigned), which will be recorded in the CRF. [redacted]. Patients will be randomized to a treatment regimen by assigning treatments in sequential order. At the end of the study, after all the clinical data has been entered and the study database has been locked, a copy of the randomization will be sent to the statistician.

9.4.4 Study Blind

The Investigator, staff at the study site, study monitors, and data analysis/management personnel will be blinded to the patient assignment. To maintain the Investigator-Blind, the Independent Dispenser will be responsible for dispensing and collecting study medication. The patient will be requested not to discuss the appearance of the study medication with the Investigator or study staff.

Each study site will have at least one Independent Dispenser. The role of the Independent Dispenser is to dispense and collect all study medication from the patients and to ensure the study medication logs are completed. They should not be involved in collecting any efficacy data in the study thus ensuring the integrity of the study blind.

To ensure information that could potentially bias handling of data is not disclosed at clinical sites, a third party will hold the randomization scheme until after database lock. For each patient an individual code break card describing the actual treatment will be provided with the study medication, to be un-blinded only in the case of medical emergency and should be kept at the site with the study documents until the study is completed. Whenever possible, the [redacted] Medical Monitor must be contacted before breaking the blind for any patient. The code break cards should be stored in a secure location at all times and maintained at the site for all randomized patients after the completion of the study.

At the conclusion of the study, after the database has been locked, each site will be sent an envelope containing the full study randomization scheme that should be retained with the study documents in case needed during an FDA Inspection.

9.4.5 Compliance

Patients will be provided with a diary to record the time and date of dosing, other concomitant medications and adverse events. A single dose is defined as application of 2 g cream. Patients administering fewer than 75% (i.e., < 6), or more than 125% (i.e., > 8)

of the required doses, or who missed > 1 dose will be considered non-compliant with dosing. Compliance with dosing will be verified by the use of the patient diaries.

9.5 Study Conduct

9.5.1 Visit 1 (Day -14-Day 1): Screening

1. **Informed Consent:** Patients, who are willing to comply with study procedures will read, understand and sign the informed consent as appropriate.
2. **Medical History and Baseline Demographics:** Patient's demographic and medical history including concomitant medication use within the last 6 months will be reviewed.
3. **Vital Signs:** Blood pressure, pulse, temperature and respiration rate will be recorded for each patient.
4. **Inclusion/Exclusion**: Confirm the patient meets all inclusion/exclusion criteria.
5. **Symptom Rating**: Patients will be asked to complete a rating scale to record severity of signs and symptoms for atrophic vaginitis. Refer to Appendix A.
6. **Physical and Pelvic Examination:** A general physical exam, including a pelvic examination will be conducted to determine overall patient health. Refer to section 9.6.5.
7. **Vaginal Ultrasound:** A vaginal ultrasound will be performed for patients with an intact uterus.
8. **Breast Exam:** A physical breast examination will be conducted.
9. **Mammogram**: Results from a mammogram performed within the last 9 months will be obtained. If unavailable, then a mammography will be scheduled.
10. **Vaginal Cytology and pH**: A specimen will be obtained for vaginal cytology and vaginal pH testing will be performed. Refer to section 9.6.9.
11. **PAP smear: Obtain the r**esults of a PAP smear conducted within the last 12 months or conduct a PAP smear during the pelvic exam.
12. **Blood Sample: Collect** a fasted blood sample for laboratory testing (FSH and Triglycerides). Refer to Appendix A and Section 9.6.8.
13. Schedule Visit 2.

9.5.2 Visit 2 (Day 1): Randomization

1. **Medical History:** Patient's medical history including concomitant medication use since last visit will be reviewed.
2. **Inclusion/Exclusion**: Confirm the patient meets all inclusion/exclusion criteria.

3. **Vital Signs:** Blood pressure, pulse, temperature and respiration rate will be recorded.
4. **Symptom Rating**: Patients will be asked to complete a rating scale to record severity of signs and symptoms for atrophic vaginitis. Refer to Appendix A.
5. Dispense study medication, applicator, instructions and patient diary to patients eligible for randomization.
6. Schedule Visit 3.

