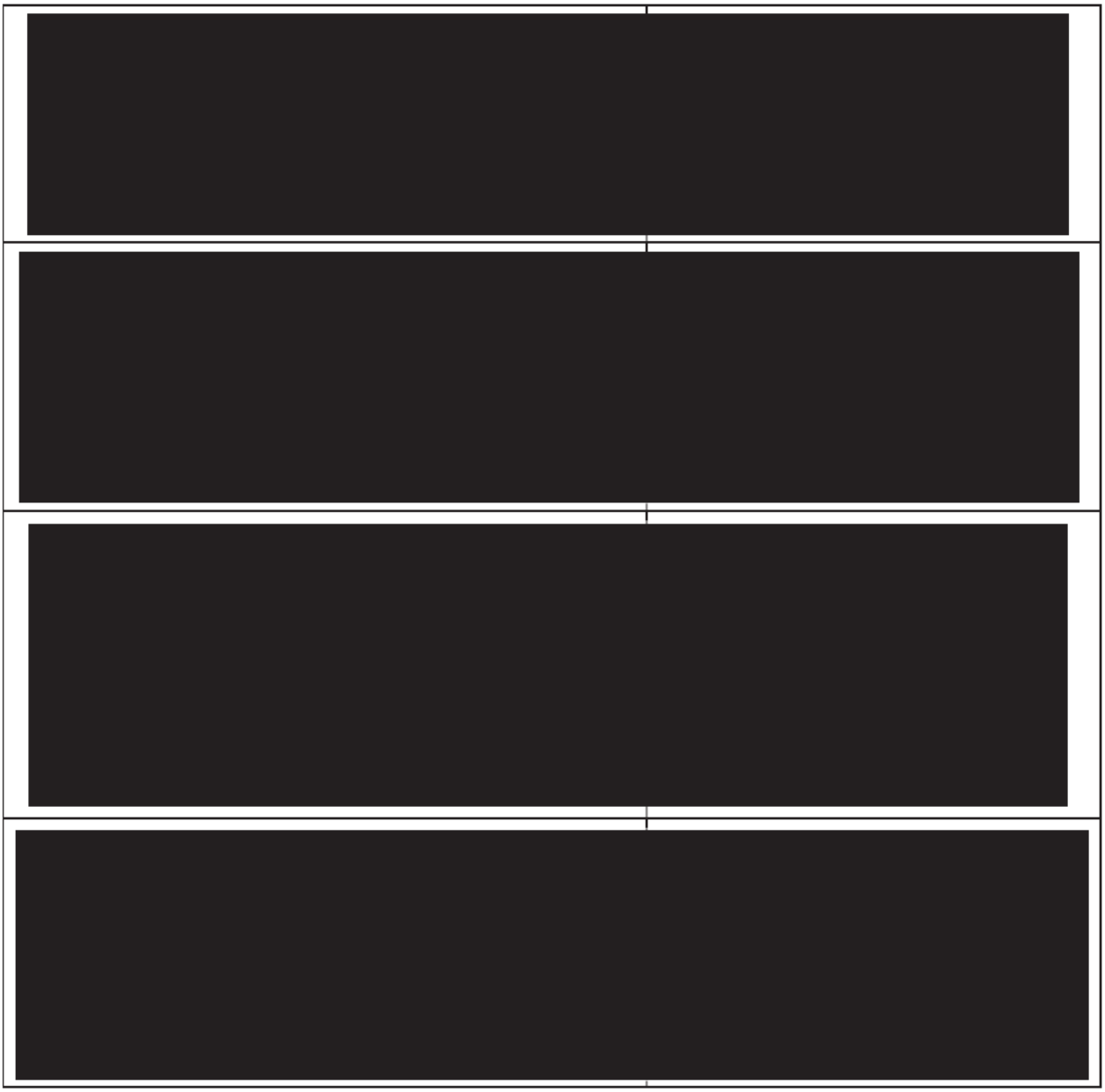
STATISTICAL ANALYSIS PLAN

STUDY TITLE	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multiple-Site Study to Evaluate the Therapeutic Equivalence of Estradiol Vaginal Inserts 4 mcg (Teva Pharmaceuticals, Inc.) with IMVEXXY® (estradiol vaginal inserts) (TherapeuticsMD, Inc.) in the Treatment of Dyspareunia in Women with Vulvar and Vaginal Atrophy
[redacted]	[redacted]
[redacted]	[redacted]
SPONSOR	Teva Pharmaceuticals, Inc. 400 Interpace Pkwy, Building A Parsippany, NJ 07054 USA
CLINICAL RESEARCH ORGANIZATION	[redacted]
DATE AND VERSION	20 March 2024 – Version 2.0

SAP Final Version Approvals

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multiple-Site Study to Evaluate the Therapeutic Equivalence of Estradiol Vaginal Inserts 4 mcg (Teva Pharmaceuticals, Inc.) with IMVEXXY® (estradiol vaginal inserts) (TherapeuticsMD, Inc.) in the Treatment of Dyspareunia in Women with Vulvar and Vaginal Atrophy



Revision History

VERSION	DATE	DESCRIPTION OF REVISIONS	REVISED BY
Draft 0.1	24 Aug 2023	New Document	[redacted]
Draft 0.2	08 Sep 2023	Incorporated Sponsor Comments	[redacted]
Final 1.0	18 Sep 2023	Incorporated Sponsor Comments and Finalized Document	[redacted]
Draft 1.1	08 March 2024	Revised population definitions	[redacted]
Draft 1.2	14 March 2024	Incorporated Sponsor Comments	[redacted]
Draft 1.3	19 March 2024	Incorporated Sponsor Comments	[redacted]
Final 2.0	20 March 2024	Finalized Document	[redacted]

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADaM	Analysis Dataset Model
AE	Adverse event
°C	Degrees Celsius
CDISC	Clinical Data Interchange Consortium
CI	Confidence Interval
EOS	End-of-study
eCRF	Electronic case report form
FDA	Food and Drug Administration of the United States
FSH	Follicle Stimulating Hormone
hr	Hour
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
in	Inch
lbs	Pounds
LOCF	Last Observation Carried Forward
Max.	Maximum
mcg	Microgram
Mean	Arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
Min.	Minimum
mITT	Modified Intent to Treat Population
mL	Milliliter
mmHg	Millimeter of mercury
PI	Principal Investigator
PT	Preferred term
PPD	Per-protocol Population (Dyspareunia)
PPR	Per-protocol Population (Responder)
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TEAE	Treatment emergent adverse event
US(A)	United States of America
VVA	Vulvar and vaginal atrophy

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1 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on the final Clinical Study Protocol No. [redacted] (Amendment 6) dated 07 December 2023. The SAP provides details on the planned statistical methodology for the analyses 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 No. / [redacted] (Amendment 6) dated 07 December 2023
- Electronic Case Report Form (eCRF) Spec Version 2.7 dated 11 August 2023
- Annotated Case Report Form (aCRF) Version Date: 31 May 2023

If there is a discrepancy between the protocol and the SAP with respect to a statistical consideration, the text in the SAP will take precedence.

