Statistical Analysis Plan

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

Study Number 71436001

NCT03294538

Statistical Analysis Plan Approval Date: 04 August 2016

[redacted]

STATISTICAL ANALYSIS PLAN

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

Protocol Number: 71436001
[redacted] Study Number: 71436001

Sponsor:
Teva Pharmaceuticals, USA
1090 Horsham Rd
North Wales, PA 19454

Contract Research Organization:
[redacted]

August 4, 2016

Final Version 1.0

[redacted]

Estradiol Vaginal Cream USP, 0.01% **Protocol/Study Number 71436001**

SAP FINAL VERSION APPROVALS

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

Written By: Signature: [redacted]	Date:_____
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Approved By: Signature: [redacted] Teva Pharmaceuticals, USA	Date:_____

[redacted]

STATISTICAL ANALYSIS PLAN

Estradiol Vaginal Cream USP, 0.01% Protocol/Study Number 71436001

Revision History

VERSION	DATE	DESCRIPTION OF REVISIONS	REVISED BY
Draft 1.0	July 25, 2016	New Document	[redacted]
Final 1.0	August 4, 2016	Incorporate client comments and finalize SAP	

List of Abbreviations and Definition of Terms

ADaM	Analysis Data Model
AE	Adverse Event
C	Celsius
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
dL	Deciliter
F	Fahrenheit
FDA	Food & Drug Administration
FSH	Follicle-stimulating hormone
Hg	Mercury
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
LOCF	Last Observation Carried Forward
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	modified Intent-to-Treat Population
mL	Milliliter
mm	Millimeter
OGD	Office of Generic Drugs
PAP	Papanicolaou
pH	Measure of acidity/alkalinity
PPP	Per-Protocol Population
RLD	Reference Listed Drug
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SDTM	Study Data Tabulation Model
U.S.A	United States of America

TABLE OF CONTENTS

1. INTRODUCTION

This Statistical Analysis Plan (SAP) is based on the final Clinical Study Protocol 71436001 (Rev 0) dated 02-11-2015. The SAP provides details on the planned statistical methodology for the analysis of the study data. The SAP also outlines the statistical programming specifications for the tables, listings and figures.

This SAP describes the study endpoints, derived variables, anticipated data transformations and manipulations, and other details of the analyses not provided in the study protocol. This SAP therefore outlines in detail all other aspects pertaining to the planned analyses and presentations for this study.

The following documents were reviewed in preparation of this SAP:

- Final Clinical Study Protocol 71436001 (Rev 0) dated 02-11-2015
- Case Report Form Booklet Version 1.0 for Study No. 71436001

The reader of this SAP is encouraged to also read the clinical protocol for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a patient in this study.

2. 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.

3. OVERALL STUDY DESIGN

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 will be randomized, to obtain a 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.

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		
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*

4. RANDOMIZATION AND BLINDING

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.

The Investigator, staff at the study site, study monitors, and data analysis/management personnel will be blinded to the patient assignment.

5. 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 per active group in the PP population [redacted] to demonstrate bioequivalence (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] to demonstrate superiority of active over placebo.

[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).

6. ANALYSIS POPULATION

Per-Protocol (PP) Population

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

- Met the inclusion/exclusion criteria as defined in the 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).

Modified Intent-to-Treat (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

Safety Population

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

7. STUDY 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.

8. STATISTICAL ANALYSIS METHODS

If not otherwise specified, statistical significance is defined as $p<0.05$ and is two-tailed. Data will be summarized with respect to demographic and baseline characteristics, efficacy variables and safety variables.

For categorical variables, the number and percent of each category within a parameter will be calculated for non-missing data. For continuous variables, statistics will include n, mean, standard deviation, median, minimum and maximum values.

All statistical analyses will be conducted using SAS®, Version 9.4 or higher. Datasets will be prepared using headings from Clinical Data Interchange Consortium (CDISC) Study Data Tabulation Model (SDTM) implementation for human clinical trials and ADaM (Analysis Dataset Model).