9.5.3 Visit 3 (Day 8+ 1): End of Study/Early Termination

The patient should not dose on the day of Visit 3. Visit 3 is to be scheduled the day after the last day of dosing.

1. **Concomitant Medications:** Patient diary will be reviewed for concomitant medication use since last visit.
2. **Adverse Events:** Patient diary will be reviewed and patients questioned about adverse events since last visit.
3. **Vital Signs:** Blood pressure, pulse, temperature and respiration rate will be recorded.
4. **Symptom Rating**: Patients will be asked to complete a rating scale to record severity of signs and symptoms for atrophic vaginitis. See Appendix A.
5. **Physical and Pelvic Examination:** A general physical exam, including a pelvic examination will be conducted to determine overall patient health.
6. **Breast Exam:** A physical breast examination will be conducted.
7. **Vaginal Cytology and pH**: A specimen will be obtained for vaginal cytology and vaginal pH testing will be performed. See section 9.6.9.
8. **Collect Study Product:** Empty/used/unused tubes of study medication and applicators will be collected for accountability
9. **Review Diary:** Dosing compliance will be reviewed based on patient diary
10. Review completeness of all source documents and discharge from the study.

9.6 Study Procedures

9.6.1 Informed Consent

No patient will be entered into the study without reading, understanding, and signing an informed consent. For illiterate patients, verbal consent should be obtained in the presence of and be countersigned by a literate witness. If any other language is required, translation will be performed by a certified translator.

9.6.2 Demographics

At Visit 1 each patient shall be required to provide basic demographic information including date of birth, gender, ethnicity and race.

9.6.3 Medical History

At Visit 1 patients will be questioned about medical history, including acute and chronic medical history and medical history relevant to their vaginal atrophy, as well as all concomitant medication use within the previous 6 months. At Visit 2 medical history will be reviewed and updated if changes have occurred.

9.6.4 Vital Signs

The patient's vital signs will be recorded (pulse, blood pressure, temperature and respiration rate) at Visits 1, 2 and 3. At Screening and Randomization blood pressure reading cannot exceed 150/90 to qualify for randomization.

9.6.5 Physical Exam, Pelvic Exam and Breast Exam

At Visit 1 the Investigator will perform a general physical exam including pelvic exam and breast exam. The results of this exam should, in the Investigator's opinion, be consistent with a diagnosis of estradiol-deficient vaginal/vulvar atrophy for the patient to be eligible for inclusion in the study. Additionally this exam should exclude the possibility that the symptoms could be caused by any concurrent disease (e.g., bacterial vaginosis, candida infection). Any patient diagnosed with, or with any suspected concurrent vaginal infection or other vaginal disease will be excluded from the study.

At Visit 3 the Investigator will perform a general physical exam including pelvic and breast exams, any negative findings on exam should be reported as Adverse Events.

9.6.6 Rating of Symptoms

At Visits 1, 2 and 3 the blinded clinical staff or Investigator will question the patient regarding the severity of their atrophic vaginitis symptoms (see Appendix B for rating scales). The following symptoms will be evaluated:

- Vaginal Dryness
- Vaginal/Vulvar irritation/itching
- Dysuria
- Vaginal Pain associated with Sexual Activity
- Vaginal Bleeding

The severity of each symptom will be recorded on the source documents. The patients will be asked to identify which symptom is considered to be the most bothersome symptom at each visit.

The worsening in severity of the signs and symptoms need not be additionally included as an adverse event, unless the patient requires additional treatment or the condition is an AE in the opinion of the Investigator.

9.6.7 Concomitant Medication Use

All concomitant medication use within 6 months of Visit 1 and throughout the study will be recorded.

9.6.8 Laboratory Evaluations

All patients will have a blood sample taken for evaluation of serum FSH levels. Serum FSH will be evaluated by a central clinical laboratory. Patients must have a Serum FSH > 40mIU/ml to be eligible for participation in the study.