This SAP has been developed and finalized prior to lock of the clinical database for Study [redacted]

2 STUDY OBJECTIVES

The objectives of this study are to:

1. Evaluate the therapeutic equivalence of the Test product (estradiol vaginal inserts 4 mcg) from Teva Pharmaceuticals, Inc. to the marketed product IMVEXXY® (estradiol) vaginal inserts 4 mcg from TherapeuticsMD, Inc. in the treatment of dyspareunia in women with vulvar and vaginal atrophy (VVA) due to menopause.
2. Demonstrate the superiority of the efficacy of the Test and Reference (active) products over that of Placebo (vehicle).
3. Compare the safety of Test, Reference and Placebo products.

3 OVERALL STUDY DESIGN

This randomized, double-blind, placebo-controlled, parallel-design, multiple-site study is designed to evaluate the clinical (therapeutic) effect of a generic estradiol 4 mcg vaginal insert (Teva Pharmaceuticals, Inc.) compared to IMVEXXY® (estradiol) 4 mcg vaginal inserts (TherapeuticsMD, Inc.) in patients with moderate to severe dyspareunia, a symptom of VVA due to menopause. Additionally, both the Test and Reference products will be tested for superiority against a Placebo.

Approximately 1026 postmenopausal females 40 to 75 years of age with moderate to severe dyspareunia with VVA will be randomized in a 1:1:1 (Test:Reference:Placebo) ratio to one of the three study products as follows:

- **Test**: Estradiol 4 mcg vaginal insert [redacted]
- **Reference**: IMVEXXY® 4 mcg estradiol vaginal inserts (TherapeuticsMD, Inc.)
- **Placebo**: Placebo (vehicle) vaginal insert [redacted]

Eligible patients will be randomized and visit the investigative site for a total of three scheduled visits.

- **Visit 1**: Screening (Day -21 to -1)
- **Visit 2**: Randomization (Day 1)
- **Telephone Contact:** (Day 7 to 9)
- **Visit 3**: End of Study (Day 15 ± 2) or Early Termination

After randomization, patients will administer one vaginal insert once daily for 14 days. Evaluations will be performed in accordance with the study schematic below.

Safety assessments will include monitoring of adverse events (AEs), a physical examination, and vital sign measurements. Clinical assessments will include vaginal cytology, vaginal pH and VVA signs and symptoms scores.

STUDY SCHEMATIC

	Visit 1 Screening (Day -21 to Day -1)	**Visit 2** Randomization (Day 1)	**Telephone Contact** (Day 7-9)	**Visit 3** End of Study (Day 15 ± 2) or Early Termination
Informed Consent	X			
Baseline Demographics	X			
Medical History	X	X		
Vital Signs	X	X		X
VVA Signs and Symptoms*	X	X		X
Physical Exam (including breast and pelvic exam)	X			X
12-Lead ECG	X			
Vaginal Cytology	X			X
pH Testing	X			X
PAP Smear†	X			
Laboratory Sample Collection**	X			X
Mammogram‡	X			
Vaginal Ultrasound§	X			
Concomitant Medications	X	X		X
Inclusion/Exclusion Criteria Review	X	X		
Dispense Study Product		X		
Collect Study Product				X
Dispense Patient Diary		X		
Patient Reminder Regarding Study Compliance¤		X	X	
Collect/Review Patient Diary				X
Adverse Events	X	X	X	X

* Please see Appendix B of the clinical study protocol.
** Fasted blood sample should be collected for FSH, triglycerides [redacted] laboratory testing at Screening. [redacted].
† Patients who do not have documentation of a PAP smear completed within the last 12 months.
‡ Patients 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.
[redacted]

4 RANDOMIZATION

Randomization will be pre-planned according to a computer-generated randomization schedule, generated by an independent third-party. The packaging list taking into account this randomization will be shared with the independent packaging site [redacted] for appropriate randomizing, packaging and blinding. The randomization will be generated in "blocks", each containing three patients worth of study product (1 Test, 1 Reference, and 1 Placebo). Each of these study products (test/reference/placebo) [redacted]

[redacted]

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 schedule will be sent to the statistician.

5 SAMPLE SIZE

1026 eligible patients will be enrolled [redacted]

6 ANALYSIS POPULATION

6.1 PER-PROTOCOL POPULATION (RESPONDER)

The Per-protocol Population for Responders (PPR) will include patients who:

- [redacted]

- [redacted]

6.2 PER-PROTOCOL POPULATION (DYSPAREUNIA)

The Per-protocol Population for Dyspareunia (PPD) will include all patients who:

- [redacted]

6.3 MODIFIED INTENT TO TREAT POPULATION

The Modified Intent-to-Treat (mITT) population will include all patients who used at least one dose of IMP and completed a post-baseline visit.

Any patient who withdrew from the study because of lack of efficacy or significant worsening of VVA (after at least one dose of IMP) will also be included in mITT as a Non-Responder. LOCF may be performed using data from the last completed visit.

Patients who discontinue early for reasons other than lack of efficacy or significant worsening of VVA, should be included in the mITT population as long as the patient completed a post-baseline visit. LOCF may be performed using data from the last completed post-baseline visit.

6.4 SAFETY POPULATION

The Safety population will include all patients who were randomized and used at least one dose of IMP.

7 STATISTICAL ANALYSIS METHODS

Statistical services will be performed by [redacted]. Datasets will be prepared using headings from Clinical Data Interchange Consortium (CDISC) Study Data Tabulation Model (SDTM) implementation for human clinical trials and Analysis Dataset Model (ADaM).

Data will be summarized with respect to demographic, baseline characteristics, 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 number of observations, mean, standard deviation, median, minimum and maximum values.

7.1 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

7.1.1 Demographics and Baseline Characteristics

Demographic and baseline information collected at screening includes age, sex, ethnicity, race, body weight (lbs), height (in), postmenopausal status, vaginal pH, VVA signs and symptoms (vaginal dryness, vaginal/ vulvar irritation and itching, dysuria, dyspareunia, vaginal bleeding), and vaginal cytology.

All data will be listed by treatment and patient. A summary table with descriptive statistics will be presented by treatment group for the safety, PPR, PPD and mITT populations.

7.1.2 Medical History

At Visit 1, patients will be questioned about medical history, including acute, chronic and general history within the last year, and medical history relevant to their VVA.

Medical history data will be listed by treatment and patient.

7.1.3 Patient Disposition

Patient disposition will be summarized for the safety population. The summary table will present the number and percentage of patients who completed and the number and percentage of patients who discontinued along with the reasons for discontinuation.

7.1.4 Dosing Compliance

Compliance with dosing will be verified by the use of the patient diaries. Patients who dose less than 75% or more than 125% of the intended doses or miss more than two consecutive doses will be considered noncompliant with dosing. For example:

	Range	
Intended Doses	75%	125%
14	11	18

If a subject does not return the patient diary at the final visit, every attempt will be made to retrieve it and have them share the patient diary at a later date (but complete the visit as planned).

