Shionogi Study Title:	A Phase 3, Randomized, Double-blind, Placebo controlled Multicenter Study to Evaluate the Efficacy and Safety of Ospemifene in Patients with Moderate to Severe Vaginal Dryness, a Symptom of Vulvo-vaginal Atrophy (VVA) due to Menopause
Shionogi Study Number:	1517I0231
ClinicalTrials.gov registration No.	NCT02638337
Study Document	Protocol (Version 3 dated 02 November 2016)

History of Protocol Amendments

Original (Version 1)	06 October 2015
Version 2	11 March 2016
1. Standardized the wording for endpoints to be consistent with previous studies and labeling 2. Changed the limits for BMI for consistency with the demographics of the US population of postmenopausal women 3. Identified the readers and clarified the process for blinding various data, e.g., photographs, mammograms and DXA scans 4. Clarified the process for the pathologist's blinded reading of the endometrial histological samples 5. Improved the list of prohibited concomitant medications that might affect sex hormone levels including drugs involved in drug interactions and herbal supplements	
Version 3	02 November 2016
1. Because of very slow recruitment, the 104 week double blind, placebo controlled study consisting of a 12 week efficacy period followed by a 92 week safety period was shortened to only the 12 week efficacy period followed by a 2 week safety period. This change required concomitant changes throughout the protocol to text, tables, and figures, and adjustments to the measurements that were to be made. 2. Made the requirement for vaginal imaging optional as it is not needed for the dryness endpoint 3. Clarified the process for handling data for patients entering the study with the 11 March protocol and having already entered the 92 week safety period.	

CLINICAL STUDY PROTOCOL: 1517I0231

Study Title:	A Phase 3, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Ospemifene in Patients with Moderate to Severe Vaginal Dryness, a Symptom of Vulvo-vaginal Atrophy (VVA) due to Menopause
Study Number:	1517I0231
Study Phase:	3
Product Name:	Ospemifene
IND Number	67,216
Sponsor:	Shionogi Inc. 300 Campus Drive, Florham Park, NJ 07932 USA
Sponsor Contact:	PPO Shionogi Inc. 300 Campus Drive, Florham Park, NJ 07932 USA TEL: PPO FAX: PPO

Issue Date:

Original (Version 1)	06 October 2015
Version 2	11 March 2016
Version 3	02 November 2016

SYNOPSIS

Study Title:

A Phase 3, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Ospemifene in Patients with Moderate to Severe Vaginal Dryness, a Symptom of Vulvo-vaginal Atrophy (VVA) due to Menopause.

Study Number:

1517I0231

Study Phase: 3

Objective

The objective of this study is to evaluate the efficacy and safety of ospemifene 60 mg once daily (QD) compared with placebo in treatment of vulvo-vaginal atrophy (VVA) due to menopause in women with moderate to severe vaginal dryness as the most bothersome symptom (MBS) of VVA.

Study Design:

This is a multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of ospemifene 60 mg QD in postmenopausal women with vaginal dryness as the MBS of VVA due to menopause.

The study was previously designed as a two part study; Part A (12 week efficacy and safety assessment period) and Part B (long term, 92 week safety assessment period, beginning at week 12 and ending at week 104). The current version of the protocol has been amended to remove Part B based on enrollment challenges and site feedback. Data will be handled as described in the Note at the end of the Synopsis.

This study consists of 3 periods: a Screening Period of up to 4 weeks during which eligibility will be assessed; a Treatment Period of 12 weeks during which efficacy and safety will be assessed, and a Follow-up Period of 2 weeks after the last dose of study medication.

Study Population:

Approximately 600 subjects will be randomized to this study.

Eligibility Criteria

Postmenopausal women, 40 to 80 years old who have VVA due to menopause and their MBS is vaginal dryness which is moderate to severe in severity, will be able to participate if they meet all eligibility criteria as defined in the protocol.

Study Drug, Dose, and Mode of Administration:

Ospemifene tablet 60 mg QD, oral administration.

Control Drug, Dose, and Mode of Administration:

Placebo matching ospemifene 60 mg tablet QD, oral administration.

Duration of Treatment:

After screening, subjects who meet all eligibility criteria will be randomized in a 1:1

ratio to treatment with ospemifene 60 mg or matching placebo, once daily for 12 weeks.

Prohibited Concomitant Therapy:

The following medications will be prohibited after screening and at least two weeks before receiving the study drug whichever is the earlier timepoint and during the treatment period:

- Dietary supplements and herbal therapies with assumed clinically significant estrogenic vaginal effects (See Appendix 1)
- Any hormonal products regardless of the route of administration
- Any selective estrogen receptor modulators
- Any vaginal lubricant or moisturizer other than that provided by the Sponsor for use in the study
- Use of systemic fluconazole, rifampicin, rifabutin, carbamazepine, phenytoin, St John's wort

Efficacy Assessments:

- Percentage of parabasal cells in the maturation index of the vaginal smear
- Percentage of superficial cells in the maturation index of the vaginal smear
- Vaginal pH
- Severity of self-reported symptoms of vaginal dryness
- Severity of VVA symptoms other than vaginal dryness (ie, dyspareunia, vulvar/vaginal itching/irritation, dysuria, and/or vaginal bleeding associated with intercourse)
- Vaginal health index (VHI)
- Vulvar health index (VuHI)
- Female Sexual Function Index (FSFI)
- Urogenital Distress Inventory (UDI-6)
- Markers of bone metabolism

Safety Assessments:

Safety assessments will include gynecological examination, breast examination, endometrial thickness (for subjects with an intact uterus), endometrial histology, physical examination, vital signs, clinical laboratory tests, and adverse events (AEs).

Statistical Methods:

Efficacy

For percentage of parabasal cells, percentage of superficial cells and vaginal pH, a Mixed-effects Model Repeated Measures (MMRM) approach will be used. In the model, repeated measurements of the change from baseline at Week 4, Week 8 and Week 12 will be the response variable. Baseline value and study center may be modeled as covariates. Superiority of ospemifene to placebo will be evaluated by

testing the mean difference between the two treatment groups at Week 12.

For dryness as the MBS, Generalized Estimating Equations (GEE) model will be used to fit a marginal proportional odds model to the longitudinal ordered categorical data (Fitzmaurice et al., 2011). In the model, repeated measurements of the change from baseline in dryness at Week 4, Week 8 and Week 12 will be the response variable. Baseline severity of dryness and study center may be modeled as covariates. Superiority of ospemifene to placebo will be evaluated by comparing the two treatment groups at Week 12.

Safety

The number and percentage of subjects who experience treatment-emergent adverse events (TEAEs) will be summarized by treatment group, and during Treatment Period and Follow-up period seperately. Serious adverse events (SAEs) and AEs leading to discontinuation will be tabulated in a similar manner. Details will be described in the Statistical Analysis Plan (SAP).

Study Duration:

Subjects may be participating in the study for up to 18 weeks.

Date of Original Version: 06 October 2015

Date of Version 2: 11 March 2016

Date of Latest Amendment: 02 November 2016

NOTE:

For subjects consented under Protocol version 11 March 2016:

- Dual-Energy X-ray Absorptiometry (DXA) Scan

  Bone mineral density (BMD) was determined using DXA scans. Images of the hip and lumbar spine were sent to a central reader. The date of imaging was entered in the eCRF. Detailed procedures are specified in a separate document. Details about the central BMD laboratory are provided in Section 10.1.

- Standard mammogram scans used to determine Breast Density .

  Breast density was determined using standard mammogram scans. Images were sent to a central reader. The date of imaging was entered in the eCRF. Detailed procedures are specified in a separate document. Details about the central mammogram laboratory are provided in Section 10.1. For subjects who had a normal mammogram within 9 months prior to screening for which the results were available and could be sent to the central reader, do not require a new mammogram to be performed for eligibility assessment.

- Early Termination Procedures

  For subjects who have completed Visit 5, the following measurements and/or evaluations will be made and recorded in the eCRF:

  - Record concomitant therapy
  - Assess for AEs
  - Assess symptoms of VVA

- Assess FSFI
- Assess UDI-6
- Measure vital signs (BP, pulse rate, and oral temperature performed after subject is in seated or in a recumbent position ≥3 minutes) including weight
- Perform physical examination
- Perform breast examination
- Perform gynecological examination
- Measure vaginal pH
- Obtain vaginal smear for assessment of maturation index
- Assess VHI
- Assess VuHI
- Obtain vulvo-vaginal imaging (optional)
- Perform TVU and measure endometrial thickness. Capture images to be sent to the central reader
- Perform endometrial biopsy (do not perform if done within 6 months of ET visit)
- Obtain blood samples for safety laboratory tests, hormone levels and serum markers of bone metabolism
- Obtain urine sample for urinalysis and urinary marker of bone metabolism
- Assess study medication returned and assess compliance with study medication
- Conduct follow-up call on Day 14 after last dose of study medication

Safety (After Visit 5)

The subjects who experienced treatment-emergent adverse events (TEAEs) will be summarized by treatment group. Details will be described in the SAP.

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LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ASC-H	atypical squamous cells – cannot exclude HSIL
ASCUS	atypical squamous cells of undetermined significance
AST	aspartate aminotransferase
BSAP	bone specific alkaline phosphatase
BIN	bottle identification number
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
BSP	bone sialoprotein
BUN	blood urea nitrogen
Ca	calcium
CI	confidence interval
CK	creatine kinase
Cl	chloride
CTM	clinical trial manager
CTX	C-terminal telopeptide of type 1 collagen
DXA	dual-energy X-ray absorptiometry
DPD	deoxypyridinoline
E_2	estradiol
ECG	electrocardiogram/electrocardiography
eCRF	electronic case report form
eDiary	electronic diary
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FSFI	Female Sexual Function Index
FSH	follicle-stimulating hormone
GCP	good clinical practice
GEE	generalized estimating equations
GGT	gamma glutamyl transferase
HBsAg	hepatitis B surface antigen
HCT	hematocrit
HDL	high-density lipoprotein

HDL-C	HDL cholesterol
HgB	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HPV	human papilloma virus
HSIL	high-grade squamous intraepithelial lesion
HT	hormone therapy
ICF	informed consent form
ICH	International Conference on Harmonisation
IPR	independent panel review
IRB	institutional review board
ITT	intent-to-treat
IxRS	interactive web or voice response system
K	potassium
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LDL-C	LDL cholesterol
LFT	liver function test
LH	luteinizing hormone
MBS	most bothersome symptom
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model repeated measures
MPV	mean platelet volume
Na	sodium
NOS	not otherwise specified
NTX	N-terminal telopeptide of type 1 collagen
OTC	over-the-counter
P1NP	N-terminal propeptide of type I collagen
PAP	Papanicolaou (Test)
PP	per-protocol
QD	once daily
RBC	red blood cell count
RDW	red blood cell distribution width
SAE	serious adverse event

SAP	statistical analysis plan
SD	standard deviation
SERM	selective estrogen receptor modulator
SHBG	sex hormone binding globulin
SIL	squamous intraepithelial lesion
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
TC	telephone call
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TRACP-5b	tartrate-resistant acid phosphatase 5b
TVU	transvaginal ultrasound
UDI	Urogenital Distress Inventory
ULN	upper limit of normal
UTI	urinary tract infection
VHI	Vaginal Health Index
VLDL	very low-density lipoprotein
VLDL-C	VLDL cholesterol
VuHI	Vulvar Health Index
VVA	vulvo-vaginal atrophy
WBC	white blood cell count
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

Vulvo-vaginal atrophy (VVA) often referred to as vaginal atrophy, urogenital atrophy, or atrophic vaginitis, is a condition associated with the declining estrogen levels during peri- and post-menopause [1, 2].