All patients will have a blood sample taken for fasting triglyceride testing. These samples will be sent to the central laboratory for testing. Patients with fasting triglyceride values > 350 mg/dL will not be eligible for inclusion in the study.

9.6.9 Vaginal Cytology, pH Testing and PAP smear

At Visits 1 and 3, a vaginal cytology specimen will be collected by scraping the right and left lateral vaginal walls (mid-way between the fornix and introitus) with a spatula. The cells and mucus will be mixed and fixed according to the instructions provided by the central laboratory. Samples will be sent to the central laboratory for cytology testing.

The central laboratory will report the cytology results to the Investigative site before randomization. To protect the study blind, the central laboratory will not release the results of any other cytology tests other than the screening results to either the Investigator or [redacted] until the study is completed.

The patient's vaginal pH will be measured by inserting standardized pH paper into the vagina and comparing the color change result to the manufacturer's color chart. All Investigators will use the same type of provided pH paper (e.g., pHEM-ALERT, Gynex Corporation). pH paper should be able to read at a minimum 0.5 unit of pH changes.

At Visit 1 Patients will have a PAP smear completed during the pelvic exam if the Investigator does not have results from a PAP smear completed within the last 12 months. PAP smear samples will be sent to the central laboratory (ACM Medical Lab., Inc.) for testing.

9.6.10 Dosing Instructions and Diary

Patients will be given a dosing diary with instructions on dosage administration and diary completion. Patients will be asked to record the time and date of each dose, AEs, and concomitant medications throughout the study. The diary will be reviewed by the study staff at Visit 3/end of the study.

9.6.11 Dosing Compliance

Dosing compliance will be checked by site staff at Visit 3 by reviewing patient diary entries. Patients will be considered compliant with dosing if they administer 75% (i.e. 6 doses)-125% (i.e., 8 doses) of the required number of doses, and do not miss more than 1 dose.

9.6.12 Dispensing Study Drug

An Independent Dispenser will dispense randomized study medication at Visit 2 with dosing instructions. The Independent Dispenser will ensure the study medication logs are reported correctly.

9.6.13 Collecting Study Drug

Study medication tubes will be collected at Visit 3 by the Independent Dispenser .

9.7 Adverse Events

The patients will be monitored throughout the study for any adverse experiences. AEs will be collected through both solicited and unsolicited means and subsequently coded in tabular form using the MedDRA Version 17.0 or higher adverse event dictionary. The patients will be encouraged to report signs, symptoms, and any changes in health to the clinic staff. Severity of each AE will be determined by the clinic staff based on observation and questioning of the patient. The Investigator will judge the relationship of the event to the study treatments.

Definitions

An adverse event is any untoward medical occurrence in a clinical investigational patient administered a pharmaceutical product, regardless of whether it has a causal relationship with this treatment. In this study, any adverse event occurring after the patient has signed the informed consent form should be recorded and reported as an adverse event.

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of the study, or significant worsening of the disease under study or of any concurrent disease, whether or not considered related to the study drug. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during the study will not be considered adverse events.

Abnormal results of diagnostic procedures, including laboratory findings, are considered to be AEs if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event (SAE)
- is associated with clinical signs or symptoms
- is considered by the physician to be of clinical significance

This includes events not seen at baseline, or worsened if present at baseline.

Recording and Reporting Adverse Events

For adverse event recording, the study period is defined for each patient as that time period from signature of the informed consent form through the follow-up period. For this study, the follow-up period is defined as 30 days after the last study visit.

All adverse events that occur during the defined study period must be recorded on the source documentation and transcribed onto the CRF, regardless of the severity of the event or judged relationship to the study drug. For serious adverse events, the Serious Adverse Event Form must also be completed and the serious adverse event must be reported immediately (see Section 9.8.2.). The investigator does not need to actively monitor patients for adverse events once the study has ended.

At each contact with the patient, the investigator or designee must query the patient for adverse events by asking an open-ended question. All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, on the Serious Adverse Event Form.

The clinical course of each adverse event will be monitored at suitable intervals until resolved or stabilized or returned to baseline, or until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made.