If the subject does not return the subject diary, but they return the IMP, the Independent Dispenser is allowed to assess IMP compliance based on patient interview and the quantity returned.

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

7.1.5 Concomitant Therapy

Concomitant medications used during the study will be listed by patient.

7.2 EFFICACY ANALYSIS

Vaginal Cytology and pH

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.

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.

Results will be listed by patient and treatment.

VVA Signs and Symptoms

At each visit the Investigator or designee will question the patient regarding their symptoms of VVA, using the scale in Appendix B of the clinical study protocol. The following patient self-assessed symptoms of vulvar and vaginal atrophy should be evaluated on a scale of 0 to 3 where 0 = none, 1=mild, 2=moderate and 3 = severe:

- Vaginal dryness
- Vaginal/ vulvar irritation and itching
- Dysuria
- Dyspareunia
- Vaginal bleeding (absent or present)

The severity of each symptom will be recorded on the source documents. The patients will be asked to identify their most bothersome symptom at Visit 1 and Visit 2. For inclusion in the study the most bothersome symptom at both Visit 1 and Visit 2 (Baseline) must be dyspareunia with a score of moderate (2) or severe (3).

Results will be listed by patient and treatment.

7.2.1 Efficacy Endpoints

The primary efficacy endpoints are:

- % Responders in the Per Population for Responders (PPR), where 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
  - Vaginal pH < 5.0 with a change from baseline vaginal pH of at least 0.5
- Mean change from baseline to Visit 3 in dyspareunia score (the self-identified most bothersome symptom in women with VVA) in the PPD population.

The secondary efficacy endpoint is the proportion of patients in each treatment group in the PPD that are considered a Treatment Success at the end of the treatment period evaluated on Visit 3. A "Treatment Success" is defined as a score of 0 or 1 at Visit 3 for dyspareunia (the self-identified most bothersome symptom at baseline).

7.2.2 Statistical Analyses

Therapeutic Equivalence:

Therapeutic equivalence of the Test product to the Reference product based on the primary endpoints will be evaluated at Visit 3. Therapeutic equivalence will be evaluated for the primary

endpoint of response rate (cytology and vaginal pH) in the PPR population. If the 90% confidence interval calculated using Yates' correction on the absolute difference between the proportion of patients identified as Responders (primary endpoint) in the Test and Reference groups (pT - pR) is contained within the range [-20%, +20%] then therapeutic equivalence of the Test product to the Reference product will be considered to have been demonstrated.

Therapeutic equivalence will be evaluated for the primary endpoint of dyspareunia in the PPD population. The baseline dyspareunia score will be subtracted from the post-dose score to obtain the baseline-corrected score at Visit 3.

Under the assumptions of normally distributed data, the adjusted 90% confidence interval will be calculated for the Test/Reference ratio of the mean change from baseline in dyspareunia score at Visit 3, using an iterative procedure outlined in Appendix A.

The analysis for calculating 90% confidence intervals will be conducted using mean baseline dyspareunia. The mean baseline value for use in the iterative procedure will be determined from the baseline score of all subjects receiving active treatment on Day 1 in the PPD population, without regard to the treatment received. The value will be included as the initial baseline value in the ESTIMATE statement of the iterative procedures outlined in Appendix A.

The statistical analyses will involve Analysis of Covariance (ANCOVA) with terms for treatment and site as fixed effects and using baseline score as a covariate in the model.

SAS PROC GLM procedure will be used in the analysis. The initial statements of a SAS PROC GLM analysis would be

Proc glm;

class site trt;

model *Y* = site trt Baseline;

Where Y = change from baseline in dyspareunia

Baseline = subject specific mean baseline

The ESTIMATE statements will be:

estimate 'ratio = *c*, baseline = *b*' intercept (1- *c*) trt 1 – *c* Baseline (1- *c*) *b*;

where Baseline is subject specific mean baseline, 'b' is the mean baseline value determined from the baseline scores of all subjects receiving active treatment on Day 1, without regard to the treatment received.

If the adjusted 90% confidence interval for the least-squares mean Test/Reference ratio is within 80.00-125.00% for the primary endpoint, then therapeutic equivalence of the Test to Reference product will be considered to have been demonstrated.

[redacted]

[redacted]

Superiority to Placebo

The superiority to Placebo will be evaluated for the primary endpoints in the mITT population.

The superiority of the Test and Reference products over Placebo for the primary endpoint of response rate (cytology and vaginal pH) is concluded if the proportion of Responders in the Test and the Reference product groups is superior to that of the Placebo at the 5% significance level ($p < 0.05$, two-sided) using a CMH test. The same statistical approach will be conducted for analysis of the secondary endpoint of success rate.

The superiority of the Test and Reference products over Placebo for the primary endpoint of mean change in dyspareunia score is concluded if the values for mean baseline-adjusted dyspareunia score are statistically superior to those respective values of the Placebo at the 5% significance level ($p < 0.05$, two-sided). The superiority of Test and Reference treatments over the Placebo will be evaluated in similar ANCOVA models for Test vs. Placebo and Reference vs. Placebo.

To declare superiority of the Test and Reference products over Placebo, superiority needs only be demonstrated for the primary endpoints in the mITT population. Secondary endpoint results are presented for informational purposes. The purpose of the superiority test is not to demonstrate the efficacy of the Reference product (which has already been established), but rather to determine whether the present study can detect a difference between treatment groups, thereby validating the equivalence test between Test and Reference products. Therefore, if superiority over Placebo cannot be shown for the Test and Reference products separately, the two active treatments (Test and Reference) may be pooled into a single treatment group and compared to the Placebo group. If superiority can be demonstrated in this comparison, these results may be presented to support the equivalence assessment.

7.3 SAFETY ANALYSIS

No formal statistical testing will be performed on safety variables. Safety will be assessed using recorded AEs and changes in physical examination and vital sign measurements. Clinical assessments will include vaginal cytology, vaginal pH and VVA signs and symptoms scores, as specified in the study schematic.

Evaluation of safety will be performed for all patients in the safety population.

7.3.1 Adverse Events

Adverse events (AEs) and Serious Adverse Events (SAEs) will be collected through both solicited and unsolicited means from the signing of the ICF until the end of the study.

Signs and symptoms of atrophic vaginitis will not be considered AEs, 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 prescribed an alternative treatment for their condition.

AEs will be classified using standard Medical Dictionary for Regulatory Activities (MedDRA) terminology (Version 26.0 or higher) and presented by treatment group for the safety population.

The type, date of onset, date of resolution, incidence, severity, outcome, action taken, and Investigator's opinion of relationship to the study product will be presented by treatment group for AEs reported after randomization.

The Sponsor's Pharmacovigilance Department will determine the expectedness for all serious adverse events. CRO and Investigators will not determine the expectedness.

Adverse events will be listed by patient, treatment, system organ class, and preferred term.

The incidence of AEs will be summarized by system organ class (SOC), preferred term (PT) and treatment. Patients will be counted once per preferred term, per treatment. The system organ classes will be ordered alphabetically. The preferred terms within each system organ class will also be ordered alphabetically.