Because the vaginal wall and surrounding tissues have estrogen receptors, circulating estrogen levels have a direct effect on the epithelium and the underlying connective tissue; these affect the physiology of the vulva, vagina, and other pelvic structures [1, 2]. Physiologic estrogen concentrations are associated with a thickened and mature vaginal mucosa with appropriate vaginal blood flow, lubrication, mechanical sensitivity, and elasticity. Estrogen stimulation produces glycogen that is used by lactobacilli, naturally existing in the vagina, to produce lactic acid, which keeps vaginal pH levels low (3.5 to 4.5). This is part of the body's natural defense against vaginal and urinary tract infections [1, 2].

The decline in estrogen levels after menopause is followed by many histologic transformations including thinning of the vaginal epithelium, proliferation of connective tissue, fragmentation of elastin, and hyalinization of collagen. These changes result in granulation, fissures, friability of the vaginal mucosa, and decreased elasticity. Changes in tissue composition are not limited to the genital tract; they also occur in the urinary tract, as well. Vaginal and urethral epithelia change adversely in an estrogen-deprived environment [2, 4].

Genital atrophic changes include decreased maturation of the vaginal epithelial cells and progressive decrease in vascularity in the surrounding tissue [1, 2]. The glycogen content of vaginal epithelial cells decreases, resulting in reduced colonization by lactobacilli. This is followed by increased vaginal pH and increases the incidence of vaginal and urinary tract infections [2].

A decrease in vaginal lubrication due to hormone insufficiency is an early hallmark of VVA. Genital symptoms of VVA include dryness, burning, dyspareunia, loss of vaginal secretions, leucorrhea, vulvar pruritus, feelings of pressure, itching, and yellow malodorous discharge. Also associated with VVA are urinary symptoms including urethral discomfort, urinary frequency, hematuria, urinary tract infection, dysuria, and stress incontinence. Over time, the lack of vaginal lubrication often results in sexual dysfunction and associated emotional distress [2, 3, 5, 6, 7, 8].

The incidence of postmenopausal women with symptoms of VVA is estimated to be from 10% to 40% [5] up to more than 75% [2]. However, only 20% to 25% of the estimated symptomatic women seek medical attention [2, 6], suggesting that VVA is an underdiagnosed condition.

Current treatment options for VVA include systemic hormone therapy (HT), transvaginal estrogen products, and non-hormonal lubricants and moisturizers [1, 2, 3]. Ospemifene is an oral, non-hormonal option for the treatment of dyspareunia as a symptom of VVA due to menopause. Ospemifene is a selective estrogen receptor modulator (SERM) with

estrogenic or anti-estrogenic effects in different tissues of the body. In the vulva, the vagina, and surrounding tissues, ospemifene acts as an estrogen agonist and has demonstrated a clinically significant increase in the number of superficial vaginal cells, a decrease in the number of parabasal vaginal cells, and a reduction in vaginal pH. Ospemifene has also demonstrated improvement in dyspareunia associated with postmenopausal VVA. In one study (Study 15-50310), ospemifene therapy was associated with statistically significant improvement compared with placebo in vaginal dryness associated with postmenopausal VVA. In a second study (Study 15-50821), there was a trend towards improvement relative to placebo; however, the difference between groups was not statistically significant.

Over the 12 weeks of the Treatment Period, this study will assess the effect of ospemifene compared with placebo as treatment of vaginal dryness in postmenopausal women with VVA due to menopause who report vaginal dryness as the MBS. This will be followed by a 2-week follow up period in which use of concomitant medication and adverse events will be assessed.

2. STUDY OBJECTIVES

2.1 Primary Objectives

Objective 1: To assess the efficacy of ospemifene 60 mg daily at 12 weeks of treatment, relative to placebo, in the treatment of vaginal dryness, a symptom of vulvar and vaginal atrophy, due to menopause.

Hypothesis: After 12 weeks of treatment, ospemifene 60 mg QD, relative to placebo, significantly improves all 4 co-primary efficacy endpoints:

- Percentage of parabasal cells in the maturation index of the vaginal smear
- Percentage of superficial cells in the maturation index of the vaginal smear
- Vaginal pH
- Severity of self-reported MBS of vaginal dryness

Objective 2: To assess the safety and tolerability of ospemifene 60 mg QD during 12 weeks of treatment, relative to placebo.

2.2 Secondary Objectives

Objective 1: To assess the effect of ospemifene 60 mg relative to placebo in change from baseline to Week 12 on:

- Severity of other VVA symptoms different from vaginal dryness (ie, dyspareunia, vulvar/vaginal itching/irritation, dysuria [difficult/painful urination], vaginal bleeding associated with intercourse)
- Markers of bone metabolism
- Vaginal health Index (VHI)
- Vulvar health Index (VuHI)

Objective 2: To assess the effect of ospemifene 60 mg relative to placebo in change from baseline to Week 12 on:

- Female Sexual Function Index (FSFI)
- Urinary Distress Inventory (UDI-6)

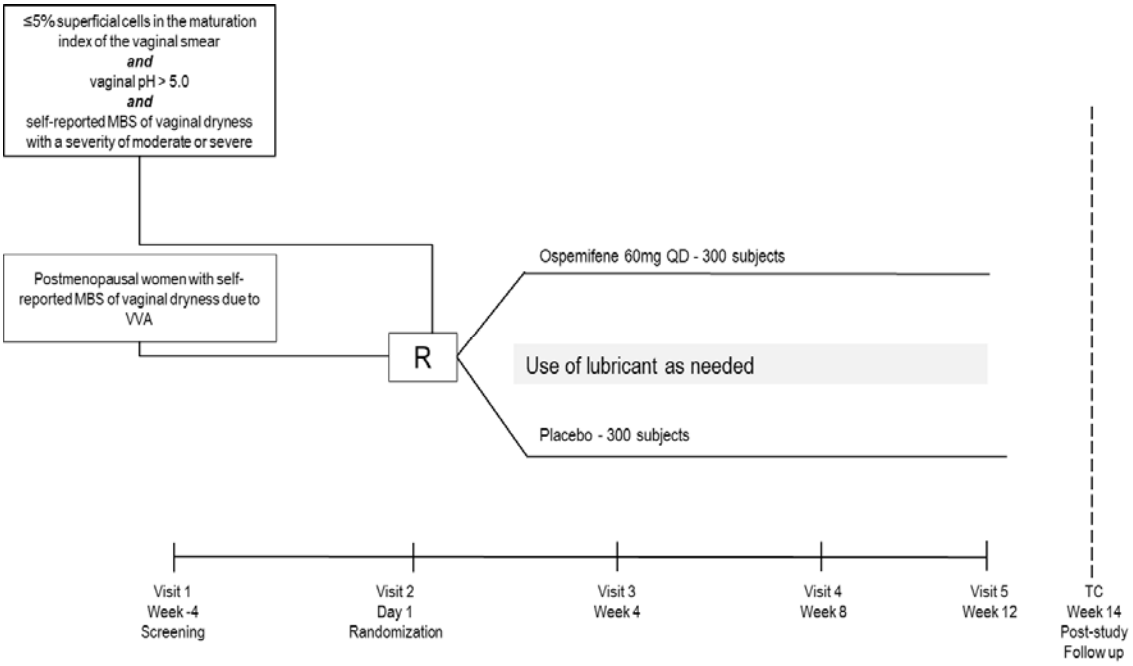
Objective 3: To assess the effect of ospemifene 60 mg QD, relative to placebo, over 12 weeks on endometrial histology

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 3 multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of ospemifene in postmenopausal women with vaginal dryness as MBS of VVA due to menopause. After screening, subjects who have ≤5% superficial cells in the maturation index of the vaginal smear, a vaginal pH >5.0 and vaginal dryness as MBS of VVA based on self-assessment, who also meet all other eligibility criteria, will be randomized in a 1:1 ratio to receive either ospemifene 60 mg QD or matching placebo for 12 weeks. Randomization will be stratified by severity of MBS of vaginal dryness at Visit 2 and by the presence or absence of the uterus. Randomization of subjects without a uterus will be limited to 60% of the study population. The treatment period of this study consists of a 12-week efficacy and safety assessment period after which the primary objective of the study will be assessed. Two weeks after the last dose of study medication, subjects will have a follow-up visit/telephone contact to assess for adverse events and use of concomitant therapy. Subjects will remain in the study for up to 18 weeks. The study design schematic is shown in Figure 3.1-1. The Schedule of Time and Events is shown in Table 3.1-1.

Figure 3.1-1 Study Schematic



TC = telephone call; R = randomization.

Table 3.1-1 Schedule of Time and Events

Evaluation	Screening	Randomization	Treatment			FU[q]
	V1	V2	V3	V4	V5	TC
	Within 4 Weeks Prior to Day 1 [a]	Day 1	Wk 4	Wk 8	Wk 12/ ET	Wk 14
Informed Consent	X					
Assign Subject ID Number [b]	X					
I/E Criteria	X	X				
Demographics	X					
Medical History [c]	X					
Physical Examination	X	X			X	
Electrocardiogram	X					
Breast Examination	X	X			X	
Gynecological Examination	X[o]	X[p]			X	
Safety Laboratory Tests [d]	X	X [e, p]			X [e]	
Hormone Levels [f]		X			X	
FSH [g]	X					
Markers of Bone Metabolism [h]		X			X	
Urinalysis	X	X			X	
Urine Dipstick [i]	X	X				
Vital Signs (blood pressure, pulse, body temperature)	X	X	X	X	X	
Height	X					
Weight (BMI)	X	X	X	X	X	
Prior Therapy	X	X				
Concomitant Therapy			X	X	X	X
Adverse Events	X [j]	X	X	X	X	X

Evaluation	Screening	Randomization	Treatment			FU[q]
	V1	V2	V3	V4	V5	TC
	Within 4 Weeks Prior to Day 1 [a]	Day 1	Wk 4	Wk 8	Wk 12/ ET	Wk 14
Cervical PAP Smear	X[o]					
Vaginal pH	X[o]	X[p]	X	X	X	
Vaginal Smear/ Maturation Index	X[o]	X[p]	X	X	X	
Vaginal Health Index (VHI)		X	X	X	X	
Vulvar Health Index (VuHI)		X	X	X	X	
Vulvo-Vaginal Imaging [k]		X			X	
Endometrial Thickness (TVU)	X				X	
Endometrial Histology (Biopsy)	X				X [n]	
Mammogram	X [l]					
Dispense eDiary/Return eDiary		X			X	
eDiary Compliance			X	X	X	
Assessment of symptoms of VVA	X[o]	X[p]	X	X	X	
Dispense Study Medication		X	X	X		
Dispense Lubricant		X	X	X		
Study Medication Compliance [m]			X	X	X	
Reinforce Compliance with Study Medication		X	X	X		
Study Medication Return			X	X	X	
Female Sexual Function Index (FSFI)		X	X	X	X	

Evaluation	Screening	Randomization	Treatment			FU[q]
	V1	V2	V3	V4	V5	TC
	Within 4 Weeks Prior to Day 1 [a]	Day 1	Wk 4	Wk 8	Wk 12/ ET	Wk 14
Urinary Distress Inventory (UDI-6)		X	X	X	X	

ET = Early termination; **FU** = Follow-up; **TC** = Telephone call.