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding study drug, treatment administered, and outcome for each adverse event must be recorded on the source documentation and transcribed onto the CRF.

The relationship of each adverse event to study drug treatment and study procedures, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

Severity of an Adverse Event

The severity of each adverse event must be recorded as 1 of the choices on the following scale:

Mild:	No limitation of usual activities
Moderate:	Some limitation of usual activities
Severe:	Inability to carry out usual activities

Causality Assessment of Adverse Events

The relationship to the study treatment is characterized as:

TERM	DEFINITION	CLARIFICATION
No Reasonable Possibility (not related)	This category applies to those adverse events which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to those adverse events for which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the test drug.	An adverse experience may be considered No Reasonable Possibility if it is clearly due to extraneous causes or when (must have two): ▪ It does not follow a reasonable temporal sequence from the administration of the IMP. ▪ It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. ▪ It does not follow a known pattern of response to the test drug. ▪ It does not reappear or worsen when the drug is re-administered.
Reasonable Possibility (related)	This category applies to those adverse events which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the IMP.	An adverse experience may be considered a reasonable possibility of being related if or when (at least three of the following): ▪ It follows a reasonable temporal sequence from administration of the IMP. ▪ It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject. ▪ It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists. • It follows a known pattern of response to the IMP.

9.8 Serious Adverse Events

9.8.1 Definition of a Serious Adverse Event

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- death
- a life-threatening adverse event (i.e., the patient was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death

- inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event. Hospitalizations scheduled for an elective procedure or for treatment of a pre-existing condition that has not worsened during participation in the study will not be considered serious adverse events.
- persistent or significant disability or incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.

Expectedness

A serious adverse event that is not included in the Adverse Reaction section of the relevant reference safety information by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The reference safety information for this study is the ® Estrace® drug label.

The sponsor's Global Patient Safety & Pharmacovigilance Department will determine the expectedness for all serious adverse events.

9.8.2 Reporting Serious Adverse Events

It is the responsibility of the CRO to report a Serious Adverse Event (SAE) to the FDA within proper time constraints as per the Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies.[19] Confirmation of this report must then be provided to Teva's study representative as well as their Pharmacovigilance department (contact information below).

Any serious adverse event (SAE) that occurs after the start of the study period must be reported by the study site, in English, within 24 hours of becoming aware of the SAE, to the study representative at [redacted] as well as one of the contacts listed below. All serious adverse events occurring during the study period, whether or not considered to be related to the study drug, must be reported within 24 hours to the study representative at [redacted] as well as the two contacts below.:

[redacted]

Or

[redacted]

[redacted] will be responsible for reporting the SAE to Teva using the following guidelines.

PLEASE NOTE THAT EMAIL IS THE PREFERRED MEANS OF COMMUNICATION.

[redacted]

Teva Pharmaceuticals USA

[redacted]

AND

Teva Pharmacovigilance

[redacted]

These SAE reports must contain the following information:

- Study name/number (for EU also the Eudract number)
- Study Drug
- Investigator details (name, phone, fax, e-mail)
- Patient Number
- Patient Initials
- Patient Demographics
- Clinical Event
  - Description
  - Date of onset
  - Treatment (drug, dose, dosage form)
  - AE Relationship to study drug
  - Action taken regarding study drug in direct relationship to the AE

Additional information may include the following:

- date of first dose of study drug
- date and amount of last administered dose of study drug
- action taken
- outcome, if known
- severity
- concomitant therapy (including doses, routes, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death:
- cause of death (whether or not the death was related to study drug)
- autopsy findings (if available)

For the purposes of SAE reporting, the study period is defined as the time period from the first dose through the follow-up period. For this study, the follow-up period is defined as 30 days after the last study visit. All SAEs occurring during the study period, whether or not considered to be related to the study drug, must be reported within 24 hours to the study representative at [redacted] as well as the two contacts above. [redacted] will report the SAE to Teva. Even though the investigator does not need to actively monitor patients for adverse events once the study has ended, serious adverse events occurring to a patient after their treatment has ended should be reported to [redacted] if the investigator becomes aware of them.