A frequency summary table of the number of AEs by SOC, PT, and severity will be presented by treatment. Severity will be classified as "Mild", "Moderate" or "Severe". Similarly, a frequency summary table of the number of AEs by SOC, PT, and relationship to a study drug will be presented by treatment. Relationship to a study drug will be classified as "Not Related" or "Related".

All AEs occurring after the patient has signed the informed consent form until the end of follow-up period will be included on the AE listing. Summary tables will present only treatment-emergent AEs. A treatment-emergent AE is any AE that occurs after initiation of study medication, or any event already present that worsens in either intensity or frequency following exposure to study medication.

The summary tables for adverse events will be based upon the safety population.

7.3.2 Vital Signs

Vital signs (sitting blood pressure, pulse, temperature and respiration) will be recorded at each study visit. Patients must remain in a seated position for at least 5 minutes before vital signs are obtained.

A by-patient listing of all vital sign values for the safety population will be provided.

7.3.3 Physical Examination

At Visit 1 (screening) and Visit 3 (end of study), the Investigator will perform a general physical exam including pelvic exam and breast exam. Any clinically significant abnormal findings on the

Visit 3 exam should be reported as AEs if they differ from the patient's baseline at Visit 1. At a minimum, the physical examination will include the following: assessment of general appearance, skin, Head, Eyes, Ears, Nose and Throat (HEENT), heart, lungs, musculoskeletal system, lymph nodes, neurological systems, abdomen, and extremities.

Only abnormal physical exam data, if they exist, will be presented and listed by treatment and patient.

7.3.4 Clinical Laboratory Tests

All patients will have clinical laboratory evaluations (serum FSH, fasting triglycerides, thyroid function, vaginal cytology and PAP smear) performed at screening (all tests) and end of study (thyroid function and vaginal cytology only).

Clinical laboratory results will be listed by patient and treatment. Additionally, a listing of out-of-range values will be presented, if applicable.

8 TABLE, LISTING AND FIGURE SHELLS

The following shells are presented 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.

General Programming Note: All tables and listings not created in Excel will have a standard page header and footer as shown below:

[redacted]

Listing/Table *number and title*

Footer information:

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For appendix listings and tables (Listing 16.2.1 though Listing 16.2.8.4), header and footer information should be included as page header/footer so that the information repeats on all pages.

Table 10.1 Patient Disposition

Category	Test N (%)	Reference N (%)	Placebo N (%)	Overall N (%)
Enrolled				xxxx
Randomized	xxx	xxx	xxx	xxx
Patients completing study	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxxx (xx.x%)
Patients discontinued	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Adverse Event: *specify*	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Investigator Decision	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Lack of efficacy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Lost to follow-up	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Noncompliance with study drug	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Other: *specify*	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Pregnancy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Protocol Deviation: *specify*	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Serious Adverse Event: *specify*	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Significant worsening of condition requiring alternative or supplemental therapy	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Study Termination	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Unblinded	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Withdrawal by patient	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

N = Number of patients
% = Number of patients in category/Number of patients randomized × 100

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Table 10.1 Summary of Protocol Deviations

	Test (N)	Reference (N)	Placebo (N)	Overall (N)
Total Patients with Protocol Deviations	xxx	xxx	xxx	xxx
Total Deviations	xxx	xxx	xxx	xxx
Randomized in Error: *specify inclusion/exclusion criterion*	xxx	xxx	xxx	xxx
Restricted Medication: *specify*	xxx	xxx	xxx	xxx
Restricted Procedure: *specify*	xxx	xxx	xxx	xxx
Other: *specify*	xxx	xxx	xxx	xxx
etc.				

N = Number of patients

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Table 11.1 Summary of Patients Excluded from Efficacy Analysis (Population Determination)

		Test (N)	Reference (N)	Placebo (N)	Overall (N)
Randomized	Total	xxx	xxx	xxx	xxxx
Safety Population	Total	xxx	xxx	xxx	xxx
Excluded from Safety	Total	xxx	xxx	xxx	xxx
	Did Not Dose	xxx	xxx	xxx	xxx
	etc.				
mITT Population	Total	xxx	xxx	xxx	xxx
Excluded from mITT	Total	xxx	xxx	xxx	xxx
	Did not complete a post-baseline visit	xxx	xxx	xxx	xxx
	etc.				
PPR Population	Total	xxx	xxx	xxx	xxx
Excluded from PPR	Total	xxx	xxx	xxx	xxx
	Did not meet all inclusion/exclusion criteria	xxx	xxx	xxx	xxx
	Dosed <75% or >125% of intended doses	xxx	xxx	xxx	xxx
	EOS visit outside window or not completed	xxx	xxx	xxx	xxx
	Missed >2 consecutive doses	xxx	xxx	xxx	xxx
	Protocol Deviation				
	etc.				
PPD Population	Total	xxx	xxx	xxx	xxx
Excluded from PPD	Total	xxx	xxx	xxx	xxx
	Did not meet all inclusion/exclusion criteria	xxx	xxx	xxx	xxx
	Dosed <75% or >125% of intended doses	xxx	xxx	xxx	xxx
	Missed >2 consecutive doses	xxx	xxx	xxx	xxx
	Protocol Deviation	xxx	xxx	xxx	xxx
	No sexual intercourse Day 10-13 with dyspareunia assessment	xxx	xxx	xxx	xxx
	etc.				

N = Number of patients

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Table 11.2 Summary of Patients Included in Analysis Population by Study Center

Site No.	Total Randomized (N)	Safety				mITT				PPR				PPD			
		Test (N)	Ref (N)	Placebo (N)	Overall (N)	Test (N)	Ref (N)	Placebo (N)	Overall (N)	Test (N)	Ref (N)	Placebo (N)	Overall (N)	Test (N)	Ref (N)	Placebo (N)	Overall (N)
xx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
xx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx

N = Number of patients

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Table 11.2.1 Summary of Demographic Data (Safety Population)

		Test N = xx	Reference N = xx	Placebo N = xx	Overall N = xx	p-value†
Age (years)	Mean ± SD	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	x.xxxx
	Median	xx.x	xx.x	xx.x	xx.x	
	Range	xx - xx	xx - xx	xx - xx	xx - xx	
Age Groups	< 18	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x.xxxx
	18 – 40	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
	41 – 64	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
	65 – 75	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
	> 75	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
Sex	Female	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x.xxxx
Ethnicity	Hispanic or Latino	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x.xxxx
	Not Hispanic or Latino	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
Race	American Indian or Alaska Native	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x.xxxx
	Asian	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
	Black or African American	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
	Native Hawaiian or Other Pacific Islander	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
	White	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
	Multiple	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
Height (in)	Mean ± SD	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	x.xxxx
	Median	xx.x	xx.x	xx.x	xx.x	
	Range	xx - xx	xx - xx	xx - xx	xx - xx	
Weight (lbs)	Mean ± SD	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	x.xxxx
	Median	xx.x	xx.x	xx.x	xx.x	
	Range	xx - xx	xx - xx	xx - xx	xx - xx	
Postmenopausal Status	Natural (Spontaneous Amenorrhea)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x.xxxx
	Hysterectomy without bilateral oophorectomy	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
	Bilateral oophorectomy with or without hysterectomy	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
	Other	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	