8.1 Baseline Characteristics

8.1.1 Patient Disposition

The patient accountability and disposition information will be summarized by study treatment group. The number of patients enrolled, randomized, and the number of patients in each analysis population will be tabulated. In addition, completion status and primary reason for withdrawal will be summarized by study treatment group.

8.1.2 Demographic and Other Baseline Characteristics

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

Summary tables by treatment group will be presented. Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, maximum).

Categorical variables will be summarized using frequencies and percentage. Baseline treatment comparisons will be presented using Cochran-Mantel-Haenszel test for the categorical variables, and Analysis of Variance for the continuous variables.

All data will be listed by treatment and patient.

8.1.3 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. At Visit 2 medical history will be reviewed and updated if changes have occurred.

Medical history data will be listed by treatment and patient.

8.1.4 Concomitant Medications

At Visit 1 patients will be questioned about all concomitant medication use within the previous 6 months.

All prior and concomitant medications taken since screening until the end of the study will be listed by treatment and patient.

8.1.5 Physical Exam

At Visit 1 the Investigator will perform a general physical exam including pelvic exam and breast exam. At Visit 3 the Investigator will perform a general physical exam including pelvic exam, any negative findings on exam should be reported as Adverse Events.

Physical examination results will be listed by treatment and patient.

8.1.6 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.

Laboratory evaluation results will be listed by treatment and patient.

8.1.7 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% - 125% of the required number of doses, and do not miss more than 1 dose.

Drug administration and dosing compliance will be listed by treatment and patient.

8.2 Efficacy Analyses

The following symptoms (see Appendix A for detailed rating scales) will be evaluated at Visits 1, 2 and 3 by the blinded clinical staff or Investigator.

Symptoms	Rating Scales
Vaginal Dryness	0=None, 1=mild, 2=moderate, 3=severe
Vaginal/Vulvar irritation/itching	0=None, 1=mild, 2=moderate, 3=severe
Dysuria	0=None, 1=mild, 2=moderate, 3=severe
Vaginal Pain associated with Sexual Activity	0=None, 1=mild, 2=moderate, 3=severe
Vaginal Bleeding	0= Absent, 1= Present

The patients will be asked to identify which symptom is considered to be the most bothersome symptom at Visit 1 and Visit 2. Vaginal Pain associated with Sexual Activity or Vaginal

Bleeding are acceptable to be considered most bothersome symptom only if patient is currently sexually active and plans to remain so throughout the study.

8.2.1 Analysis of Primary Efficacy Endpoint

Therapeutic Bioequivalence 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.

Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in success proportions between test and reference treatment should be contained within [-0.20, +0.20] in order to establish equivalence.

The compound hypothesis to be tested is:

$H_0: \ P_T - P_R < -.20 \ or \ P_T - P_R > .20$ versus

$H_A: -.20 \leq P_T - P_R \leq .20$

where P_T = cure rate of test treatment
P_R = cure rate of reference treatment.

Let

n_T = sample size of test treatment group
cn_T = number of cured patients in test treatment group
n_R = sample size of reference treatment group
cn_R = number of cured patients in reference treatment group

$\hat{P}_T = cn_T/n_T \qquad \hat{P}_R = cn_R/n_R$, and

$se = \left(\hat{P}_T\,(1-\hat{P}_T)/n_T + \hat{P}_R\,(1-\hat{P}_R)/n_R\right)^{1/2}$

The 90% confidence interval for the difference in proportions between test and reference will be calculated as follows, using Yates' correction:

$L = \left(\hat{P}_T - \hat{P}_R\right) - 1.645\,se - (1/n_T + 1/n_R)/2$

$U = \left(\hat{P}_T - \hat{P}_R\right) + 1.645\,se + (1/n_T + 1/n_R)/2$

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.

Superiority to Placebo Analysis

The mITT population and LOCF will be used to evaluate the superiority of both the Test and Reference product to Placebo.

For the determination of superiority the proportion of patients who are considered as "Responders" in the test and reference product groups will each be compared to the proportion of "Responders" in the placebo product group. On condition that both the test and the reference group demonstrate statistically greater proportion of "Responders" ($p< 0.05$, 2-sided) than the placebo group then superiority shall be concluded and the sensitivity of the methodology confirmed.