a Enough time between Visit 1 and Visit 2 should be allowed to receive the results of tests conducted as part of Visit 1, therefore, Visit 2 should not take place earlier than 1 week after Visit 1.
b Subject ID number will be assigned through the interactive web or voice response system (IxRS).
c Medical history should be captured for the 2 years prior to screening, except for any history of cancer which should be captured regardless of the time.
d Safety laboratory tests: red blood cell (RBC) count, white blood cell (WBC) count, differential, platelet count, hemoglobin (HgB), hematocrit (HCT), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), RBC distribution width (RDW), mean platelet volume (MPV), albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, estimated glomerular filtration rate (eGFR), total protein, glucose, uric acid, blood urea nitrogen (BUN), creatine kinase (CK), thromboplastin time, fibrinogen, antithrombin III, factor V Leiden (screening only), protein-C, protein-S, lipids total cholesterol, LDL cholesterol (LDL-C), HDL cholesterol (HDL-C) and triglycerides.
e Subjects should be fasting for at least 8 hours prior to blood sample collection.
f Hormones: Estradiol (E2), follicle stimulating hormone (FSH), luteinizing hormone (LH), sex hormone-binding globulin (SHBG), free and total testosterone
g FSH values may be measured for confirmation of postmenopausal status (inclusion criterion # 3) in women ≥45 years old who do not remember the date of the last spontaneous menstrual period OR women who have had a hysterectomy WITHOUT oophorectomy
h Markers of bone metabolism: Markers of bone resorption: serum N-terminal telopeptide of type 1 collagen (NTX), serum C-terminal telopeptide of type 1 collagen (CTX), serum bone sialoprotein (BSP), urinary deoxypyridinoline (DPD), and serum tartrate-resistant acid phosphatase 5b (TRACP-5b). Markers of bone formation: serum total alkaline phosphatase, serum bone specific alkaline phosphatase (BSAP), serum N-terminal propeptide of type 1 collagen (P1NP), and serum osteocalcin
i At Visits 1 and 2, in addition to obtaining a sample for urinalysis, a urine dipstick will be used to rule out urinary tract infections prior to randomization. Subjects otherwise eligible, who are found to have a urinary tract infection should receive treatment and may continue after confirmation of cure.
j Adverse events spontaneously reported after signature of the informed consent should be captured.
k Unless subject withdraws consent for Vaginal Imaging during the course of the study, if the quality of the photographs is not adequate as assessed by Canfield, a re-shoot should be scheduled as soon as possible but no more than seven days after the original shoot day.
l May be omitted in subjects with a normal mammogram within 9 months prior to screening for which the results are available.
m To be assessed based on pill count. When there is a discrepancy between the pill count and the subject-reported compliance, the subject-reported compliance should be used.
n Do not perform if discontinuation (early termination) occurs PRIOR to VISIT 5 (Week 12).
o Repeat after cure of infection at V1.

p Repeat after cure of infection at V2.
q Follow-up call should occur ON Day 14 after last dose. In case subject does not respond, three follow-up attempts should be made.

3.2 Rationale for Study Design and Control Group

In the US, ospemifene 60 mg is the approved dose for the treatment of dyspareunia, a symptom of VVA. In a prior study (Study 15-50310), this dose demonstrated efficacy in the treatment of vaginal dryness due to menopause. Therefore, subjects in the treatment group of this study will receive ospemifene 60 mg QD.

For this study, placebo has been chosen as the comparator since there is no other oral non-hormonal therapy approved for treatment of vaginal dryness due to postmenopausal VVA; the current clinical standard of care is non-hormonal lubricants. Subjects in this study will be provided with K-Y Jelly® to be used as needed for treatment of vaginal dryness. The 12 week treatment duration is following the regulatory guidance for treatment of symptoms of VVA due to menopause.

3.3 Study Duration

3.3.1 Study Duration in Individual Subjects

Subjects may be participating in the study for up to 18 weeks.

3.3.2 Planned Duration for the Study

The study is expected to require approximately 60 weeks for enrollment of subjects and 14 weeks after the last subject is randomized for a total study duration of approximately 74 weeks.

4. STUDY POPULATION SELECTION

4.1 Study Population

The study population will consist of approximately 600 female subjects aged ≥ 40 and ≤ 80 years who have moderate to severe vaginal dryness, as self-reported MBS of VVA due to menopause. Those who meet the following eligibility criteria may be randomized.

4.2 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible to participate in the study:

AT VISIT 1 - SCREENING VISIT:

1. Subject understands the study procedures and risks and voluntarily agrees to participate by giving written informed consent.
2. Subject is ≥40 and ≤80 years old at time of signing informed consent.
3. Subject is a postmenopausal woman as defined by one of the following:
   a. Is ≥45 years old; her last spontaneous menstrual bleeding must have been ≥12 months prior to screening
   b. Is ≥45 years old; she does not remember the date of her last spontaneous menstrual bleeding and has follicle-stimulating hormone (FSH) levels >40 IU/L
   c. Has had a hysterectomy **WITHOUT** oophorectomy and serum FSH levels >40 IU/L
   d. Has had a bilateral oophorectomy at least 6 weeks prior to screening
4. The subject has 5% or fewer superficial cells in the maturation index of the vaginal smear.
5. Subject has vaginal pH >5.0.
6. Subject has moderate to severe vaginal dryness as the self-reported MBS of VVA.

AT VISIT 2 - RANDOMIZATION:

7. Subject has an intact uterus with double layer endometrial thickness <4 mm at screening, as determined by a centrally-read ultrasound ***OR*** had a hysterectomy.
8. Subject has an intact uterus and has no evidence of hyperplasia, cancer, or other pathology in an endometrial biopsy ***OR*** had a hysterectomy.
9. Subject has a negative screening mammogram (obtained at screening or within 9 months prior to screening) and a normal clinical breast examination at screening.

   Note: Mammograms obtained within 9 months of screening must be available.
10. Subject has ≤5% superficial cells in the maturation index of the vaginal smear <u>at screening</u> (results will be from Visit 1).

11. Subject has vaginal pH >5.0.
12. Subject has moderate to severe vaginal dryness as the self-reported MBS of VVA.

4.3 Exclusion Criteria

Subjects who meet any of the following exclusion criteria are not eligible to participate in the study:

AT VISIT 1 - SCREENING VISIT:

1. Subject has clinically significant abnormal findings in the physical examination.
2. Subject has a body mass index (BMI) equal to or greater than 38 Kg/m^2.
3. Subject has uncontrolled hypertension (systolic blood pressure [BP] ≥140 mmHg or diastolic BP ≥90 mmHg on two measurements at least 5 minutes apart).
4. Subject has clinically significant abnormal findings in the gynecological examination other than signs of vaginal atrophy (eg, uterine or vaginal prolapse ≥Grade 2).
5. Subject has uterine/vaginal bleeding of unknown origin.
6. Subject has a vaginal infection and refuses treatment, or the infection doesn't respond to the treatment.
7. Subject has taken any of the following hormonal medications:
   a. Vaginal hormonal products (rings, creams, gels) within 14 days prior to screening,
   b. Oral or transdermal estrogen and/or progestin therapy within 60 days prior to screening,
   c. Intrauterine progestin therapy within 60 days prior to screening,
   d. Progestin implants or estrogen-alone injectable drug therapy within 90 days prior to screening, or
   e. Estrogen pellet therapy or progestin injectable drug therapy within 6 months prior to screening.
   f. Other sex hormones or medications that are expected to clinically significantly affect sex hormone levels within 60 days prior to screening
8. Subject has taken a SERM (raloxifene, tamoxifen, toremifene, or clomiphene), tibolone, or any other medication that is expected to have clinically-significant estrogenic and/or antiestrogenic effects within 60 days prior to screening.
9. Subject has regularly used any dietary supplement or herbal therapy, including black cohosh, soy (including soy milk), phytoestrogens, or over the counter agents known to possibly have estrogenic vaginal effects within 30 days prior to screening.
10. Subject is currently using any of the other prohibited medications listed in Protocol Section 6.2.1 Prohibited Therapy.
11. Subject consumes >14 alcoholic drinks per week. (One drink= 1.5 oz of distilled spirits, 12 oz of beer, or 5 oz of wine).

12. Subject is suspected of having or confirmed to have a malignancy or has history of malignancy within 10 years prior to screening (Except for non-melanoma skin cancer or carcinoma in situ of the cervix). Women with a history of breast cancer in remission for >10 years and not taking any adjuvant therapy are eligible to participate.
13. Subject has any history of thromboembolic or blood coagulation disorders.
14. Subject has any history of cerebrovascular accident (eg, bleeding, stroke, or transient ischemic attack [TIA]) or cardiac ischemic disorder (eg, myocardial infarction, unstable angina).
15. Subject participated in another clinical study within 30 days prior to screening.
16. Subject has any physical or mental condition which, in the opinion of the Investigator, may interfere with the subject's ability to comply with the study procedures.
17. Subject has previously taken ospemifene as a treatment.
18. Subject has any condition or situation which, in the opinion of the Investigator, might pose a risk to the subject or interfere with participation in the study.
19. Subject has an abnormal Papanicolaou (PAP) test result at screening with any of the following findings according to the Bethesda System (2001) Classifications:
    a. Atypical Squamous Cells of Undetermined Significance (ASCUS) (human papilloma virus [HPV] High Risk Positive),
    b. Atypical Squamous Cells - cannot exclude high-grade squamous intraepithelial lesion (HSIL),
    c. Atypical Glandular Cells (Endocervical, Endometrial, not otherwise specified [NOS]),
    d. Low Grade squamous intraepithelial lesion (SIL),
    e. High Grade SIL,
    f. Carcinoma, or
    g. Unsatisfactory specimen (one retest will be allowed).
20. Subject has uterine polyps.
21. Subject has symptomatic and/or large uterine fibroids (estimated size >3 cm).
22. Subject has clinically significant abnormalities on electrocardiogram (ECG).
23. Subject has clinically significant abnormalities in any safety laboratory tests.
24. Subject has liver enzyme levels (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) > 3 times the upper limit of normal (ULN).
25. Subject is heterozygous or homozygous for Factor V Leiden.
26. Subject has moderate to severe renal impairment (estimated glomerular filtration rate [eGFR] based on Modification of Diet in Renal Disease [MDRD equation] < 60 mL/min/1.73 m^3).
27. Subject has a history of hepatic impairment (including chronic hepatitis C, hepatitis B, Child-Pugh class B, or Child-Pugh class C).

AT VISIT 2 – RANDOMIZATION:

28. Subject has any condition or situation which, in the opinion of the Investigator, might pose a risk to the subject or interfere with participation in the study.

4.4 Screen Failures

Screen failures are defined as patients who consent to participate in the study but are not subsequently randomized to the study drug. Minimal information collected will include informed consent date, baseline subject characteristics, all of the eligibility criteria not met, reasons for screen failure, adverse events (AEs) that led to screen failure, and any serious adverse events (SAEs); these will be entered in the electronic case report form (eCRF).

5. STUDY TREATMENT(S)

5.1 Description of Treatment(s)

Study treatment will be ospemifene 60 mg or matching placebo taken once daily with food.

5.1.1 Test Drug

Ospemifene will be provided as a white to off-white, oval, film-coated, biconvex tablet with one side engraved with "60." Test drug will be manufactured by:

CPI [redacted]

5.1.2 Placebo

Placebo will be provided as a white to off-white, oval, film-coated, biconvex tablet with one side engraved with "60," which will match the test drug. Placebo will be manufactured by:

CPI [redacted]

5.2 Treatments to be Administered

Each subject who qualifies for entry into the study will be randomized to 1 of 2 treatment groups. Subjects will be instructed to take one tablet of either ospemifene 60 mg or matching placebo, orally, once a day with food for 12 weeks (Treatment Period).