		Test N = xx	Reference N = xx	Placebo N = xx	Overall N = xx	p-value†
Vaginal Dryness	None	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x.xxxx
	Mild	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
	Moderate	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
	Severe	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
Vaginal/Vulvar Irritation/Itching	None	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x.xxxx
	Mild	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
	Moderate	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
	Severe	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
Dysuria	None	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x.xxxx
	Mild	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
	Moderate	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
	Severe	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
Dyspareunia (vaginal pain during sexual activity)	None	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x.xxxx
	Mild	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
	Moderate	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
	Severe	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
Vaginal bleeding during or after sexual activity	Absent	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x.xxxx
	Present	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	
% of basal/parabasal cells	Mean ± SD	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	x.xxxx
	Median	xx.x	xx.x	xx.x	xx.x	
	Range	xx - xx	xx - xx	xx - xx	xx - xx	
% of intermediate cells	Mean ± SD	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	x.xxxx
	Median	xx.x	xx.x	xx.x	xx.x	
	Range	xx - xx	xx - xx	xx - xx	xx - xx	
% of superficial cells	Mean ± SD	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	x.xxxx
	Median	xx.x	xx.x	xx.x	xx.x	
	Range	xx - xx	xx - xx	xx - xx	xx - xx	
Vaginal pH	Mean ± SD	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	x.xxxx
	Median	xx.x	xx.x	xx.x	xx.x	
	Range	xx - xx	xx - xx	xx - xx	xx - xx	

* Categories based on FDA Guidance *Collection of Race and Ethnicity Data in Clinical Trials*, Issue Date: October 26, 2016.
†Cochran–Mantel–Haenszel test (CMH) test was used for categorical data and F-Test for continuous data.
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Note (not for inclusion in final output):

- All patients reporting multiple race categories can be grouped together in Multiple category (i.e., individual combinations of multiple races as reported by patients do not need to be presented separately).

Note: Similar tables will be created for the PPR, PPD and mITT populations.

Table 11.2.2 Summary of Demographic Data (PPR Population)

Table 11.2.3 Summary of Demographic Data (PPD Population)

Table 11.2.4 Summary of Demographic Data (mITT Population)

Table 11.4.1.1 Summary of Analysis Results of Co-Primary Efficacy Endpoint of Dyspareunia Score (Mean change from baseline to Visit 3)

Equivalence: Per-Protocol Population of Dyspareunia (PPD)

Treatment Group	Number of Patients (N)	LSMeans	Std Err LSMeans	Test-to-Reference Ratio	90% CI Evaluation*
Test	xxx	xxx.x	xxx.x	xx.x	xx.x – xx.x
Reference	xxx	xxx.x	xxx.x		

Superiority: modified Intent-to-Treat Population (mITT)

				Treatment vs. Placebo			
Treatment Group	Number of Patients (N)	LSMeans	Std Err LSMeans	LSMeans Difference	Std Err LSMeans Difference	95% CI Evaluation	p-value†
Placebo	xxx	xxx.x	xxx.x				
Test	xxx	xxx.x	xxx.x	xxx.x	xxx.x	xx.x – xx.x	x.xxxx
Reference	xxx	xxx.x	xxx.x	xxx.x	xxx.x	xx.x – xx.x	x.xxxx

*The 90% confidence interval for the test-to-reference ratio was calculated using an iterative procedure based on a mean dyspareunia baseline score of *x.xx*. Bioequivalence is demonstrated if the confidence bounds are contained within the range [80%, 125%].

†p-value of treatment effect in ANCOVA model.

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Table 11.4.1.2 Summary of Analysis Results of Co-Primary Efficacy Endpoint of Response Rate

Equivalence: Per-Protocol Population for Responders (PPR)

Treatment Group	Number of Patients (N)	Number of Responders (n)	Proportion of Responders (%)	Difference (%)	90% CI Evaluation*
Test	xxx	xxx	xx.x	xx.x	xx.x - xx.x
Reference	xxx	xxx	xx.x		

Superiority: modified Intent-to-Treat Population (mITT)

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

*The 90% confidence interval for the difference in proportions between test and reference was calculated using Yates' correction. Bioequivalence is demonstrated if the confidence bounds are contained within the range [-20%, 20%].

†Superiority of Active treatments over Placebo were tested using a two-sided Cochran-Mantel-Haenszel (CMH) test, stratified by clinical site, at the 5% significance level using last observation carried forward (LOCF).

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Table 11.4.1.3 Summary of Analysis Results of Secondary Efficacy Endpoint of Success Rate

Equivalence: Per-Protocol Population for Dyspareunia (PPD)

Treatment Group	Number of Patients (N)	Number of Treatment Successes (n)	Proportion of Treatment Success (%)	Difference (%)	90% CI Evaluation*
Test	xxx	xxx	xx.x	xx.x	xx.x - xx.x
Reference	xxx	xxx	xx.x		

Superiority: modified Intent-to-Treat Population (mITT)

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

*The 90% confidence interval for the difference in proportions between test and reference was calculated using Yates' correction. Bioequivalence is demonstrated if the confidence bounds are contained within the range [-20%, 20%].

†Superiority of Active treatments over Placebo were tested using a two-sided Cochran-Mantel-Haenszel (CMH) test, stratified by clinical site, at the 5% significance level using last observation carried forward (LOCF).

Table 12.2.2.1 Overall Summary of Adverse Events (Safety Population)

	Test n (%)	Reference n (%)	Placebo n (%)	Total n (%)
Patients in Safety Population	N	N	N	N
Patients with at least one AE	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)
Patients discontinued study drug due to AE	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)
Total number of AEs reported	xxx	xxx	xxx	xxx
Mild	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)
Moderate	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)
Severe	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)
Not Related	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)
Related	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)
Death	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)
Serious AE	xx (x.x%)	xx (x.x%)	xx (x.x%)	xx (x.x%)

N = Number of patients dosed with respective study treatment
n = Number of patients reporting AE
% = (n / N) × 100

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Table 12.2.2.2 Summary of Treatment Emergent Adverse Events by System Organ Class and MedDRA Preferred Term (Safety Population)

System Organ Class / MedDRA Term	Test N = # *patients dosed*		Reference N = # *patients dosed*		Placebo N = # *patients dosed*	
	Patients n (%)	**Events e**	**Patients n (%)**	**Events e**	**Patients n (%)**	**Events e**
Patients with at least one TEAE	x (x.x%)	x	x (x.x%)	x	x (x.x%)	x
System Organ Class						
Preferred Term	x (x.x%)	x	x (x.x%)	x	x (x.x%)	x
System Organ Class						
Preferred Term	x (x.x%)	x	x (x.x%)	x	x (x.x%)	x
Preferred Term	x (x.x%)	x	x (x.x%)	x	x (x.x%)	x