Summary table with frequency and percentage on the proportion of responders by treatment group will be presented. Treatment comparison for Test vs. Placebo and Reference vs. Placebo will be performed by continuity-corrected Z-tests. The superiority of Test and Reference treatments over the Placebo will be evaluated identically in separate Z-Test analyses.

8.2.2 Analysis of Secondary Efficacy Endpoint

Therapeutic Bioequivalence Analysis

Similar to the analysis for primary endpoint above, 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 to Placebo Analysis

The mITT population and LOCF will be used to evaluate the superiority of both the Test and Reference product to Placebo.

Similar to the analysis for primary endpoint above, superiority of the Test and Reference products against the Placebo for 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.

8.3 Safety Analysis

8.3.1 Adverse Events

All the adverse events (AEs) reported will be coded and classified according to the MedDRA (Medical Dictionary for Regulatory Activities) coding dictionary (Version 17.0 or higher). Each adverse event is to be evaluated for date of start and end, seriousness, severity, causal relationship with the study drugs, action taken and outcome.

All AEs will be listed by patient and treatment.

The total number and percentage of patients with at least one AEs, discontinued study drug due to AEs, AE severity and AEs related to investigational product, serious AEs and death will be summarized by treatment groups and overall.

A summary table of the number and percent of patients with AEs by system organ class, preferred term, and treatment group will be presented. Each patient will be counted only once within each preferred term.

A frequency summary table of the number of AEs by system organ class, preferred term, severity, and treatment group will be presented. Severity will be classified as “Mild”, “Moderate”, or “Severe”.

Similarly, a frequency summary table of the number of AEs by system organ class, preferred term, and relationship to a study drug, and treatment group will be presented. Relationship to a study drug will be classified as “Related” or “Not Related”.

Should sufficient data exist, adverse event frequencies will be compared between treatments using the Chi-square testing (Fisher’s exact test if appropriate).

8.3.2 Vital Signs

The patient's vital signs will be recorded (pulse, blood pressure, temperature and respiration rate) at Visits 1, 2, and 3 or end of study.

Descriptive summaries (n, mean, standard deviation, minimum, median and maximum) will be provided by treatment and visit. The summary table will be based on safety population randomized.

All data will be listed by treatment and patient.

8.4 Statistical Analysis Issues

As this is a multiple-site study, treatment-by-site interaction analysis will be examined using the Cochran-Mantel-Haenszel Test for the primary efficacy variable, the proportion of patients in the PPP that are considered to be a "responder" at Visit 3. A site(s) with a low enrollment rate(s) may be pooled with its geographically closest site. The pooling will be done for low enrolling sites that account for less than 4-7% of the total number of patients in the PP population (equivalence test) and mITT population (superiority tests) at the site with the highest enrolling rate.

8.5 Multiple Comparisons

No multiple comparison adjustment will be made in this study.

8.6 Methods for Handling Missing Data

For demographic and baseline characteristics, each variable will be analyzed using all available data. Patients with missing data will be excluded only from analyses for which data are not available.

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).

8.7 Interim Analyses

There is no interim analysis planned in this study.

9. TABLE, LISTING AND FIGURE SHELLS

The following shells are provided in order to provide a framework for the display of data from this study. These shells may not be reflective of every aspect of this study but are intended to

show the general layout of the Tables, Listings and Figures that will be included in the final clinical study report. Tables, Listings and Figures are numbered following the ICH structure. Table headers, variables names and footnotes will be modified as needed following data analyses. All descriptive and inferential statistical analyses will be performed using SAS® statistical software Version 9.4 or higher, unless otherwise noted.

TABLE, LISTING AND FIGURE SHELLS

T16.1.9.1 Summary of Discontinued Patients

Patients	Test	Reference	Placebo	Total
Screened				xxx
Screen failures				xxx
Randomized	xxx	xxx	xxx	xxx
Completed Study	xxx	xxx	xxx	xxx
Terminated Early	xxx	xxx	xxx	xxx
Early Termination Reason				
Adverse Event	xxx	xxx	xxx	xxx
Lack of efficacy	xxx	xxx	xxx	xxx
Lost to Follow-Up	xxx	xxx	xxx	xxx
etc.				