5.3 Selection and Timing of Dose for Each Subject

Subjects will be randomly assigned to either ospemifene or placebo for the 12-week duration of the treatment period.

Study drug should always be taken with food. Study subjects will be instructed to identify the most appropriate time for dosing each day (ie, time of day most likely to be associated with highest compliance and convenience). After the time of dosing is established, every effort should be made to take study medication at approximately the same time each day. To assess exposure, dates in which the subject took study drug will be captured in the eCRF.

5.4 Method of Assigning Subjects to Treatment Groups

At screening, the interactive web or voice response system (IxRS) will be used to assign each subject with an ID number that will be used to identify a subject in all data systems.

At randomization, study drug treatment, ospemifene 60 mg or matching placebo, will be assigned in a 1:1 ratio using IxRS according to the randomization schedule. Randomization will be stratified by the subject's severity of vaginal dryness (moderate or severe) and the presence or absence of a uterus, such that both treatment groups will have similar proportions of subjects with moderate or severe vaginal dryness and with or without a uterus at the start of the study.

5.5 IxRS Blinding and Unblinding

This study will be conducted in a double-blind manner using a placebo matching the test drug in appearance, labeling, and packaging. All subjects, the Investigator, all study personnel, and the Sponsor will be blinded to the treatment assigned at randomization until database lock. Following database lock, the Sponsor will be unblinded to the randomization codes.

The randomization schedule will be maintained by the IxRS in a blinded manner and will not be accessible to anyone until unblinding, except for the Sponsor's drug supply management staff, IxRS clinical coordinator(s), and IxRS vendor staff.

Emergency unblinding of the study drug should only be undertaken when it is critical to the safety and effective medical treatment of a subject. Prior to unblinding, and if the situation allows it, the Investigator should try to contact the Sponsor's medical monitor in order to obtain additional information about the study drug. The Investigator will contact the IxRS to provide the subject's study identification information and confirm the necessity for unblinding. The Investigator will subsequently be provided with the subject's assigned drug treatment as well as a confidential fax or e-mail confirming this information. The system will automatically inform the medical monitor, site monitor, Clinical Trial Manager (CTM), drug safety, and the Sponsor that a randomization code has been broken.

If the blind is broken for any study subject for whatever reason, the Investigator must document the Subject ID, date and time of breaking the blind, and must clearly explain the reasons for breaking the code, and document this in the eCRF.

The blind will be broken by designated Drug Safety personnel for an individual subject for purposes of submitting a suspected unexpected serious adverse reaction (SUSAR) or an expedited report to health authorities based on regulatory requirements.

Once a subject is unblinded, she is no longer eligible to receive the study drug treatment and must be discontinued from the study and follow-up assessments must be completed.

5.6 Packaging and Labeling

Study drug will be packaged in bottles that will be provided to the subject at Visits 2, 3, and 4. Each bottle will contain 35 tablets. Throughout the study the same size bottle will be used and will be labeled in English with a label that specifies the Sponsor, the study number, bottle identification number (BIN), number of tablets, cautionary statement, and storage conditions.

After randomization, at Visits 2, 3, and 4, each subject will receive adequate drug supply to take home; this supply will be sufficient to provide the study drug until the next clinic visit. Regardless of randomization assignment, all subjects will be required to take 1 tablet of study drug every day during the treatment period.

The Sponsor or designee will provide the Investigator with adequate quantities of the study drug. The site pharmacist or medically qualified staff member will dispense the study drug to each subject as described in Sections 5.2, 5.3 and 5.7.

5.7 Storage and Accountability

Bottles of study drug (ospemifene and placebo) should be stored at 20ºC to 25ºC (68°F to 77°F); excursions permitted to 15°C to 30ºC (59ºF to 86ºF) and under secure conditions.

A qualified person at the study site must be designated to receive, handle, and store the study drug. The Investigator (or designee) will maintain an accurate record of the receipt of the study drug as shipped by the Sponsor (or designee). One copy of this receipt will be returned to the Sponsor (or designee) when the contents of the study drug shipment have been verified.

Upon receipt, all study drugs should be stored safely, properly, and securely in compliance with the specified instructions. Only the Investigator and authorized associates should have access to the study drug.

The Investigator or qualified member of the study team must maintain an accurate record of the study drug dispensed to and returned by the subjects. Subjects will be asked to return all unused study drug and empty bottles at required study visits, at the end of the study, or at the time of study drug discontinuation.

At completion of the study, a final reconciliation of all study drugs will be performed and all unused study drug and empty bottles will be returned or disposed of as instructed by the Sponsor (or designee).

Drug accountability records will be available for verification by the designated monitors at each monitoring visit. The study drug must not be used for any purpose other than for this study.

5.8 Investigational Product Retention at Study Site

No study drug will be retained at the study site in this study.

5.9 Treatment Compliance

The Investigator and/or study personnel will assess treatment compliance at each visit using pill counts and information provided by the subject. The Investigator should stress to the subject the importance of compliance and ensure that she understands the dosing instructions. Compliance checks by tablet count will be performed by qualified site

personnel in order to verify that the correct number of doses have been taken based on the actual number of days that have elapsed between designated clinic visits.

A record of the study drug taken by the subject will be made in the eCRF as required. In the event of discrepancy between the tablet count and the information provided by the subject, the information provided by the subject will be recorded in the eCRF.

Based on compliance checks, a subject will be counseled by the site about the importance of taking the study drug as directed if < 100% of the required study drug has been taken by that subject. If compliance issues persist and overall dosing compliance is < 80%, the Investigator may consider discontinuing the subject from the study.

In the event a subject has interrupted or discontinued study drug, the subject must inform the Investigator and the rationale must be provided in the source document. The subject may continue in the study after agreement with the Investigator. If the study drug has been temporarily discontinued for safety reasons, the Investigator must document the reasons in the source document and discuss with the medical monitor prior to the subject reinitiating study drug. All interruptions of study drug (≥1 day) should be captured in the eCRF.

In the event a subject is withdrawn for compliance reasons (eg, missed doses or visits), the Investigator will notify the Sponsor or designee promptly and will make every effort to complete the early termination assessments and the Completion/Discontinuation eCRF. The Investigator must register all subject discontinuations in the IxRS.

6. RESTRICTIONS

6.1 Prior Therapy

Prior therapies are defined as therapies which were taken prior to the initiation of study treatment.

Any prior therapy (prescription drugs, over-the-counter [OTC] drugs, herbal supplements, procedures without any medication) taken by the subject within 6 months prior to screening will be recorded in the eCRF and the information will include the name of the medication/procedure, administration route of drug(s), duration of treatment, and reason for use.

6.2 Concomitant Therapy

For randomized subjects, all medications taken (prescription and OTC) and all procedures performed after Randomization and through the end of the study, including the 2-week follow up call, will be recorded in the eCRF. The information will include the medication/procedure, duration of treatment and the reason for it. Additionally for medications, administration route of drug(s) will be captured.

AEs requiring medication or changes to medication must be recorded on the appropriate eCRFs. Medication taken for a procedure will also be included.

6.2.1 Prohibited Therapy

Prohibited medications should not be taken by subjects at any time during the study. Use of prohibited concomitant therapy(ies) may result in study discontinuation. The following medications are prohibited:

- Dietary supplements and herbal therapies with assumed clinically significant estrogenic vaginal effects (See Appendix 1)
- Any form of local vaginal hormonal products
- Any form of oral or transdermal estrogen or progestin
- Any form of progestin implants (subdermal or intrauterine) or estrogen implants (pellets)
- Any form of estrogen-alone or progestin-alone injectable drug therapy
- Sex hormones or medications that are expected to affect clinically significant sex hormone levels
- Any SERMs
- Any vaginal lubricant or moisturizer other than that provided by the Sponsor for use in the study
- Use of systemic fluconazole, rifampicin, rifabutin, carbamazepine, phenytoin, St John’s wort

Additional medications identified that may have a significant impact on the study drug or the indication studied should also be prohibited at the Investigator's discretion.

7. STUDY PROCEDURES AND METHODS OF ASSESSMENTS

7.1 Informed Consent

The Investigator or Sub-investigator will fully explain the nature of the study to the subject using the institutional review board (IRB)-approved informed consent form (ICF). When the subject agrees to participate in the study, the subject must voluntarily sign the ICF prior to the initiation of any study procedures. A copy of the signed and dated ICF will be given to the subject. The signed and dated original consent form will be retained by the Investigator. Informed consent will be obtained from all subjects. A subject cannot be entered into the study until she has signed and dated the consent form.

In the event a subject withdraws consent of vaginal imaging after signing ICF, the withdrawal will be documented on appropriate page of the already signed ICF and in the subject file. The photographs taken prior to withdrawal of consent will be used for study research purposes as described in the informed consent.

The Investigator or Sub-investigator is responsible for ensuring that the subject understands the risks and benefits of participating in the study, including answering any questions the subject may have throughout the study and sharing any new information in a timely manner that may be relevant to the subject's willingness to continue her participation in the study.

7.2 Demographics, Baseline Subject Characteristics, and Medical History

Demographic data and medical history, including current medical condition(s), will be collected at Visit 1 (Screening) and concurrent medical signs and symptoms will be reviewed prior to Visit 2 (Day 1, Randomization).

Baseline subject characteristics will be obtained and entered in the eCRF. These include date of signed informed consent, date of birth, gender, race, ethnicity, duration of VVA, severity of symptoms of VVA and identification of the most bothersome for the subject, presence or absence of a uterus, prior therapy, and medical history for the 2 years prior to screening, except for any history of cancer. Any history of cancer should be captured in the eCRF regardless of how long ago it occurred.

Medical history may include but is not limited to evaluation for past or present cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, metabolic, lymphatic, hematologic, immunologic, dermatologic, psychiatric, genitourinary, drug abuse, or any other diseases or disorders, surgical history, and history of diagnosis of VVA.

7.3 Enrollment in the Study and Dispensing Study Drug

At screening, after a subject signs the informed consent, the Investigator, Sub-investigator, or designee will contact the IxRS to obtain a subject ID.

At Visit 2, after a subject is determined to be eligible according to the inclusion/exclusion criteria, the Investigator, Sub-investigator, or designee will contact the IxRS to randomize the patient. After randomization of the subject, the Investigator, Sub-investigator, or site pharmacist will dispense the study drug as specified in Section 5 using the BIN provided by IxRS.

7.4 Electronic Diary (eDiary)

During the Treatment Period, subjects will document daily in an eDiary, their use of study drug, use of lubricant, and sexual intercourse. Subjects will also be asked to record overall satisfaction with treatment on a weekly basis. At Visit 2, after randomization, subject will be asked to use an eDiary and clear instructions will be provided on how to use it. Subjects will be allowed to use their own smartphone or tablet as the eDiary by downloading an application, as instructed by the site's personnel. For subjects who do not have a smartphone, an eDiary device will be provided.

7.5 Efficacy Assessments

During the treatment phase of the study, access to the results of some key efficacy assessments will be restricted from the Investigators and key Sponsor personnel who are involved in the conduct of the study until the study database has been locked. This is specified in a separate document and follows Section II.C (Design Techniques to Avoid Bias) of ICH's Guidance for Industry (E9) Statistical Principles that state that "The double-blind nature of some clinical trials may be partially compromised by apparent treatment induced effects. In such cases, blinding may be improved by blinding investigators and relevant sponsor staff to certain test results...". In the sections below it is specified for which endpoints access will be limited. Specific details of who will have access to each endpoint will be captured in a separate document.