N = Number of patients dosed with respective study treatment
n = Number of patients reporting TEAE
e = Number of events for each AE system organ class
% = (n / N) × 100

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Table 12.2.2.3 Summary of Frequency of Treatment Emergent Adverse Events by System Organ Class, MedDRA Preferred Term, and Severity (Safety Population)

System Organ Class / MedDRA Term	Test E = # of Events e (%)			Reference E = # of Events e (%)			Placebo E = # of Events e (%)		
	Mild	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Total TEAEs	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)
System Organ Class									
Preferred Term	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)
System Organ Class									
Preferred Term	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)
Preferred Term	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)

E = Total number of events in each treatment group; Percentage is based on total number of events.
e = Number of events for each AE system organ class
% = (e / E) × 100

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Table 12.2.2.4 Summary of Frequency of Treatment Emergent Adverse Events by System Organ Class, MedDRA Preferred Term and Relationship (Safety Population)

System Organ Class / MedDRA Term	Test E = # of Events e (%)		Reference E = # of Events e (%)		Placebo E = # of Events e (%)	
	Related	**Not Related**	**Related**	**Not Related**	**Related**	**Not Related**
Total TEAEs	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)
System Organ Class						
Preferred Term	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)
System Organ Class						
Preferred Term	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)
Preferred Term	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)	x (x.x%)

E = Total number of events in each treatment group; Percentage is based on total number of events.
e = Number of events for each AE system organ class
% = (e / E) × 100

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Table 12.2.2.5 Summary of Frequency of Serious Adverse Events (Safety Population)

System Organ Class / MedDRA Term	Test # of Events		Reference # of Events		Placebo # of Events	
Total SAEs	xx	xx	xx	xx	xx	xx
System Organ Class						
Preferred Term	xx	xx	xx	xx	xx	xx
Preferred Term	xx	xx	xx	xx	xx	xx

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Table 14.2.1 Descriptive Summary of Co-Primary Efficacy Endpoint of Dyspareunia Score (Mean change from Baseline to Visit 3 - (Per-Protocol Population for Dyspareunia)

	Statistic	Test (N = xxx)	Reference (N = xxx)	Placebo (N = xxx)	Overall (N = xxx)
Baseline	n	xxx	xxx	xxx	xxx
	Mean ± SD	x.xx ± x.xx	x.xx ± x.xx	x.xx ± x.xx	x.xx ± x.xx
	Median	x.xx	x.xx	x.xx	x.xx
	Range	x.xx - x.xx	x.xx - x.xx	x.xx - x.xx	x.xx - x.xx
Visit 3	n	xxx	xxx	xxx	xxx
	Mean ± SD	x.xx ± x.xx	x.xx ± x.xx	x.xx ± x.xx	x.xx ± x.xx
	Median	x.xx	x.xx	x.xx	x.xx
	Range	x.xx - x.xx	x.xx - x.xx	x.xx - x.xx	x.xx - x.xx
Change from Baseline	n	xxx	xxx	xxx	xxx
	Mean ± SD	x.xx ± x.xx	x.xx ± x.xx	x.xx ± x.xx	x.xx ± x.xx
	Median	x.xx	x.xx	x.xx	x.xx
	Range	x.xx - x.xx	x.xx - x.xx	x.xx - x.xx	x.xx - x.xx

N= number of patients in the treatment group
n= number of patients with data available

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Listing 14.3.4.1 Out-of-Range Laboratory Test Results (Safety Population)

Patient No.	Treatment Group	Visit	Lab Test	Result	Units	Test Repeated (Y/N)	Repeat Result	Repeat Units
xxxx	Test	3	[redacted]	xx	U/L	Y	xx	U/L
xxxx	Reference							
xxxx	Placebo							
…			…					

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Note (not for inclusion in final output):

- Listing will be sorted by visit, patient number and lab test

Listing 16.2.1 Discontinued Patients

Patient No.	Treatment Group	Discontinuation Reason	Date of Discontinuation	Time of Discontinuation	Discontinuation Related to COVID-19 Pandemic
xx-xxx-xxx	Test	Adverse Event: *specify*	DDMMMYYYY	hh:mm	Yes
	Reference	Investigator Decision			No
	Placebo	Lack of efficacy			
		Lost to follow-up			
		Noncompliance with study drug			
		Other			
		Pregnancy			
		Protocol Deviation: *specify*			
		Serious Adverse Event: *specify*			
		Significant worsening of condition requiring alternative or supplemental therapy			
		Study Termination			
		Unblinded			
		Withdrawal by patient			

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OR if no data (still must provide listing file with header/footer/title and following text)
No discontinued patients

Note (not for inclusion in final output):
- Sort order: by Patient number

Listing 16.2.2 Protocol Deviations

Patient No.	Treatment Group	Type of Protocol Deviation	Date of Deviation	Deviation Related to COVID-19 Pandemic
xx-xxx-xxx	Test	Randomized in Error: *specify inclusion/exclusion criterion*	DDMMMYYYY	Yes
	Reference	Restricted Medication: *specify*		No
	Placebo	Restricted Procedure: *specify*		
		Other: *specify*		
		etc.		

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OR if no data (still must provide listing file with header/footer/title and following text)
No protocol deviations

Note (not for inclusion in final output):
- Sort order: by Patient number, by Date of Deviation

Listing 16.2.3.1 Patients Excluded from Population: Per-Protocol Population (Responder)

Patient No.	Treatment Group	Exclusion Reason
xx-xxx-xxx	Test	Dosed <75% or >125% of intended doses
	Reference	Did not meet all inclusion/exclusion criteria
	Placebo	[redacted]
		Missed more than 2 consecutive doses
		Protocol deviation that significantly affects evaluation of primary endpoint
		etc.

OR if none (still must provide listing file with header/footer/title and following text)
No patients excluded from population

Note: A similar table will be constructed for the PPD and mITT populations:

Listing 16.2.3.2 Patients Excluded from Population: Per-Protocol Population (Dyspareunia)

Listing 16.2.3.3 Patients Excluded from Population: Modified Intent-to-Treat

Note (not for inclusion in final output):
- Data for this listing is NOT captured in the SDTMs, but rather must be provided by biostatistician after analysis is completed.
- Sort order is by Patient number.