[redacted] will be responsible for notifying the Investigative sites as required. Under 21 CFR 320.31 (d)(3) the Investigator must inform other investigators involved in the study plus the FDA within 15 days of becoming aware of the occurrence of the serious AEs. Serious AEs that occur with the study drugs must be reported.[19]

10.0 STATISTICAL METHODS

10.1 Statistical Plan

A Statistical Analysis Plan (SAP) including study data report format, following FDA guidance "Draft Guidance on Estradiol Cream 0.01% revised Sept 2014)detailing the intended statistical analysis of the study data, will be prepared as a separate document and finalized before database lock. Any deviation from the original statistical plan will be

described and justified in the final report, as appropriate. The procedure for accounting for missing, unused and spurious data will be included in the Statistical Analysis Plan.

All statistical analysis will be conducted using SAS®, Version 9.4 or higher.

10.2 Determination of Sample Size

The primary statistical analysis of interest is the proportion of patients in the Per Protocol (PP) population that are identified as "Responders" at the end of the treatment period evaluated on Day 8 + 1.

[redacted] a sample size of 224 patients [redacted]

[redacted] Using a 2:1 (active: placebo) randomization scheme, and assuming the conversion rate from mITT to PP will be about 90%, 250 patients in each of active groups and 125 patients in the placebo group of the mITT population [redacted]

[redacted] To allow for about 5% of patients who may drop out from the study or are otherwise non-evaluable, up to 660 patients may be randomized to obtain 625 patients in the mITT population (i.e., 250 in each active group and 125 in the Placebo group).

10.3 Study Populations

10.3.1 Per-Protocol Population

Patients will be eligible for inclusion in the PP population if they:

- Met the inclusion/exclusion criteria as defined in this protocol at Visit 1 and 2
- Did not take any prohibited medications throughout the study
- Did not have any significant deviations from the protocol
- Did not develop any concurrent vaginal infection or illness exhibiting symptoms similar to atrophic vaginitis, or symptoms that in the Investigator's opinion would interfere with primary and secondary endpoint assessments

- Completed the last study visit (Visit 3) Day 8 + 1.
- Were compliant with dosing between 75%-125% of the required doses (6 – 8 doses), and did not miss more than 1 dose
- Any patient who withdrew from the study because of lack of efficacy will be included in the PP population as a Non-Responder. Patients who discontinue early for other reasons should be excluded from the PP population and included in the mITT population using Last Observation Carried Forward (LOCF).

10.3.2 mITT Population

The mITT population will include all patients in the PP population, AND patients who:

- Administered at least one dose of randomized study medication and
- Had a post-randomization evaluation

10.3.3 Safety Population

The safety population will include all patients who are randomized and administered at least one dose of study drug.

10.4 Baseline Comparability

Baseline comparability of all treatment groups will be evaluated separately in the PP, mITT and Safety populations. The following baseline demographics (determined from their initial study visit) will be evaluated:

- Age (years)
- Gender (male/female)
- Ethnicity (Hispanic/non Hispanic)
- Race (White, Black/African American, Native Hawaiian or Other Pacific Islander, Asian, American Indian or Alaska Native, Other)
- natural or surgical menopause
- duration of postmenopausal status
- baseline signs and symptoms
- baseline % of the three major vaginal wall cell types (basal/parabasal cells, intermediate cells and superficial cells)
- vaginal pH

Descriptive statistics by treatment group will be presented.

10.5 Efficacy Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients in the PP population that are identified as "Responders" at the end of the treatment period evaluated on Day 8 + 1.

A responder is defined as a patient with at least a 25% reduction from baseline in the sum of % basal/parabasal + % intermediate cells on vaginal cytology AND vaginal pH < 5.0 with a change from baseline vaginal pH of at least 0.5.

Secondary Efficacy Endpoint

The secondary efficacy endpoint is the proportion of patients in the PP population that are identified as "Treatment Success" at the end of the treatment period evaluated on Day 8 + 1.