7.5.1 Percentage of Parabasal Cells and Superficial Cells in the Maturation Index of the Vaginal Smear

Vaginal smear samples will be taken from the middle third of the lateral vaginal wall and will be evaluated throughout the study at the central laboratory by a qualified pathologist. The central-laboratory pathologist will perform the cell count associated with the maturation index and determine the proportions of parabasal, intermediate and superficial cells for each sample.

The results of the maturation index at Visit 1 (Screening) will be forwarded to the Investigator for the assessment of eligibility. Date of specimen collection will be entered in the eCRF. If the subject has a vaginal infection (requiring medication) at Visit 1, the infection should be treated, and the vaginal smear must be repeated after resolution of the infection and prior to randomization. The maturation index from the infection-free time point will be used as the baseline value and for assessing eligibility.

Results of the maturation index at Visit 2 (Randomization) will be used as baseline.

During the treatment phase of the study, access to the maturation index results will be restricted from the Investigators (except at Visit 1) and key Sponsor personnel involved in the conduct of the study until the study database has been locked.

7.5.2 Vaginal pH

Vaginal pH will be measured by the Investigator using a pH indicator strip. The pH measurement will be done by pressing the indicator strip against the middle third of the vaginal wall and read while still wet. Two types of pH strips with different ranges will be provided to the study sites. The strips with a pH range from 4 to 7 should be used first. If the measurement is out of the 4 to 7 range, the second pH strip with a range from 2 to 9 should be used. Date of specimen collection and the results will be entered in the eCRF.

The subject will be advised to not use vaginal lubricant and not to have sexual intercourse within 24 hours prior to study visits. If the subject has a vaginal infection (requiring medication) at screening, the pH measurement of the vagina will be repeated after resolution of the infection and prior to the planned randomization. The vaginal pH from the infection-free time-point will be used as the baseline value and for assessing eligibility.

The pH at Visit 2 will be used as baseline.

During the treatment phase of the study, access to the pH results will be restricted from key Sponsor personnel involved in the conduct of the study until the study database has been locked.

7.5.3 Severity of Self-Reported VVA Symptoms

Symptoms of VVA (vaginal dryness, vaginal and/or vulvar irritation/itching, dysuria, vaginal pain associated with sexual activity, and vaginal bleeding associated with sexual activity) will be assessed through the VVA questionnaire (see Appendix 2), to be completed by the subject at every visit. The severity of each symptom will be assessed as none, mild, moderate, or severe by the subject. The study personnel will enter date of questionnaire completion and the subject's responses in the eCRF.

Subjects must have moderate to severe vaginal dryness at Visit 1 in order to be eligible for further screening procedures for the study. Additionally, at Visit 1 and Visit 2, the subject will record which symptom of VVA she finds most bothersome. To be eligible for the study, the subject must report vaginal dryness as her MBS at both Visits 1 and 2.

The severity of vaginal dryness at Visit 2 will be used as baseline and for stratification purposes.

During the treatment phase of the study, access to the VVA symptom data will be restricted from key Sponsor personnel involved in the conduct of the study until the study database has been locked.

7.5.4 Vaginal Health Index [9] (VHI; Appendix 3)

The Investigator will perform an evaluation of the vagina, assessing overall elasticity, fluid secretion, pH, condition of epithelial mucosa and moisture. The severity of each characteristic will be assessed with a five-grade evaluation. Date of evaluation and results of the evaluation will be entered in the eCRF.

If the subject has a vaginal infection (needing medication) at randomization, the visual evaluation of the vagina will be repeated after resolution of the infection and prior to randomization. The assessments from the infection-free time-point will be used as the baseline value.

During the treatment phase of the study, access to the VHI data will be restricted from key Sponsor personnel involved in the conduct of the study until the study database has been locked.

7.5.5 Vulvar Health Index (VuHI; Appendix 4)

Similarly to the VHI, the Investigator will perform a visual examination of the vulva, assessing the labia majora, labia minora, clitoris, introitus appearance and elasticity, color, discomfort and pain, and presence of other findings (eg, petechiae, excoriations, ulcers, etc.). The severity of each characteristic will be assessed as normal/ mild/ moderate/ severe. Date of evaluation and results of the evaluation will be entered in the eCRF.

If the subject has a vaginal infection (needing medication) at randomization, the visual examination of the vulva will be repeated after resolution of the infection and prior to randomization. The assessments from the infection-free time-point will be used as the baseline value.

During the treatment phase of the study, access to the VuHI data will be restricted from key Sponsor personnel involved in the conduct of the study until the study database has been locked.

7.5.6 Vaginal Imaging (Appendix 5)

For patients who agree to participate in the optional vaginal imaging, photographs of the vulva and the vagina will be taken by trained site personnel following the standard procedure described in Appendix 5.

The Sponsor, in cooperation with Canfield Scientific, Inc. (Parsippany, NJ), will provide standardized camera equipment and photography procedures for clinical serial photography of the vulva and the vagina. Photographs will be taken per the vaginal imaging visit schedule, as specified in the Schedule of Time and Events (Table 3.1-1). The photographs will be sent electronically to Canfield as the central repository. Instructions for obtaining and submitting photographs will be provided by Canfield. Date of visit and whether or not the pictures were taken will be entered in the eCRF. After submission, Canfield will assess the quality of the photographs and will

provide a written confirmation of receipt of the photographs and feedback of their quality. If the quality of the photographs is not adequate, a re-shoot should be scheduled as soon as possible but no more than seven days after the original shoot day.

Photographs will be assessed by an Independent Panel Review (IPR) in a blinded fashion and the results of their review will be documented. Canfield will facilitate such review and will collect the data. Access to the Canfield repository where photographs and results of the IPR assessment will be stored, will be restricted from the Sponsor and from the Investigators.

During the treatment phase, access to the photographs and results of the IPR assessment will be restricted from the Investigators and key Sponsor personnel involved in the conduct of the study until the study database has been locked.

Procedures to be followed by the IPR will be described in a separate document (IPR charter).

7.5.7 Female Sexual Function Index (FSFI; Appendix 6)

Subjects will complete the Female Sexual Function Index (FSFI) [10] questionnaire and study personnel will enter the date of completion and the responses in the eCRF.

7.5.8 Urinary Distress Inventory (UDI-6; Appendix 7)

The presence or absence of urinary symptoms (urgency, frequency, incontinence, retention, and pain or discomfort) will be assessed using the Urinary Distress Inventory (UDI-6) [11]. The subject will complete the questionnaire and the study personnel will enter the date of completion and the responses in the eCRF.

7.5.9 Efficacy laboratory Tests

The following hormones will be measured in serum:

- Estradiol (E_2)
- Follicle-stimulating Hormone (FSH)

  FSH levels may also be measured at Screening (Visit 1) only to confirm menopausal status, Inclusion Criterion #3 b. Is ≥45 years old; she does not remember the date of her last spontaneous menstrual bleeding and has follicle-stimulating hormone (FSH) levels >40 IU/L ***OR*** c. Has had a hysterectomy **WITHOUT** oophorectomy and serum FSH levels >40 IU/L, as needed.
- Luteinizing hormone (LH)
- Sex hormone binding globulin (SHBG)
- Free testosterone
- Total testosterone

The serum hormones will be analyzed by the central laboratory. The date of specimen collection will be entered in the eCRF.

During the treatment phase of the study, access to results of hormone levels will be restricted from the Investigators (except FSH at Visit 1) and key Sponsor personnel involved in the conduct of the study until the study database has been locked.

7.5.10 Markers of Bone Metabolism

Markers of bone metabolism will be measured during the Treatment Period of the study to assess the early effect of ospemifene on bone metabolism. Blood and urine samples to measure markers of bone metabolism will be obtained and sent to a central laboratory for analysis. Date of specimen collection will be entered in the eCRF. Markers of bone metabolism will include the following:

7.5.10.1 Markers of Bone Resorption:

- Serum N-telopeptide of type 1 collagen (NTX)
- Serum C-terminal telopeptide of type 1 collagen (CTX)
- Serum Bone sialoprotein (BSP)
- Urinary Deoxypyridinoline (DPD)
- Serum tartrate-resistant acid phosphatase 5b (TRACP-5b)

7.5.10.2 Markers of Bone Formation:

- Serum total alkaline phosphatase
- Serum bone specific alkaline phosphatase (BSAP)
- Serum aminoterminal propeptide of type 1 collagen (P1NP)
- Serum Osteocalcin

During the treatment phase of the study, access to results of markers of bone metabolism will be restricted from key Sponsor personnel involved in the conduct of the study until the study database has been locked.

7.5.11 Special Considerations Concerning Efficacy Variables

7.5.11.1 Urine Dip-Stick Test

At Visits 1 and 2, a urine dip-stick test will be performed and read at the site to screen for a urinary tract infection (UTI). If the result indicates a UTI is present, the UTI must be treated to resolution before any efficacy assessments are completed.

Any UTI diagnosed after the time of Informed Consent will be recorded as a Medical History or AE, and should be treated according to the clinical judgment of the Investigator. Any concomitant treatments for UTI should be recorded in the eCRF.

7.5.11.2 Vaginal Infection

At all visits the sequence of procedures should follow Section 8. However, if a vaginal infection requiring medication (e.g. candida vaginitis) is identified at Visit 1 (screening) or at Visit 2 prior to randomization, the infection must be treated to resolution. After the vaginal infection is treated, 2 weeks (14 days) should be allowed to restore the local environment before continuing the screening or randomization procedures. The time necessary to treat the infection will not count against the 4-week duration of the screening period. If a vaginal infection is identified please follow these procedures:

1. If the vaginal infection is discovered during the gynecological examination (Visit 1 or Visit 2), the vaginal pH, the vaginal smear for maturation index, and the sample for cervical PAP, along with the rest of the remaining assessments for that visit, should not be conducted until the resolution of the infection is confirmed. The VVA questionnaire needs to be repeated as it should have been conducted before the gynecological examination.
2. If the infection is identified based on the results of cervical pap or vaginal smear for maturation index obtained at Visit 1, the infection should be treated until resolution. The patient should then return for an Unscheduled Visit (prior to Visit 2) for a repeat of the VVA questionnaire, gynecological examination, vaginal pH, vaginal smear (maturation index), and cervical pap, to confirm eligibility. If eligible based on these results the subject may continue to Visit 2.
3. If the infection takes longer than 30 days to treat, safety laboratory tests (hematology and chemistry) should be repeated at an Unscheduled Visit at the infection-free timepoint to confirm eligibility. If eligible based on these results the subject may continue to Visit 2 if the infection was diagnosed prior to Visit 2 or continue with the outstanding procedures from Visit 2 if the infection was diagnosed at Visit 2.
4. In the situations described in items 2 and 3 above, results of tests repeated between Visit 1 and Visit 2, at the infection-free timepoint, will be used to confirm eligibility (Visit 1) as well as baseline values (Visit 2) and do not need to be repeated again at Visit 2. The TVU, endometrial biopsy, and ECG do not need to be repeated even if they were assessed prior to the discovery of the infection.

Any vaginal infection diagnosed after the time of the informed consent will be recorded as an AE and should be treated according to the clinical judgment of the Investigator. Any medication used as treatment for a vaginal infection should be recorded in the Concomitant Medication eCRF.

7.6 Safety Assessments

7.6.1 Gynecological Examination

The Investigator will perform a gynecological examination as per the usual clinical practice. Information about all gynecological examinations must be included in the source documentation at the study site and be signed and dated by the Investigator or designee. Only new, abnormal findings in the gynecological examination should be

captured in the eCRF. Significant changes should be assessed by the Investigator or Sub-investigator and considered for potential reporting as an AE. Date of examination will be entered in the eCRF.