Listing 16.2.4.1 Patient Characteristics

Patient No.	Treatment Group	Sex	Age (yrs)	Ethnicity	Race	Height (in)	Weight (lbs)	Postmenopausal Status
xx-xxx-xxx	Test	Female	xx	Not Hispanic or Latino	American Indian or Alaska Native	xx	xxx	Natural
	Reference			Hispanic or Latino	Asian			Hysterectomy without bilateral oophorectomy
	Placebo				Black or African American			Bilateral oophorectomy
					Native Hawaiian or Other Pacific Islander			Other: *specify*
					White			
					Multiple (*1st selected; 2nd selected; 3rd selected*)			

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Note (not for inclusion in final output):

- Sort order: by Patient number

Listing 16.2.4.2 Listing of Patient Characteristics (Baseline Signs and Symptoms)

		Baseline Signs and Symptoms						Baseline %			
Patient Number	**Treatment Group**	**Vaginal Dryness**	**Vaginal/Vulvar Irritation/Itching**	**Dysuria**	**Dyspareunia**	**Vaginal Bleeding**	**Most Bothersome Symptom**	**Superficial Cells**	**Basal/ parabasal Cells**	**Intermediate Cells**	**Baseline Vaginal pH**
xx-xxxx	Test	None	None	None	None	Absent	Dyspareunia	x	x	xx	x.x
	Reference	Mild	Mild	Mild	Mild	Present					
	Placebo	Moderate	Moderate	Moderate	Moderate						
		Severe	Severe	Severe	Severe						

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Note (not for inclusion in final output):

- Sort order: by Patient number

Listing 16.2.4.3 Medical History

Patient No.	Treatment Group	System	Reported Term	Onset Date	End Date	Ongoing	Clinical Significance
xx-xxx-xxx	Test	Cardiovascular		DDMMMYYYY	DDMMMYYYY	Yes	CS
	Reference	Dermatological				No	NCS
	Placebo	Endocrinological					
		Gastrointestinal/Hepatic					
		Genito-Urinary/Reproductive System					
		HEENT					
		Hematological/Lymphatic					
		Immunological					
		Metabolism and Nutrition					
		Musculoskeletal					
		Neurological					
		Other					
		Psychological and Psychiatric/Behavioral					
		Respiratory					
		Surgical Procedure					

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Note (not for inclusion in final output):

- Sort order: by Patient number, System (alphabetical), Reported Term (alphabetical)

Listing 16.2.4.4 Concomitant Medications

Patient No.	Medication	Indication	Dose	Route	Frequency*	Date Started	Date Stopped	Therapeutic Drug Class
xx-xxx-xxx	Multivitamin	General Health	1 Capsule	Oral	QD	DDMMMYYYY MMYYYY YYYY	DDMMMYYYY MMYYYY YYYY Ongoing Unknown	

*PRN - As needed; QD – Daily (once per day); Q4H - Every 4 hours; Q8H - Every 8 hours; Q12H - Every 12 hours; BID - Twice per day; TID - 3 times per day; QID - 4 times per day; QOD - Every other day; QS - Every week; QM - Every month; Q3M - Every 3 months

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OR if no data (still must provide listing file with header/footer/title and following text)
No concomitant medications

Note (not for inclusion in final output):

- Sort order: by Patient number, by Date Started, By Medication
- Only include footnotes for Frequency codes presented in table.

Listing 16.2.5.1 Visit Date Information

Patient No.	Treatment Group	Informed Consent Date	ICF Reconsent Date (if applicable)	Visit 1 Date	Visit 2 Date	Telephone Contact Date	Visit 3 or Early Termination Date
xx-xxx-xxx	Test	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY
	Reference	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY
	Placebo	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY

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Note (not for inclusion in final output):
- Sort order: by Patient number

Listing 16.2.5.2 Drug Administration

Patient No.	Treatment Group	Date of First Dose	Date of Last Dose	Total Doses Applied	Dosing Compliance (%)
xx-xxx-xxx	Test	DDMMMYYYY	DDMMMYYYY	x	xxx%
	Reference	DDMMMYYYY	DDMMMYYYY		
	Placebo	DDMMMYYYY	DDMMMYYYY		
		DDMMMYYYY	DDMMMYYYY		

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Note (not for inclusion in final output):

- Sort order is by Patient number

Listing 16.2.5.3 Study Compliance

Patient No.	Treatment Group	Patient Diary Collected?	EOS Visit 3 Completed?	[redacted]					
xx-xxx-xxx	Test	Yes	No	Yes	Yes	No	No	No	No
	Reference	No	Yes	No	No	Yes	Yes	Yes	Yes
	Placebo								

Created on: DDMMMYYYY

Note (not for inclusion in final output):

- Sort Order: by Patient Number

Listing 16.2.6.1 Listing of Vaginal Cytology Results

		Visit 1 (Baseline)					Visit 3							
Patient No.	**Treatment Group**	**Basal/ Parabasal %**	**Inter-mediate %**	**Basal/ Parabasal +Inter-mediate%**	**Super-ficial Cells%**	**pH**	**Basal/ Parabasal %**	**Inter-mediate%**	**Basal/ Parabasal +Inter-mediate%**	**Super-ficial Cells%**	**pH**	**Cytology Changes From Baseline**	**pH Changes From Baseline**	**Responder Yes/No**
xx-xxxx	Test	xx	xx	xxx	xxx	x.x	xx	xx	xx	xxx	x.x	xx	x.x	Yes
	Reference													No
	Placebo													

Note (not for inclusion in final output):

- Sort Order: by Patient Number

Listing 16.2.6.2 Dyspareunia Ratings and Secondary Endpoint (Success)

Patient Number	Treatment Group	Score at Baseline	Score at Visit 3	Success (Yes/No)
xx-xxxx	Test	3	0	Yes
	Reference			
	Placebo			

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Note (not for inclusion in final output):

- Sort Order: by Patient Number

Listing 16.2.6.3 VVA Signs and Symptoms: Visits 2 and 3

		Visit 2						Visit 3				
Patient Number	**Treatment Group**	**Vaginal Dryness**	**Vaginal/Vulvar Irritation/Itching**	**Dysuria**	**Dyspareunia**	**Vaginal Bleeding**	**Most Bothersome Symptom (Baseline)**	**Vaginal Dryness**	**Vaginal/Vulvar Irritation/Itching**	**Dysuria**	**Dyspareunia**	**Vaginal Bleeding**
xx-xxxx	Test	None	None	None	None	Absent	Dyspareunia	None	None	None	None	Absent
	Reference	Mild	Mild	Mild	Mild	Present		Mild	Mild	Mild	Mild	Present
	Placebo	Moderate	Moderate	Moderate	Moderate			Moderate	Moderate	Moderate	Moderate	
		Severe	Severe	Severe	Severe			Severe	Severe	Severe	Severe	

Created on: DDMMMYYYY

Note (not for inclusion in final output):

- Sort order: by Patient number

Listing 16.2.7 Adverse Events (Safety Population)

Patient No.	System Organ Class / MedDRA Preferred Term / PI Term / AE Term	Trt.	Local	Onset Date Time	Resolution Date Time	Intensity	Relationship	Outcome	Action Taken with IMP	Other Action Taken	SAE
xx-xxx-xxx	System Organ Class / MedDRA Preferred Term / PI Term / AE Term	T	Yes	DDMMMYYYY hh:mm	DDMMMYYYY hh:mm	Mild	Related	Recovered/ Resolved	Drug Withdrawn	None	No
		R	No	DDMMMYYYY hh:mm	Unknown	Moderate	Not Related	Recovering /Resolving	Dose Not Changed	Con Med Given	Yes
		P				Severe		Recovered/ Resolved with sequelae	Not Applicable	Other	
		-						Not Recovered/ Not Resolved			
								Fatal			
								Unknown			

T = Test, R = Reference, P = Placebo, - = AE reported prior to treatment administration

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OR if no data (still must provide listing file with header/footer/title and following text)
No adverse events

Note (not for inclusion in final output):

- Sort order: by Patient number, by Onset Date Time, by System Organ Class / MedDRA Preferred Term, AE Term
- Resolution Date Time: If blank in SDTM, output “Unknown”.