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)

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T16.1.9.2 Summary of Protocol Deviations
(Safety Population)

	Test	Reference	Placebo	Total
Total Patients with Protocol Deviations	xxx	xxx	xxx	xxx
Total Deviations	xxx	xxx	xxx	xxx
Dosing Non-Compliance (Missed > one doses)	xxx	xxx	xxx	xxx
Failure to meet randomization criteria	xxx	xxx	xxx	xxx
Lost to Follow-up	xxx	xxx	xxx	xxx
Outside Visit Window	xxx	xxx	xxx	xxx
Patient Dosed on the Day of Visit 3	xxx	xxx	xxx	xxx
Restricted Medication	xxx	xxx	xxx	xxx
Total Dosing Non-Compliance	xxx	xxx	xxx	xxx
Other	xxx	xxx	xxx	xxx

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)

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T16.1.9.3.1 Summary of Patients Excluded from Efficacy Analysis (Population Determination)

		Test	Reference	Placebo	Total
Randomized	Total	xxx	xxx	xxx	xxx
Safety Population	Total	xxx	xxx	xxx	xxx
Excluded from Safety	Did Not Dose	xxx	xxx	xxx	xxx
mITT Population	Total	xxx	xxx	xxx	xxx
Excluded from mITT	Inclusion/Exclusion	xxx	xxx	xxx	xxx
	etc.				
PP Population	Total	xxx	xxx	xxx	xxx
Excluded from Excluded from PPP	Restricted Medication	xxx	xxx	xxx	xxx
	Outside of Visit 3 Window				
	etc.				

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)

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T16.1.9.3.2 Summary of Patients Included in Analysis Population by Study Center

Site No.	Name	Total Randomized	PPP				mITT				Safety			
			Test	Ref	Placebo	Total	Test	Ref	Placebo	Total	Test	Ref	Placebo	Total
xx	xxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
xx	xxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx

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)

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T16.1.9.4 Summary of Baseline Demographic Data (Safety Population)

		Test (N = xxx)	Reference (N = xxx)	Placebo (N = xxx)	P-value
Age (years)	n	xxx	xxx	xxx	x.xxxx
	Mean ± SD	xx.x ± xx.xx	xx.x ± xx.xx	xx.x ± xx.xx	
	Median	xx.x	xx.x	xx.x	
	Range	xx.x - xx.x	xx.x - xx.x	xx.x - xx.x	
Race	American Indian or Alaska Native	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	x.xxxx
	Asian	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	
	Black/African American	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	
	Native Hawaiian or other Pacific Islander	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	
	White	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	
	Other	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	
Gender	Female	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	x.xxxx
	Male	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	
Ethnicity	Hispanic or Latino	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	x.xxxx
	Not Hispanic or Latino	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	

N= number of patients in the treatment group; n= number of patient with data available; % is based on N
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)

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T16.1.9.4 Summary of Baseline Demographic Data (Safety Population)

		Test (N = xxx)	Reference (N = xxx)	Placebo (N = xxx)	P-value
Natural or Surgical Menopause	Natural	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	x.xxxx
	Surgical	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	
Vaginal Dryness	None	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	x.xxxx
	Mild	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	
	Moderate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	
	Severe	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	
Vaginal/Vulvar Irritation/Itching	None	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	x.xxxx
	Mild	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	
	Moderate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	
	Severe	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	

Note: N= number of patients in the treatment group; n= number of patient with data available; % is based on N
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)

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T16.1.9.4 Summary of Baseline Demographic Data (Safety Population)

		Test (N = xxx)	Reference (N = xxx)	Placebo (N = xxx)	P-value
Dysuria	None	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	x.xxxx
	Mild	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	
	Moderate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	
	Severe	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	
Vaginal Pain during Sexual Activity	None	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	x.xxxx
	Mild	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	
	Moderate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	
	Severe	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	
Most Bothersome Sign or Symptom	Vaginal Dryness	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	x.xxxx
	Vaginal/Vulvar Irritation/Itching	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	
	Dysuria	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	
	Vaginal Pain during Sexual Activity	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	
	Vaginal Bleeding	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	