Subjects with uterine or vaginal prolapse of ≥Grade 2 or higher at screening should not be included in the study. The recommended grading to be used for evaluation at screening can be found in Appendix 8.

7.6.2 Breast Examination

A standard breast examination should be conducted by the Investigator. Information about all breast examinations must be included in the source documentation at the study site and be signed and dated by the Investigator or designee. Only new, abnormal findings in the breast examination should be captured in the eCRF. Significant changes should be assessed by the Investigator and considered for potential reporting as an AE. The date of examination will be entered in the eCRF.

7.6.3 Cervical Cytology (Papanicolau) Smear

Cervical smear samples will be analyzed by Cytotechnologists and a pathologist at the central pathology laboratory and will be classified according to the Bethesda 2001 System. Date of specimen collection will be entered in the eCRF. Subjects with the following classifications at Visit 1 are not eligible for the study:

- Atypical Squamous Cells of Undetermined Significance (ASCUS) (human papilloma virus [HPV] High Risk Positive),
- Atypical Squamous Cells - cannot exclude high-grade squamous intraepithelial lesion (HSIL),
- Atypical Glandular Cells (Endocervical, Endometrial, not otherwise specified [NOS]),
- Low Grade squamous intraepithelial lesion (SIL),
- High Grade SIL,
- Carcinoma, and
- Unsatisfactory specimen (one retest will be allowed).

Detailed procedures for sample collection, handling, labeling, storage, and shipping will be specified in a separate document. Details about the central pathology laboratory are provided in Section 10.1.

7.6.4 Transvaginal Ultrasound (for Subjects with an Intact Uterus Only)

A transvaginal ultrasound (TVU) will be conducted to assess the uterus and adnexa. Images obtained will also be used to determine endometrial thickness at the central ultrasound laboratory. Date of the TVU will be entered in the eCRF. The TVU must be performed by a trained study staff member and images must be sent to a central reader. The results of the TVU at Visit 1 (Screening), including centrally-determined endometrial

thickness, will be used to assess eligibility. The subject should not be randomized until the centrally read TVU result indicates the endometrial thickness (double-layer) is <4 mm.

If at Screening, the locally read endometrial thickness is evidently, according to the Investigators judgment, more than 4 mm, the subject would not be eligible for the study and the images from the TVU should not be sent to the central ultrasound laboratory.

At 12 weeks (Visit 5), the TVU will be performed and the endometrial thickness (double-layer) will be determined by a central reader following the same procedure. If the subject leaves the study before Week 12, the TVU should be performed as part of the early termination visit.

Any symptomatic and/or large fibroids (estimated size >3 cm) or uterine polyps observed in the TVU at Screening (Visit 1) will exclude the subject from the study. Subjects with endometrial polyps identified during the study period will be discontinued, endometrial polyps should be reported as an AE, and the AE should be captured as the reason for discontinuation.

Detailed procedures will be specified in a separate document. Details about the central ultrasound laboratory are provided in Section 10.1.

7.6.5 Biopsy for Endometrial Histology (for Subjects with Intact Uterus Only)

The endometrial biopsy must be obtained after the TVU is performed. Use of oral pain medication is allowed before the biopsy. Local anesthesia will be used if considered necessary by the Investigator. The use of any concomitant medication must be recorded in the eCRF. Endometrial biopsy samples will be taken by the Investigator using a suction curette (Pipelle® or equivalent, aspiration technique). All endometrial samples will be shipped to the central pathology laboratory for preparation of slides.

The endometrial biopsy performed at Visit 1 will be used to evaluate the subject's eligibility for the study and to establish a baseline reading. Subjects with normal or atrophic endometrial histology are eligible to be randomized. Subjects with an insufficient biopsy sample after a valid attempt will be eligible for the study, if the endometrial thickness is <4 mm in the centrally-read TVU. If an endometrial sample cannot be obtained due to cervical stenosis (ie, cervical os cannot be penetrated), the subject is not eligible for the study.

All endometrial histological samples (slides) will be analyzed by concurrent readings by three independent pathologists. Each pathologist will be blinded to the treatment group and to the readings of the other pathologists. The concurrence of two of the three pathologists will be the final diagnosis. If there is no agreement among the three pathologists, the most severe pathologic diagnosis would be used as the final diagnosis. All pathologists will be blinded both to the study treatment and to each other's readings of the histology slides.

Assessment of biopsies will be made according to predefined and generally accepted microscopic criteria (Blaustein's classification). Subjects found to have endometrial hyperplasia or endometrial cancer at screening will be excluded from the study. Subjects found to have endometrial hyperplasia or endometrial cancer during the study will be discontinued and endometrial hyperplasia or endometrial cancer should be reported as an AE, and the AE should be captured as the reason for discontinuation. The subject will be referred for standard of care clinical management and followed to complete resolution (reports of any medical or surgical procedures and the resultant pathology must be provided to the Sponsor). The interpretation of the results by the three pathologists and their agreement or disagreement will be managed as described above in order to determine the final diagnosis for all endometrial biopsies (those scheduled during the study and "for cause" [for example, vaginal bleeding]).

The date of specimen collection will be entered in the eCRF. Details about the central pathology laboratory are provided in Section 10.1.

7.6.6 Vaginal Bleeding

If a subject reports vaginal bleeding during the study, an attempt will be made to determine the etiology. The possibility of a recent biopsy or other invasive procedure or vaginal atrophy as a cause for the bleeding should be considered. Visual inspection and gynecological examination will be performed. If no obvious reason can be identified and the subject has an intact uterus, a TVU will be performed to assess possible uterine pathology and the thickness of endometrium. In addition, the adnexa will be assessed.

If the endometrium is < 4 mm, an endometrial biopsy will be performed. If the biopsy yields an insufficient sample and bleeding persists, a hysteroscopy and guided biopsy will be performed. If the endometrium is ≥ 4 mm, a hysteroscopy and guided biopsy will be performed. The Investigator should assess the event of vaginal bleeding and its etiology for potential report as an AE. In cases, where the etiology is identified, the etiology should be reported as the AE term. When the etiology cannot be determined, the AE term should be vaginal bleeding. All drugs and procedures used for the diagnosis and/or treatment of vaginal bleeding should be captured in the eCRF.

A flowchart for the suggested process to assess vaginal bleeding in subjects with intact uterus is provided in Appendix 9.

7.6.7 Physical Examinations

The physical examination should be performed according to the normal practice of the clinical study site by the Investigator. This should include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, extremities, and body weight.

Information about all physical examinations must be included in the source documentation at the study site and be signed and dated by the Investigator or designee. Only new, abnormal findings in the physical examination should be captured in the

eCRF. Significant changes in the physical examination should be assessed by the Investigator or Sub-investigator and considered for potential reporting as an AE.

7.6.8 Vital Signs

Vital signs (BP, pulse rate, and oral temperature) will be measured by a qualified site staff member. Height will be measured in centimeters and weight in kilograms.

The BP and pulse rate will be measured after the subject has been in a sitting or recumbent position for ≥3 minutes. The BP and pulse rate will be measured by the Investigator or designee by using a blood pressure cuff of an appropriate size.

The Investigator or Sub-investigator will determine whether any abnormal changes from baseline (Visit 2) are clinically significant. Results of BP, oral temperature, pulse rate, height and weight will be entered into the eCRF. BMI will be automatically calculated in the eCRF.

7.6.9 Electrocardiograms/Electrocardiography

A standard 12-lead ECG will be performed at screening after the subject has been in a supine position for at least 5 minutes.

The Investigator or designee will be responsible for reviewing the ECG to assess whether it is normal or abnormal; abnormal ECG findings will be further divided into clinically significant and not clinically significant.

The ECGs will be retained as source documents and must be signed and dated by the Investigator or designee. Clinically significant findings observed at screening must be discussed with the Sponsor's medical monitor or designee to determine whether or not to enroll the subject in the study and must be recorded in the eCRF if enrolled. The date performed, ECG test result (normal or abnormal), and assessment of clinically significant findings will also be recorded in the eCRF.

7.6.10 Clinical Laboratory Tests

7.6.10.1 Laboratory Parameters

Safety laboratory tests are shown in Table 7.6-1 and the Schedule of Time and Events, Table 3.1-1.

Subjects will be in a seated or supine position during blood collection. At Visit 1, routine laboratory tests may not be fasting. Starting at Visit 2 patient should fast at least 8 hours prior to obtaining laboratory samples.

At Screening, a one-time follow-up blood draw is allowed for retest of abnormal values that could exclude the subject from study participation. If the retest is again abnormal, the subject should be excluded.

Table 7.6-1 Laboratory Tests

Category	Evaluation Items
Hematology Tests	hematocrit, hemoglobin, platelet count, red blood cell (RBC) count, white blood cell (WBC) count with differential (eosinophil count, basophil count, neutrophil count, monocyte count, lymphocyte count), platelet count, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), RBC distribution width (RDW), mean platelet volume (MPV)
Blood Chemistry Tests	ALP, ALT, AST, total bilirubin, GGT, LDH, BUN, creatinine, uric acid, sodium (Na), potassium (K), chloride (Cl), calcium (Ca), glucose, total protein,
Lipids	Total cholesterol, Low-density lipoprotein (LDL) cholesterol, Very-low-density lipoprotein (VLDL) cholesterol, High-density lipoprotein (HDL) cholesterol, and Triglycerides
Coagulation	Thromboplastin time, Fibrinogen, Antithrombin III, Factor V Leiden (screening only), Protein-C, and Protein-S
Urinalysis for Qualitative	pH, specific gravity, color, bilirubin, glucose, ketones, nitrite, occult blood, protein, urobilinogen, and microscopic evaluation of sediment

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; GGT = gamma glutamyl transferase; LDH, lactate dehydrogenase; BUN, blood urea nitrogen.

The Investigator or Sub-investigator will assess whether any abnormal changes from baseline (Visit 2) are clinically significant. Clinically significant changes in laboratory parameters should be considered by the Investigator for reporting as adverse experiences as long as they reflect a change/worsening from baseline. The date of specimen collection will also be entered in the eCRF.

7.6.10.2 Sample Collection, Storage, and Shipping

A study-specific laboratory manual will detail sample collection, storage, and shipping procedures. Serum or plasma samples will be stored at least one year after the date of database lock.

Blood and urine samples except for the dipstick urinalysis, will be collected by the Investigator or designee at specified time points and sent to a central laboratory for processing. Details about the central laboratory are provided in Section 10.1.

7.6.11 Adverse Events Assessments

7.6.11.1 Performing Adverse Events Assessments

An AE is defined as any untoward medical occurrence in a subject administered a pharmaceutical product (including investigational drug) during the course of a clinical investigation. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

The AEs will be found by the subject's spontaneous complaint, or as a result of non-leading questions, physical examination, vital signs, laboratory tests, or other procedures.

The AEs include any occurrences that are new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. Conditions reported as medical history at baseline that worsen during the course of the study will be considered AEs. Lack of efficacy determined by progression of symptoms of vaginal dryness, or dyspareunia are not AEs in this study.

The AEs resulting from concurrent illnesses, concomitant medications, or progression of disease states must also be reported. A procedure should not be reported as an AE; only the condition for which the procedure is required should be reported as an AE if it is new or is a worsening of a pre-existing condition. Elective procedures for which the underlying condition was present at screening and has not worsened, do not constitute an AE.

The Investigator or Sub-investigator is responsible for assessing AEs. AEs should be fully investigated and recorded in detail including onset date, end date (if outcome is other than not recovered, recovering, or unknown), severity, relationship with the study drug, action taken due to the AE, and outcome of the AE in the eCRF.