Listing 16.2.8.1 Laboratory Test Results

Patient No.	Treatment Group	Visit	Collection Date	Test	Units	Reference Interval	Result
xx-xxx-xxx	Test	1	DDMMMYYYY	Fasting Triglycerides	mg/dL	x.x - x.x	xx.x
	Reference	1		Serum FSH	mIU/mL	x.x - x.x	xx.x
	Placebo	1		[redacted]	U/L	x.x - x.x	xx.x
		1		PAP Smear	-	-	Normal
		1- Repeat 1					
		3					

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Note (not for inclusion in final output):

- Sort Order: by Patient Number, by Visit (chronological, including repeats and unscheduled), by Test (alphabetical)
- Tests, units, reference intervals and results shown above are for example purposes only. Data should be output as captured in dataset.

Listing 16.2.8.2 Vaginal Ultrasonography and Mammogram

		Vaginal Ultrasonography		Mammogram	
Patient No.	**Treatment Group**	**Collection Date**	**Does Patient Have a Confirmed Inactive Endometrial Lining of < 4 mm?***	**Collection Date**	**Are Screening Mammogram Results Normal?†**
xx-xxx-xxx	Test	DDMMMYYYY	Yes	DDMMMYYYY	Yes
	Reference		N/A		N/A
	Placebo				

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

Created on: DDMMMYYYY

Note (not for inclusion in final output):

- Sort Order: by Patient Number

Listing 16.2.8.3 Vital Signs

Patient No.	Treatment Group	Visit	Vital Sign	Result	Units
xx-xxx-xxx	Test	1	Diastolic Blood Pressure	xx	mmHg
	Reference	1	Pulse Rate	xx	beats/min
	Placebo	1	Respiratory Rate	xx	breaths/min
		1	Systolic Blood Pressure	xxx	mmHg
		1	Temperature	xx.x	°C
		2			
		2			
		2			
		2			
		2			
		3			
		3			
		3			
		3			
		3			

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Note (not for inclusion in final output):

- Sort Order: by Patient Number, by Visit (chronological, including repeats and unscheduled), by Vital Sign (alphabetical)

Listing 16.2.8.4 Abnormal Physical Examination Results (if applicable)

Patient No.	Treatment	Visit	Category	Result	Description
xx-xxx-xxx	Test	Screening	General Appearance	Abnormal (NCS)	
	Reference	End of Study/Early Termination	Skin	Abnormal (CS)	
	Placebo	Screening	Abdominal		

Created on: DDMMMYYYY

Note (not for inclusion in final output):

- Sort Order: by Patient Number, by Visit, by Category

APPENDIX A: OUTLINE OF STATISTICAL ANALYSIS METHOD USING SAS PROC GLM

Let Y = change from baseline (the endpoint of interest)

Baseline = mean score at baseline (the covariate)

Let $\mu_T(b)$ be the mean of Y for the Test product when Baseline = b

Let $\mu_R(b)$ be the mean of Y for the Reference product when Baseline = b

$\mu_T(b)$ and $\mu_R(b)$ are both *weighted* means, depending on which weights are chosen (explicitly or implicitly) for the clinical sites.

Assume that the code used for the Test treatment comes before the code used for the Reference treatment in SAS sort order (for example, if the Test product is coded as "1" and the Reference product is coded as "2", then this would be so. Similarly if Test were coded as "A" and Reference were coded as "B". On the other hand, if Test were coded as "T" and Reference were coded as "R", Reference would come before Test in SAS sort order, and the coefficients for the treatment levels in what follows would have to be reversed.)

The initial statements of a SAS PROC GLM analysis would be:

```
Proc glm;
class site trt;
model Y = site trt Baseline;
```

These statements would be followed by ESTIMATE statements, as follows:

To test the null hypothesis $H_0: \mu_T(b)/\mu_R(b) < c$, against the alternative $H_1: \mu_T(b)/\mu_R(b) \geq c$, we would use the statement

estimate 'ratio = c, baseline = b' intercept (1- c) trt 1 $-c$ Baseline (1- c) b;

In the resulting analysis, we would reject H_0 if the (two-sided) p-value given by SAS is ≤ 0.1000 and if the value of the point estimate is positive (note that if the p-value is ≤ 0.1000 but the point estimate is *negative*, we would have rejected H_0 "in the wrong direction".)

Similarly, to test $H_0: \mu_T(b)/\mu_R(b) > c$, against the alternative $H_1: \mu_T(b)/\mu_R(b) \leq c$, we would use the same ESTIMATE statement, and we would reject H_0 if the p-value is ≤ 0.1000 and if the point estimate is *negative*.

Note that in these analyses, we have not explicitly specified coefficients for the levels of site. By default, SAS PROC GLM implicitly puts *equal weight* on each site in this case. If a sponsor feels that site weights other than equal weights should be used, they should make their case in their submission. With unequal weights, the weights would have to be given explicitly in the ESTIMATE statement, with appropriate multipliers.

To find the minimum value of Baseline (this assumes that the estimated slope is positive) for which the products pass the usual bioequivalence test, first use c = 0.80, so that the ESTIMATE statement would be

estimate 'ratio = 0.80, baseline = b' intercept 0.20 trt 1 –0.80 Baseline 0.20b;

Through trial and error ("by hand" or with some sort of computer search algorithm), find the value of b for which the resulting p-value is exactly 0.1000 (and for which the point estimate is positive.) Call it b_L. b_L is the minimum value of baseline for which the products pass "on the low end". Now use c = 1.25, so that the ESTIMATE statement is

estimate 'ratio = 1.25, baseline = b' intercept -0.25 trt 1 –1.25 Baseline -0.25b;

Through trial and error ("by hand" or with some sort of computer search algorithm), find the value of b for which the resulting p-value is exactly 0.1000 (and for which the point estimate is negative.) Call it b_U. b_U is the minimum value of baseline for which the products pass "on the high end". The ***larger*** of b_L and b_U is the minimum value of baseline for which you pass both one-sided tests, and so pass the bioequivalence test.

For a given value of Baseline, for example Baseline = sample mean baseline from the study or Baseline = sample median baseline from the study, call it Baseline = b*, you can use the estimate statement

estimate 'ratio = c, baseline = b*' intercept (1- c) trt 1 – c Baseline (1- c) b*;

to obtain a confidence interval at Baseline = b* by finding ("by hand" or through computer search) the two values of c (call them c_L and c_U) that make the p-value exactly equal to 0.1000 (verifying that values of c between c_L and c_U produce a p-value > 0.1000 and values of c either below c_L or above c_U produce a p-value < 0.1000.)

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