Note: N= number of patients in the treatment group; n= number of patient with data available; % is based on N
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)

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T16.1.9.4 Summary of Baseline Demographic Data (Safety Population)

		Test (N = xxx)	Reference (N = xxx)	Placebo (N = xxx)	P-value
Vaginal Bleeding	Absent	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	x.xxxx
	Present	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	
Duration of Postmenopausal Status (Years)	xxx	xxx	xxx	xxx	
	xx.x ± xx.xx	xx.x ± xx.xx	xx.x ± xx.xx	xx.x ± xx.xx	x.xxxx
	xx.x	xx.x	xx.x	xx.x	
	xx.x - xx.x	xx.x - xx.x	xx.x - xx.x	xx.x - xx.x	
% of basal/parabasal cells	xxx	xxx	xxx	xxx	
	xx.x ± xx.xx	xx.x ± xx.xx	xx.x ± xx.xx	xx.x ± xx.xx	x.xxxx
	xx.x	xx.x	xx.x	xx.x	
	xx.x - xx.x	xx.x - xx.x	xx.x - xx.x	xx.x - xx.x	

Note: N= number of patients in the treatment group; n= number of patient with data available; % is based on N
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)

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T16.1.9.4 Summary of Baseline Demographic Data (Safety Population)

		Test (N = xxx)	Reference (N = xxx)	Placebo (N = xxx)	P-value
% of intermediate cells	n	xxx	xxx	xxx	x.xxxx
	Mean ± SD	xx.x ± xx.xx	xx.x ± xx.xx	xx.x ± xx.xx	
	Median	xx.x	xx.x	xx.x	
	Range	xx.x - xx.x	xx.x - xx.x	xx.x - xx.x	
% of superficial cells	n	xxx	xxx	xxx	x.xxxx
	Mean ± SD	xx.x ± xx.xx	xx.x ± xx.xx	xx.x ± xx.xx	
	Median	xx.x	xx.x	xx.x	
	Range	xx.x - xx.x	xx.x - xx.x	xx.x - xx.x	
Vaginal pH	n	xxx	xxx	xxx	x.xxxx
	Mean ± SD	xx.x ± xx.xx	xx.x ± xx.xx	xx.x ± xx.xx	
	Median	xx.x	xx.x	xx.x	
	Range	xx.x - xx.x	xx.x - xx.x	xx.x - xx.x	

Note: N= number of patients in the treatment group; n= number of patient with data available; % is based on N
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)

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Similar tables will be created for T16.1.9.5 and T16.1.9.6

T16.1.9.5 Summary of Baseline Demographic Data
(modified Intent-to-Treat Population)

T16.1.9.6 Summary of Baseline Demographic Data
(Per-Protocol Population)

T16.1.9.7 Summary of Analysis Results of Primary Efficacy Endpoint (Proportion of Responders Between Treatment Groups)

Equivalence: Per-Protocol Population

Treatment Group	Number of Patients (N)	Number of Responders (n)	Proportion of Responders (%)	Difference Between Treatments: Difference	Difference Between Treatments: 90% CI Evaluation
Test	xxx	xxx	xx.x%		
Reference	xxx	xxx	xx.x%	xx.x%	xx.x – xx.x

Superiority: modified Intent-to-Treat Population

Treatment Group	Number of Patients (N)	Number of Responders (n)	Proportion of Responders (%)	Treatment vs. Placebo: Difference	Treatment vs. Placebo: P-value
Placebo	xxx	xxx	xx.x%		
Test	xxx	xxx	xx.x%	xx.x%	x.xxxx
Placebo	xxx	xxx	xx.x%		
Reference	xxx	xxx	xx.x%	xx.x%	x.xxxx

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)
The 90% confidence interval for the difference in proportions between test and reference was calculated using Yates' correction.