A "Treatment Success" is defined as a score of 0 or 1 at Day 8 + 1 for the symptom identified at baseline as the most bothersome. This evaluation is to be based on patient self-assessed symptoms of vulvar and vaginal atrophy on a scale of 0 to 3 where 0 = none and 3 = severe. Refer to Appendix B for rating scales.

10.6 Therapeutic Equivalence Analysis

Therapeutic equivalence of the Test product to the Reference product based on the primary endpoint will be evaluated in the PP population after the end of treatment on Day 8 + 1. If the 90% confidence interval (calculated using Yates' continuity correction) for the absolute difference between the proportion of patients considered as "Responders" (at least a 25% reduction from baseline in the sum of % basal/parabasal + % intermediate cells on vaginal cytology AND vaginal pH < 5.0 with a change from baseline vaginal pH of at least 0.5) in the Test and Reference groups is contained within the range [-20%, +20%] then bioequivalence of the Test product to the Reference product will be considered to have been demonstrated for the primary endpoint.

Therapeutic equivalence of the Test product to the Reference product based on the secondary endpoint will be evaluated in the PP population after the end of treatment on Day 8 + 1. Secondary analysis will compare the proportion of patients considered to be a "Treatment Success" for their most bothersome symptom. A "Treatment Success" is defined as a score of 0 or 1 at Day 8 for the symptom identified at baseline as the most bothersome). If the 90% confidence interval (calculated using Yates' continuity correction) for the absolute difference between the proportion of patients considered as "Treatment Success" in the Test and Reference groups is contained within the range [-20%, +20%] then bioequivalence of the Test product to the Reference product will be considered to have been demonstrated for the secondary endpoint.

To declare therapeutic equivalence of the Test product to the Reference product, bioequivalence must be demonstrated for only the primary endpoint. Bioequivalence testing of the secondary endpoint will be conducted for supportive information.

10.7 Superiority to Placebo Analysis

Superiority of the Test and Reference products against the Placebo for primary and secondary endpoints will be tested at the 5% significance level ($p < 0.05$; using two-sided, continuity-corrected Z-test) in the mITT population using last observation carried forward. The superiority of Test and Reference treatments over the Placebo will be evaluated identically in separate Z-Test analyses.

10.8 Safety Analysis

All study patients who use at least one application of the study drugs will be included in the safety analysis. Adverse events will be classified using standard MedDRA terminology Version 17.0 or higher and summarized by treatment group. Summary tables comparing the type, incidence, severity and Investigator's opinion to drug relationship relation will be prepared by treatment group. Signs and symptoms of atrophic vaginitis will not be considered adverse events, unless in the Investigator's opinion, they have increased in frequency and/or severity to such an extent that the Investigator/patient considers that it is in the patient's best interest to be dropped from continued participation in the study and given alternative therapy for their condition. If sufficient data exist, adverse event frequencies will be compared between treatments using Fisher's exact test or a similar test. Concomitant medication use during the study will be tabulated by patient. Adverse events reported during the study will be tabulated in a summary table listing the type, incidence, severity and Investigator's opinion to drug relationship.

11.0 REGULATORY OBLIGATIONS

11.1 Institutional Review Board

The study protocol, informed consent form, Investigator's Brochure, or package insert (as applicable), and any specific advertising will be submitted to, and approved by, an Institutional Review Board (IRB) before the start of the study. A form must be signed by the chairman or designee of the IRB noting the approvals. This notification of the board's approval along with a description by profession and gender of the board's composition will be provided to the Sponsor.

11.2 Study Documentation

This study will be conducted in compliance with the protocol, Good Clinical Practices (GCPs) and all applicable regulations, including the Federal Food, Drug and Cosmetics Act, US applicable Code of Federal Regulations (title 21), parts 50, 56, 312, 320 and any IRB requirements relative to clinical studies and the Declaration of Helsinki, June 1964, as modified by the 59th World Medical Association General Assembly, October 2008.

The Investigator will permit trial-related monitoring, audits, IRB review and regulatory inspections providing direct access to source data/documents.