7.6.11.2 Timing

All AEs will be collected from the time of informed consent through the Follow-Up call. If a subject withdraws early from the study, the Investigator or Sub-investigator will make an effort to collect AEs for 2 weeks after the last dose of study drug. Any AE or SAE ongoing 2 weeks after the last dose of study drug will be followed until resolution, stabilization, the condition becomes chronic, or the subject is lost to follow-up.

7.6.11.3 Severity

The severity of an AE will be graded by the Investigator or Sub-investigator according to the following definitions:

- Mild: A finding or symptom is minor and does not interfere with usual daily activities.
- Moderate: The event is uncomfortable and causes interference with usual daily activity or affects clinical status.
- Severe: The event causes interruption of the subject's usual daily activities or has a clinically significant effect.

The highest severity during the period when the AE occurred will be recorded in the eCRF.

7.6.11.4 Relationship

The relationship (causality) of AE to the study drug should be determined by the Investigator according to the following criteria:

- **Related:** An AE for which causal relationship with the study drug can be reasonably explained. For example, the occurrence of the AE cannot be explained by other causative factors, the AE can be explained by the pharmacological effect of the study drug (eg, a similar event had been reported previously), or increase/decrease of the dose affect the characteristics of the AE (rechallenge/dechallenge), etc.
- **Not Related:** An AE for which causal relationship with the study drug cannot be reasonably explained.

7.6.11.5 Expectedness

An AE is expected if it is listed in the Adverse Reactions Section of the current ospemifene U.S. package insert.

7.6.11.6 Action Taken

Any action taken with regard to study drug as a consequence of an adverse experience, drug withdrawn, drug interrupted, dose not changed or not applicable, should be captured in the eCRF.

7.6.11.7 Laboratory Adverse Events

Abnormal laboratory test results are defined as having a value outside the reference range. For laboratory test results which are normal at baseline and become abnormal following initiation of the study or results which are abnormal at baseline and significantly worsen following the initiation of the study, the Investigator or Sub-investigator must also consider whether the results are clinically significant. Any test results considered clinically significant by the Investigator or Sub-investigator should be considered for reporting as AEs. If an abnormal laboratory finding is associated with other clinical findings for which a diagnosis can be provided, the Investigator should report only the diagnosis (and not the laboratory abnormality) as AEs.

The Investigator or Sub-investigator will consider a test result clinically significant if the test result:

- Leads to any of the outcomes included in the definition of an SAE (See Section 7.6.11.8).
- Leads to discontinuation from the study.
- Leads to a concomitant drug treatment or other therapy.
- Requires additional diagnostic testing or other medical intervention.
- Meets the management and discontinuation criteria for abnormal liver function tests (LFTs) identified in Appendix 10.

In addition, when any test result meets the management and discontinuation criteria for liver function abnormalities (Appendix 10), the results of further assessments and required follow-up should be recorded in the Liver Event Form.

7.6.11.8 Serious Adverse Events

Definition

An SAE is defined by regulation as any AE occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening condition
- Hospitalization or prolongation of existing hospitalization for treatment
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important conditions that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject's health and may require medical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The Investigator or Sub-investigator will determine the seriousness of AEs. Test results that meet the following Hy's law criteria are considered SAEs.

- AST or ALT >3 × ULN and total bilirubin (TBL) >2 × ULN

Reporting Serious Adverse Events

All SAEs must be reported to the Sponsor in detail on the SAE form within 24 hours from the point in time when the Investigator first becomes aware of the SAE. All SAEs must be reported regardless of causal relationship to the study drug. A sample of the SAE form can be found in the Site Regulatory Binder. Follow-up information about the SAE may be requested by the Sponsor.

When reporting SAEs, the Investigator should record the diagnosis whenever possible. If no diagnosis is available at the time of reporting, individual signs and symptoms can be reported.

In the event of any SAE reported or observed during the study, whether or not attributable to the study drug, site personnel must prepare an SAE Form and submit the completed form within 24 hours to:

UBC Hotline

Tel: PPO

Email: PPO

Fax: PPO

If follow-up is required or requested, the Investigator should provide new information to the Sponsor's medical monitor as it becomes available using the SAE Form, then it should be submitted. Discharge summaries, consultant reports, autopsy reports, and/or other relevant documents must be evaluated by the Investigator and all relevant information must be included on the follow-up SAE form. Copies of these reports may also be requested by the Sponsor.

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the subject's response to these measures should be recorded. Clinical, laboratory, and diagnostic measures should be used by the Investigator as needed to adequately determine the etiology of the event.

Any SAE that occurs after the AE assessment period specified in Section 7.6.11.2 that is considered by the Investigator to be related to study drug must be reported to the Sponsor.

The Investigator will be responsible for reporting all SAEs to the IRB. The Sponsor will be responsible for reporting SAEs to the regulatory authorities, as required by the applicable regulatory requirements.

7.6.11.9 Special Situations: Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error of the study drug (as defined below) must be reported by the Investigator to the Sponsor within 24 hours using a Special Situations Report Form. If there are associated SAEs, the Investigator will also complete an SAE Form and submit to the Sponsor, within 24 hours of becoming aware.

- Abuse - Persistent or sporadic intentional excessive use of an investigational product that is accompanied by harmful physical or psychological effects.
- Misuse - Intentional and inappropriate use of an investigational product at any dose other than as directed or indicated.
- Overdose - Intentional or unintentional intake of a dose of investigational product higher than the dose assigned in the protocol.
- Medication Error - Any unintended error in the prescribing, dispensing, or administration of an investigational product. If a subject misses doses of investigational products, these not considered reportable as medication errors.

7.6.11.10 Treatment-Emergent Adverse Events

AEs reported after the initial dose of randomized study drug will be considered treatment-emergent adverse events (TEAE).

7.7 Withdrawal of Subjects from the Study or Study Drug

Subjects may voluntarily withdraw from the study for any reason at any time. A subject may be considered withdrawn if she states an intention to withdraw, fails to return for visits, or becomes lost to follow-up.

In the event of a subject's early withdrawal, the Investigator will promptly notify the Sponsor and will make every effort to determine the primary reason for the premature withdrawal from the study and will record this information on the Completion/Discontinuation eCRF. All subjects withdrawn due to AEs will be followed until resolution of any AEs or at least until the unresolved AEs are judged by the Investigator to have stabilized, becomes chronic, or the subject is lost to follow-up. During the Treatment Period, the date of last dose of study drug will be entered in the eCRF. If the subject withdrew before the end of the Treatment Period, date of discontinuation and the reason for discontinuation will be entered in the eCRF.

The following require study drug discontinuation:

- Subject develops SAE or intolerable AE considered related to study drug or if the Investigator determines the subject should be withdrawn because of safety reasons
- Subject meets Liver Discontinuation Criteria (Appendix 10)
- Subject is lost to Follow-up
- Subject has a protocol deviation that results in a significant risk to the subject's safety
- Subject is unblinded
- Subject decides to discontinue her participation in the study for any reason
- Subject is diagnosed with endometrial polyps, endometrial hyperplasia or endometrial cancer

The Investigator must register all subject discontinuations in the IxRS. In the event of a subject's withdrawal, the Investigator will promptly notify the IxRS and will make every effort to complete the end-of-study (or early termination) assessments. All patients withdrawn due to AEs will be followed until resolution or until the unresolved AEs are judged by the Investigator to have stabilized, the condition becomes chronic or the patient is lost to follow-up. All subjects who withdraw or are discontinued from the study will be followed for 14 days after the last dose. Any AEs that are ongoing 14 days after the last dose will be followed until resolution or until they are judged by the Investigator to have stabilized or the condition becomes chronic.

For subjects who are lost to follow-up (ie, those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, such as dates of telephone calls, registered letters, etc.

Subjects who have been prematurely discontinued will undergo assessments as outlined in Section 8.5. A Completion/Discontinuation form must be completed for all subjects who discontinue prematurely or who are lost to follow-up.

7.8 Appropriateness of Measurements

All efficacy and safety evaluations selected for the study are typical of those for this subject population and type of investigation, and utilize widely accepted measures.

7.9 Visit Time Window

Measurements for efficacy or safety endpoints will be performed according to the schedule as shown in Schedule of Time and Events, Table 3.1-1.

In this study, no time windows are pre-specified. All efforts should be made to ensure subjects attend the study visits according to the original visit schedule. If it is completely unavoidable, and the subject must come for a visit outside of the time outlined on the visit schedule, the site personnel must ensure that the subject has enough study drug to last until the scheduled visit. If a subject comes early or late to a study visit, the time to the next visit should be adjusted to align the future study visits with the original visit schedule. Subjects should not be exposed to study drug for more than 12 weeks.

8. STUDY ACTIVITIES

The overall Schedule of Time and Events for this study is provided in Table 3.1-1.

Subjects will be required to participate in both on-site clinic visits as well as a phone call that site personnel will schedule based on the subject's initial randomization date. For the scheduled phone call, subjects will be contacted by the Investigator or designee at the end of the post-study Follow-up Period. If clinically indicated and at the Investigator's discretion, the study subject may be asked to complete an unscheduled visit.

In the sections below, activities to be performed have been listed in the order that appears to simplify the process for the site and the subject. At Screening and Randomization visits, procedures that may exclude a subject immediately are to be conducted earlier to ensure subjects that will not qualify do not undergo the most invasive/uncomfortable procedures.

8.1 Screening, Visit 1 (Up to 4 Weeks Prior to Randomization)

Screening should take place up to 4 weeks (28 days) prior to randomization. Enough time between Visit 1 and Visit 2 should be allowed to receive the results of tests conducted as part of Visit 1, therefore, Visit 2 should not take place earlier than 1 week after Visit 1. The Investigator will inform each prospective subject of the nature of thestudy, explain the potential risks, and obtain written informed consent from the subject prior to performing any study-related procedures and prior to the administration of the study drug.

- Sign ICF
- Contact IxRS to obtain subject ID number
- Obtain urine sample for urinalysis (dipstick + central laboratory) and perform dipstick assessment prior to the next procedure
- Record demographics
- Record medical history
- Record prior therapy
- Assess inclusion and exclusion criteria
- Assessment of VVA symptoms
- Measure vital signs (BP, pulse rate, and oral temperature performed after subject is in seated or in a recumbent position ≥3 minutes) including height and weight
- Perform physical examination
- Perform breast examination
- Perform gynecological examination
- Measure vaginal pH
- Obtain vaginal smear for assessment of maturation index
- Obtain sample for cervical PAP smear

- Perform TVU and measure endometrial thickness
- Perform endometrial biopsy
- Obtain 12-lead ECG (performed in a supine position after ≥5 minutes)
- Obtain blood samples for safety laboratory tests and FSH to confirm postmenopausal status in women ≥45 years old who do not remember the date of the last spontaneous menstrual period OR women who had a hysterectomy without oophorectomy.
- Assess for AEs (with a start time after signing ICF)
- Conduct/order mammogram

  For subjects who have a normal mammogram within 9 months prior to screening for which the results are available, those results can be used and a new mammogram is not required for eligibility assessment.

At the time of Screening, a one-time follow-up blood draw is allowed for the retest of abnormal values that may exclude the subject from study participation.

8.2 Randomization, Visit 2 (Day 1)

Subjects will return to the study site at Visit 2 (Day 1) for the performance of study related procedures, randomization and dispensing of study drug and lubricant. All baseline procedures are to be performed prior to the first dose of study drug. After Visit 2, study subjects will be instructed to identify the most appropriate time for dosing each day (ie, time of day most likely to be associated with highest compliance and convenience). Once the time of dosing is established, every effort should be made to take the study drug at approximately the same time each day.