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T16.1.9.8 Summary of Analysis Results of Secondary Efficacy Endpoint (Proportion of Treatment Successes Between Treatment Groups)

Equivalence: Per-Protocol Population

Treatment Group	Number of Patients (N)	Number of Treatment Successes (n)	Proportion of Treatment Successes (%)	Difference Between Treatments	
				Difference	90% CI Evaluation
Test	xxx	xxx	xx.x%		
Reference	xxx	xxx	xx.x%	xx.x%	xx.x – xx.x

Superiority: modified Intent-to-Treat Population

Treatment Group	Number of Patients (N)	Number of Treatment Successes (n)	Proportion of Treatment Successes (%)	Treatment vs. Placebo	
				Difference	P-value
Placebo	xxx	xxx	xx.x%		
Test	xxx	xxx	xx.x%	xx.x%	x.xxxx
Placebo	xxx	xxx	xx.x%		
Reference	xxx	xxx	xx.x%	xx.x%	x.xxxx

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)
The 90% confidence interval for the difference in proportions between test and reference was calculated using Yates' correction.

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T16.1.9.9 Overall Summary of Adverse Events
(Safety Population)

Description	Test N (%)	Reference N (%)	Placebo N (%)	Total N (%)
Patients Randomized	xxx	xxx	xxx	xxx
Patients with at least one AE	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Discontinued study drug due to above AE	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
AEs reported	xxx	xxx	xxx	xxx
Mild	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Moderate	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Severe	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Related	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Related	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Death	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Serious AE	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

Related = Probable, Possible, Unlikely

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)

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T16.1.9.10.1 Summary of Frequency of All Adverse Events by Body System (Safety Population)

		Test (N = xxx)		Reference (N = xxx)		Placebo (N = xxx)		Fisher's
Body System	**MedDRA Term**	**Events**	**Patients**	**Events**	**Patients**	**Events**	**Patients**	**P-value**
Patients with at least one AE	Total	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	x.xxxx
Ear and labyrinth disorders	Ear pain	xx	xx (xx.x%)	xx	xx (xx.x%)	xx	xx (xx.x%)	x.xxxx
	etc.							

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)
Comparison of treatment groups is with respect to the number of patients with at least one occurrence of the AE.

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Similar Table will be created for:

T16.1.9.10.2 Summary of Frequency for AEs Occurring in at Least 1% of Subjects by Body System (Safety Population)

T16.1.9.11 Summary of Frequency of All Adverse Events by Severity (Safety Population)

		Test # of Events (N=xx)			Reference # of Events (N=xx)			Placebo # of Events (N=xx)		
Body System	**MedDRA Term**	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Total AEs	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Ear and labyrinth disorders	Ear pain	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Hypoacusis	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

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)
N = Total number of events in each treatment group; Percentage is based on total number of events.

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T16.1.9.12 Summary of Frequency of All Adverse Events by Relationship (Safety Population)

		Test # of Events (N=xx)		Reference # of Events (N=xx)		Placebo # of Events (N=xx)	
Body System	**MedDRA Term**	**Related**	**Not Related**	**Related**	**Not Related**	**Related**	**Not Related**
Total AEs	Total	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Ear and labyrinth disorders	Ear pain	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Hypoacusis	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

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)
N = Total number of events in each treatment group; Percentage is based on total number of events.

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T16.1.9.13 Summary of Frequency of Serious Adverse Events (Safety Population)

Body System	MedDRA Term	Test # Events	Reference # Events	Placebo # Events
Injury, poisoning and procedural complications	Alcohol poisoning	xx	xx	xx

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)

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T16.1.9.14 Summary of Adverse Events by Treatment (Safety Population)

Test: Estradiol Vaginal Cream, USP, 0.01%

	Severity			Relationship to Study Drug	
Body System **MedDRA Term**	**Mild** **n (%)**	**Moderate** **n (%)**	**Severe** **n (%)**	**Related** **n (%)**	**Not Related** **n (%)**
Total AEs (N=xxx)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Ear and labyrinth disorders	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Hypoacusis	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
etc.					
etc.					
etc.					

N = Total AEs in Test Group
n (%) = Number of AEs (Percent of Total AEs in Test Group)

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Note to programmer: Similar tables will be created for Reference and Placebo groups.