11.2.1 Protocol

The Investigator indicated on FDA Form 1572 will act as the Principal Investigator at each study site. Protocols will be noted as approved by placement of the [redacted] Representative's signature on the cover page. The Sponsor of the study will also approve the protocol by having a study-responsible individual sign the protocol cover page.

11.2.2 Informed Consent

An Informed Consent Form (ICF) that includes all of the relevant elements currently required by FDA and local State regulations will be provided to each prospective study patient before enrollment into the study. The type and method of study, tests to be administered, any potential or possible hazards, and the patient's right to withdraw from the study at any time will be explained to the patients by the Investigator or designee. Once the Investigator or designee is assured that an individual candidate understands the implications of participating in this study, the patient will be asked to give consent by signing and dating in the appropriate areas of the ICF. The Investigator or designee will also sign and date the form, along with a staff member who will sign the ICF as a witness to verify that the patient has indeed received information. For illiterate patients, verbal consent should be obtained in the presence of and be countersigned by a literate witness. If any other language is required, translation will be performed by a certified translator. A copy of the ICF will be provided to the patient.

11.2.3 Protocol and Informed Consent Changes

Revisions to the original protocol will be documented in amendments, incorporated as a preface to the new version and approved by the IRB. Any revision that substantially alters the study design or increases potential risk to the patient requires the patient's consent to continue in the study. Revisions to the original ICF will also be approved by the IRB. The approvals will be processed in accordance with the established IRB procedures. Copies of all protocol and ICF amendments/revisions, along with letters noting IRB approval, will be submitted to the Sponsor.

11.2.4 Source Documents and Case Report Forms

All patients will be identified by initials, date of birth, and a unique patient number. Source documents will be used to record all study-related data. Source document entries will be used to complete Case Report Forms (CRFs). A set of CRFs will be completed for each patient enrolled in the study. All data and CRFs will be reviewed, evaluated and signed by the Investigator, as required.

The original source documents and a copy of the corresponding CRFs will be retained by the Investigator. Patients who terminate early from the study will have the Visit 3 (end of study) source/CRF completed.

11.2.5 Drug Accountability

All drug receipt, inventory, dispensing, dosing and reconciliation records will be maintained in compliance with Federal Regulations. The study drug will be dispensed to qualified study patients according to established procedures. Once the site has been notified that they may do so, all unused study medication and empty or partially used tubes of study medication may be returned to the Sponsor or designee

11.2.6 Drug Storage

All study drug will be stored at controlled room temperature protected from temperatures in excess of 40ºC (104ºF), in a secure place with access by authorized individuals only. The Investigator will be responsible for maintaining accurate records of drug receipt, dispensing, and return Once the site has been notified that they may do so, all unused study medication and empty or partially used tubes of study medication may be returned to the Sponsor or designee

Retention of Reserve Samples

Each investigator will randomly remove at least one block of study drug per shipment, and store as retention samples. A block contains five patient kits (as the study is randomized in a 2:2:1 ratio). [redacted] The number of each patient kit in each block kept for retention will be noted on the drug accountability form. These retention samples should be stored under the appropriate storage conditions for a minimum of 5 years following the application approval or, if not approved, at least 5 years after the completion of the study.

11.2.7 Reporting Safety Information to the IRB

The Investigator must promptly report to the Investigator's IRB all unanticipated problems involving risks to patients. This includes death from any cause and all serious adverse events occurring during the study, regardless of the assessed causality.[19]

11.2.8 Record Retention

All drug accountability records, CRFs, source data and related regulatory documents must be retained for at least ten years following completion of the study or for two years after the test product has been approved for marketing by the Food and Drug Administration.

11.2.9 Study Monitoring and Auditing

[redacted] will be responsible for monitoring the study according to Good Clinical Practice and applicable regulations. Monitoring visits are for the purpose of confirming adherence to the protocol and to verify complete and accurate data

collection. The clinical site will make all records associated with the study available to [redacted] representative during such visits and audits

The study may be subject to audit by the Sponsor, Sponsor Representative or by regulatory authorities. If such an audit occurs the Investigator must agree to allow access to required patient records. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation, as well as on-site review of study procedures.