T16.1.9.15 Summary of Vital Signs
(Safety Population)

Vital Signs	Visit	Statistic	Test (N = xxx)	Reference (N = xxx)	Placebo (N = xx)
Systolic Blood Pressure (mmHg)	1	n	xxx	xxx	xxx
		Mean ± SD	xxx.x ± xx.xx	xxx.x ± xx.xx	xxx.x ± xx.xx
		Median	xxx.x	xxx.x	xxx.x
		Range	xxx.x – xxx.x	xxx.x – xxx.x	xxx.x – xxx.x
	2				
	3				
Diastolic Blood Pressure (mmHg)					
Heart Rate (beats/min)					
Respiration Rate (breaths/min)					
Temperature (F)					

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)

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L16.2.1 Listing of Discontinued Patients

Treatment Group	Patient Randomization Number	Discontinuation Reason	Population
Test	xx-xxxx	Withdrew Consent	Per-Protocol
	xx-xxxx	Lost to Follow-up	Safety
Reference			
Placebo			

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)

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L16.2.2 Listing of Protocol Deviations

Treatment Group	Patient Randomization Number	Event Description	Population
Test	xx-xxxx	Outside Visit Window (Visit: 3)	Per-Protocol
Reference			
Placebo			

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)

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L16.2.3.1 Patients Excluded from the Per-Protocol Population

Treatment Group	Patient Randomization Number	Exclusion Reason
Test	xx-xxxx	Patient did not meet IE criterion
	xx-xxxx	Patient took prohibited medications
Reference		
Placebo		

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)

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L16.2.3.2 Patients Excluded from the Modified Intent-to-Treat Population

Treatment Group	Patient Randomization Number	Exclusion Reason
Test	xx-xxxx	Patient did not have at least one post-randomization evaluation
Reference		
Placebo		

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)

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L16.2.4.1 Listing of Demographic Data

Treatment Group	Patient Randomization Number	Age (years)	Gender	Ethnicity	Race	Natural or Surgical Menopause
Test	xx-xxxx	30	Female	Not Hispanic or Latino	Black or African American	Natural
				Surgical		
Reference						
Placebo						

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)

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L16.2.4.2 Listing of Patient Characteristics (Baseline Signs and Symptoms)

Treatment Group	Patient Randomization Number	Baseline Signs and Symptoms Scores						Baseline %			Baseline Vaginal pH
		Vaginal Dryness	Vaginal/ Vulvar Irritation/ itching	Dysuria	Vaginal Pain Associated With Sexual Activity	Vaginal Bleeding	Most Bothersome Symptom (Baseline)	Superficial Cells	Basal/ para Basal Cells	Intermediate Cells	
Test	xx-xxxx	1	2	2	2	1	Vaginal Dryness	6	0	94	5.5
Reference											
Placebo											

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)

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L16.2.4.3 Listing of Medical History

Treatment Group	Patient Randomization Number	System	Diagnosis or Surgical Procedure	Start Date	End Date	Ongoing
Test	xx-xxxx	Gynecologic	Menopause	2003	2003	
Reference						
Placebo						

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)

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L16.2.4.4 Listing of Concomitant Medications

Treatment Group	Patient Randomization Number	Treatment Area	Medication	Dosage	Frequency	Route	Start/End Date	Indication
Test	xx-xxxx	Yes	LISINOPRIL	20 MG	QD	PO	yyyy-mm-dd/ yyyy-mm-dd	HYPERTENSION

Reference
Placebo

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)

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L16.2.5.1 Listing of Visit Date Information

Treatment Group	Patient Randomization Number	Informed Consent Date	Visit 1	Visit 2	Visit 3 or Early Termination
Test	xx-xxxx	yyyy-mm-dd	yyyy-mm-dd	yyyy-mm-dd	yyyy-mm-dd
Reference					
Placebo					

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)

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L16.2.5.2 Listing of Drug Administration

Treatment Group	Patient Randomization Number	Date of First Dose	Date of Last Dose	Total Number of Dose Administered	Dosing Compliance (%)
Test	xx-xxxx	yyyy-mm-dd	yyyy-mm-dd	xx	xxx.x
Reference					
Placebo					

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)

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L16.2.5.3 Listing of Study Compliance

Treatment Group	Patient Randomi-zation Number	Dose on the day of Visit 3?	Use any restricted medication for the treatment of atrophic vaginitis?	Use any restricted medication other than for the treatment of atrophic vaginitis?	Administer < 6 or >8 of the intended doses?	Miss >1 dose of study medication?	Develop any concurrent vaginal infection or illness?	Require additional treatment?
Test	xx-xxxx	No	No	No	No	No	No	No

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)

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L16.2.6.1 Listing of Vaginal Cytology Results
(Test: Estradiol Vaginal Cream, USP, 0.01%)

	Baseline					Visit 3							
Patient Randomization Number	**Basal/ Parabasal %**	**Intermediate %**	**Basal/ Parabasal +Intermediate%**	**Superficial Cells%**	**pH**	**Basal/ Parabasal %**	**Intermediate %**	**Basal/ Parabasal +Intermediate%**	**Superficial Cells%**	**pH**	**Cytology Changes From Baseline**	**pH Changes From Baseline**	**Responder Yes/No**
xx-xxxx	69	31	100	100	7.0	12	43	55	100	4.5	45	2.5	Yes

Programming note: table will continue for reference and placebo group

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L16.2.6.2 Listing of Signs and Symptoms Ratings

Treatment Group	Patient Randomization Number	Most Bothersome Symptom at Baseline	Most Bothersome Score at Baseline	Baseline Most Bothersome Symptom Score at V3	Success (Yes/No)
Test	xx-xxxx	Vaginal Dryness	3	0	Yes

Reference

Placebo

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)

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L16.2.7 Listing of Adverse Events by Treatment Group

Treatment group	Patient Randomization Number	Body System/ MedDRA Term/ AE Term	Treatment Area	End Date	Severity	Relationship to Study Drug	Outcome	Action Taken	Other Action Taken	SAE?
Test	xx-xxxx	NERVOUS SYSTEM DISORDERS/ HEADACHE/ HEADACHE	Yes	yyyy-mm-dd/ yyyy-mm-dd	Mild	Not Related	Recovered	None	None	No
Reference										
Placebo										

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)

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L16.2.8.1 Listing of Laboratory Measurements

Treatment Group	Patient Randomization Number	Collection Date	Baseline FSH (mIU/ml)	Baseline Triglycerides (mg/dL)
Test	xx-xxxx	yyyy-mm-dd	99.0	76

Reference

Placebo

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)

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L16.2.8.2 Listing of Vaginal Ultrasonography and Mammogram

		Vaginal Ultrasonography		Mammogram	
Treatment Group	**Patient Randomization Number**	**Collection Date**	**Does Patient Have a Confirmed Inactive Uterine Lining of < 4 mm?***	**Collection Date**	**Are Screening Mammogram Results Normal?****
Test	xx-xxxx	yyyy-mm-dd	Yes	yyyy-mm-dd	Yes
	xx-xxxx		N/A		N/A
Reference					
Placebo					

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)
Note: * N/A = Patient has had a hysterectomy; ** N/A = patient is ≤ 40 years of age

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L16.2.8.3 Listing of Vital Signs

Treatment Group	Patient Randomization Number	Visit	Systolic BP (mmHg)	Diastolic BP (mmHg)	Heart Rate (beats/min)	Respiration Rate (breaths/min)	Temperature (F)
Test	xx-xxxx	1	120	70	84	18	98.6
		2	140	80	74	18	97
		3/EOS	130	87	74	18	99.2

Reference
Placebo

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)

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L16.2.8.4 Listing of Physical Examination

Treatment Group	Patient Randomization Number	System	Visit 1	Visit 3 /EOS
Test	xx-xxxx	General Appearance	Normal	Normal
		Cardiovascular		
		Lungs and Thorax		
		Abdominal and Gastro-Enteric		
		etc		
Reference				
Placebo				

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)

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10. APPENDICIES

Appendix A: 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.