11.2.10 End of the Trial

The end of the trial is defined as the time at which the last patient has completed their last visit in the study. Upon completion of the study, the study drug will no longer be available to the patient but the Investigator can, at their discretion, discuss alternative treatments with the patient.

11.2.11 Clinical Study Report

At the end of the study a full report per requirements of Sponsor and regulatory authorities will be prepared which will include a narrative of the clinical conduct and results of the study, a statistical report including a description of the analysis performed, and other documentation as may be appropriate. The report will be in electronic format according to eCTD and ICH formatting standards and guidelines.[20] ANDA summary tables will also be generated. Data sets will be provided in SAS® transport (.xpt) format with appropriate description (Read Me) files as required by FDA.[20]

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13.0 APPENDICES

APPENDIX A

CLINICAL LABORATORY TESTING

As part of the Screening Procedures the blood and cytology samples will be obtained for the following laboratory evaluations:

Serum FSH

Fasting Triglycerides

Vaginal Cytology

PAP Smear (as appropriate)

All samples will be sent to the central laboratory:

APPENDIX B

DEFINITIONS AND SEVERITY RATINGS FOR SIGNS AND SYMPTOMS

Vaginal Dryness		
No lubrication or secretions noted on perineum or after wiping; if sexually active loss of lubrication during coitus.		
Score	Severity	Description
0	None	No noticeable lack of vaginal lubrication or secretions reported or observed
1	Mild	Episodic loss of lubrication/secretions or noticed some reduction in general secretions, does not interfere with daily activities
2	Moderate	Symptom present most of the time, and noticeable but overall is tolerable and does not interfere with daily activities
3	Severe	Very minimal or no natural vaginal lubrication/secretions almost all of the time and interferes with normal activities

Vaginal/Vulvar Irritation/Itching		
Scratching or sand paper type feeling in vaginal/vulvar area. May feel uncomfortable with clothing or undergarments touching the perineum.		
Score	Severity	Description
0	None	No irritation or itching reported.
1	Mild	Occasional irritation/itching but does not interfere with daily activities
2	Moderate	Frequent irritation/itching that can be uncomfortable but generally does not interfere with daily activities
3	Severe	Very frequent or continuous irritation/itching of the vaginal area, may interfere with daily activities.

Dysuria		
Pain or discomfort during urination		
Score	Severity	Description
0	None	No pain or discomfort during urination reported.
1	Mild	Occasional or slight discomfort during urination but tolerable
2	Moderate	Some discomfort during urination at least 50% of the time which can be painful but overall tolerable.
3	Severe	Urination nearly always painful, usually intolerable and causing disruption to daily activities

Vaginal Pain during Sexual Activity		
Suffers discomfort or pain during sexual activity that may be restrictive.		
Score	Severity	Description
0	None	No discomfort or pain
1	Mild	Some feeling of vaginal soreness or pain, during or after sexual activity. Does restrict frequency of or type of sexual activity.
2	Moderate	Vaginal pain during sexual activity such that frequency and type of sexual activity have been disrupted. Lubrication may be needed for penetration
3	Severe	Vaginal penetration very painful and impossible without vaginal lubrication. Discomfort such that frequency of sexual activity significantly reduced.

Vaginal bleeding during or after sexual activity		
Score	Severity	Description
0	Absent	No vaginal bleeding observed
1	Present	Bleeding observed during or soon after vaginal activity

At each visit each patient must also clearly identify which is the most bothersome sign/symptom to her, even if she rates two or more symptoms the same severity rating.

APPENDIX C REVISIONS TO THE PROTOCOL

Revision	Date
1	4/18/2016

The following revisions were made to the protocol dated 02/11/2015:

- The Visit 3 allowable window was clarified to Day 8 + 1
- An end of study breast examination was added

Additionally minor typographical updates were made.

APPENDIX D

PRODUCT INSERT FOR ESTRACE®