The following measurements and/or evaluations will be made and recorded in the eCRF:

- Record any changes in prior therapy since screening
- Obtain urine sample for urinalysis, dipstick, and urine markers of bone metabolism. Dipstick assessment should be performed prior to the next procedure
- Assess inclusion/exclusion criteria (including results of safety laboratory tests, PAP smear, and endometrial biopsy obtained at screening)
- Assess for AEs
- Assess symptoms of VVA
- Assess FSFI
- Assess UDI-6
- Measure vital signs (BP, pulse rate, and oral temperature performed after subject is in seated or in a recumbent position ≥3 minutes) including weight
- Perform physical examination
- Perform breast examination
- Perform gynecological examination

- Measure vaginal pH
- Obtain vaginal smear for assessment of maturation index
- Assess VHI
- Assess VuHI
- Obtain vulvo-vaginal imaging (optional)
- Obtain blood samples for safety laboratory tests, hormone levels, and serum markers of bone metabolism
- Dispense eDiary and instruct the subject on how to use it
- Contact IxRS to randomize the subject
- Dispense study medication and lubricant
- Reinforce compliance with study medication

8.3 Treatment Period, Visit 3 (Week 4) through Visit 5 (Week 12)

8.3.1 Visit 3 (Week 4) and Visit 4 (Week 8) Procedures

The following measurements and/or evaluations will be made and recorded in the eCRF:

- Record any changes in concomitant therapy
- Assess for AEs
- Assess symptoms of VVA
- Assess FSFI
- Assess UDI-6
- Measure vital signs (BP, pulse rate, and oral temperature performed after subject is in seated or in a recumbent position ≥3 minutes) including weight
- Measure vaginal pH
- Obtain vaginal smear for assessment of maturation index
- Assess VHI
- Assess VuHI
- Assess eDiary compliance
- Assess study medication returned and assess compliance with study medication
- Dispense study medication assigned by IxRS and lubricant
- Reinforce compliance with study medication

8.3.2 Visit 5 (Week 12) End of Study Procedures

The following measurements and/or evaluations will be made and recorded in the eCRF:

- Record concomitant therapy
- Assess for AEs
- Assess symptoms of VVA

- Assess FSFI
- Assess UDI-6
- Measure vital signs (BP, pulse rate, and oral temperature performed after subject is in seated or in a recumbent position ≥3 minutes) including weight
- Perform physical examination
- Perform breast examination
- Perform gynecological examination
- Measure vaginal pH
- Obtain vaginal smear for assessment of maturation index
- Assess VHI
- Assess VuHI
- Obtain vulvo-vaginal imaging (optional)
- Perform TVU and measure endometrial thickness
- Perform endometrial biopsy
- Obtain blood samples for safety laboratory tests, hormone levels, and serum markers of bone metabolism
- Obtain urine sample for urinalysis and urinary marker of bone metabolism
- Assess eDiary compliance. For subjects who received a device, it should be collected
- Assess study medication returned and assess compliance with study medication

8.4 Telephone Call at the End of the Follow-up Period (Two Weeks after Treatment Period Completion) Procedures

Subjects will receive a follow-up telephone call two weeks after the last dose of study drug. During the phone call the study personnel will assess for AEs since the last visit. Any AEs should be captured in the eCRF. If an AE is reported and needs to be followed, procedures described in Section 7.6.11 should be followed. Information of concomitant therapy after the last dose of study drug will also be collected in the phone call.

8.5 Early Termination Procedures

If a subject discontinues from the study early (i.e., before end of treatment period Visit 5), the following measurements and/or evaluations will be made and recorded in the eCRF:

- Record concomitant therapy
- Assess for AEs
- Assess symptoms of VVA
- Assess FSFI
- Assess UDI-6

- Measure vital signs (BP, pulse rate, and oral temperature performed after subject is in seated or in a recumbent position ≥3 minutes) including weight
- Perform physical examination
- Perform breast examination
- Perform gynecological examination
- Measure vaginal pH
- Obtain vaginal smear for assessment of maturation index
- Assess VHI
- Assess VuHI
- Obtain vulvo-vaginal imaging (optional)
- Perform TVU and measure endometrial thickness. Capture images to be sent to the central reader
- Obtain blood samples for safety laboratory tests, hormone levels and serum markers of bone metabolism
- Obtain urine sample for urinalysis and urinary marker of bone metabolism
- Assess study medication returned and assess compliance with study medication
- Assess eDiary compliance. For subjects who received a device, it should be collected

9. PLANNED STATISTICAL METHODS

9.1 General Considerations

The statistical analysis will be performed by the Sponsor or designee. Detailed statistical analysis methods will be specified in a statistical analysis plan (SAP) according to this section of the study protocol. Analyses deviating from those outlined in the protocol will be clearly specified in the SAP, and the reason for deviation from the protocol will be described. The SAP will be finalized before breaking the study blind.

Unless otherwise noted, continuous variables will be summarized by using the number of non-missing observations, arithmetic mean, standard deviation (SD), median, minimum, and maximum values as descriptive statistics; categorical variables will be summarized by using the frequency count and the percentage of subjects in each category as descriptive statistics.

All statistical tests will be performed at the 0.05 significance level using two-sided tests, except where otherwise noted.

All subject study data, including data not appearing in tables, will be presented by-subject data listings. In general, all tables will be presented by treatment group. Individual subject data and any derived data will be presented by treatment and subject. All analyses and tabulations will be performed by using SAS® Version 9.2 or higher.

9.2 Determination of Sample Size

Approximately 600 subjects, about 300 subjects per arm (1:1 randomization ratio), will be randomized in the study.

Table 9.2-1 shows the difference between ospemifene and placebo and the effect size in each of 4 co-primary endpoints, namely vaginal pH, percentage of parabasal cells and percentage of superficial cells in the maturation index of the vaginal smear, and MBS of vaginal dryness for the two pivotal studies.

Table 9.2-1 Change from Baseline to Week12 in Two Pivotal Studies

Primary Efficacy Variable	Study	Ospemifene	Placebo	Difference	SDcommon	Effect Size *2)
MBS of Vaginal Dryness	15-50310	[redacted] CPI	[redacted]	[redacted]	[redacted]	[redacted]
	15-50821	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vaginal pH	15-50310	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	15-50821	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% Parabasal Cells	15-50310	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	15-50821	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% Superficial Cells	15-50310	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	15-50821	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*1) Mean±SD

*2) [redacted] ; [redacted]

For the planned study, referring to the results in

Table 9.2-1, the effect size is assumed to be 0.27 for MBS of vaginal dryness, 0.70 for vaginal pH, 0.83 for % parabasal cells and 0.68 for % superficial cells. Table 9.2-2 shows the power of two-sided t-test with significance level of 0.05 and total sample size of 600 (300 for each treatment group) for each of the 4 co-primary endpoints under the assumed effect size. A sample size of 600 patients provides ≥ 90% power to assess the 4 co-primary efficacy endpoints.

Table 9.2-2 Expected Power with Total Sample Size of 600

	MBS of Vaginal Dryness	Vaginal pH	% Parabasal Cells	% Superficial Cells	4 Co-Primary Endpoints
Effect Size	[redacted]	[redacted]	[redacted]	[redacted]	C PI
Power	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.3 Analysis Populations

The following analysis populations will be analyzed for this study.

- **Safety Population** includes all randomized subjects who receive at least one dose of the study drug. This population will be analyzed according to the treatment the subjects actually received, rather than the treatment to which the subjects were randomized.
- **Intention-to-Treat (ITT) Population** is defined as any subject that is randomized and receives at least one dose of study medication. All efficacy analyses will be based on this population. This population will be analyzed as randomized.
- **Per-Protocol Population (PP)** will be defined in the SAP and the PP population will be determined before breaking the study blind.

The primary efficacy analysis will be done on both the ITT population and PP population.

9.4 Handling of Missing Data

Missing data will not be imputed. All analyses will be based on observed data.

9.5 Subject Disposition

Among subjects randomized to each treatment group, the number and percent of the subjects who complete the study (Visit 5), and the number and percent who prematurely discontinue the study will be summarized. In addition, reasons leading to study discontinuation will be summarized for each treatment group. The number and percent of randomized subjects included in each analysis population will also be presented. For subjects who completed Part A and entered Part B, reasons for discontinuation will also be summarized.

9.6 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized with descriptive statistics by treatment group for the ITT Population. Demographic variables will include age, body weight, height, ethnicity, and race.

9.7 Treatment and Treatment Compliance

The duration of treatment exposure and percent compliance (up to Visit 5) will be summarized with descriptive statistics by treatment group for the ITT Population.

9.8 Prior Therapy

Prior medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications include all medications used prior to the first dose. Prior medication will be summarized by treatment group and will be provided in Listings. The number and percentage of subjects who report prior medications will be reported by WHO-DD classification for each of the treatment groups.

9.9 Concomitant Therapy

Concomitant medications will be coded using the WHO-DD. Concomitant medications will include all medications used after the first dose of study drug and those medications taken prior to the first dose but ending during study treatment.

The number and percentage of subjects using concomitant medications (up to Visit 5) will be calculated by appropriate WHO-DD classification for each of the treatment groups.

9.10 Efficacy Analyses

The ITT Population will be the primary population for efficacy analyses.

9.10.1 Primary Efficacy Endpoints

The primary efficacy endpoints will be the difference between ospemifene 60 mg QD and placebo in treatment of VVA due to menopause in women with moderate to severe vaginal dryness as the MBS of VVA at 12 weeks of treatment based upon:

a. Change from baseline in the percentage of parabasal cells in the maturation index of the vaginal smear after treatment with ospemifene 60 mg QD compared with placebo at 12 weeks,
b. Change from baseline in the percentage of superficial cells in the maturation index of the vaginal smear after treatment with ospemifene 60 mg QD compared with placebo at 12 weeks,
c. Change from baseline in the vaginal pH after treatment with ospemifene 60 mg QD compared with placebo at 12 weeks, and
d. Change from baseline in the severity of self-reported MBS of vaginal dryness after treatment with ospemifene 60 mg QD compared with placebo at 12 weeks.

9.10.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints will be:

- Change from baseline in percentage of parabasal cells in the maturation index of the vaginal smear after treatment with ospemifene 60 mg QD compared with placebo at 4 and 8 weeks,
- Change from baseline in percentage of superficial cells in the maturation index of the vaginal smear after treatment with ospemifene 60 mg QD compared with placebo at 4 and 8 weeks,
- Change from baseline in the vaginal pH after treatment with ospemifene 60 mg QD compared with placebo at 4 and 8 weeks,
- Change from baseline in the severity of self-reported MBS of vaginal dryness after treatment with ospemifene 60 mg QD compared with placebo at 4 and 8 weeks,
- Change from baseline in the severity of other VVA symptoms other than vaginal dryness (ie, dyspareunia, vulvar/vaginal itching/irritation, dysuria [difficult/painful urination], and/or vaginal bleeding associated with intercourse) after treatment of ospemifene 60 mg QD compared with placebo over 12 weeks,
- Change from baseline in markers of bone metabolism after treatment with ospemifene 60 mg QD compared with placebo,
- Change from baseline in VHI after treatment with ospemifene compared with placebo over 12 weeks,
- Change from baseline in VuHI after treatment with ospemifene compared with placebo over 12 weeks,
- Change from baseline in FSFI after treatment with ospemifene 60 mg QD compared with placebo over 12 weeks, and
- Change from baseline in UDI-6 after treatment with ospemifene 60 mg QD compared with placebo over 12 weeks.

9.10.3 Analyses of Efficacy Endpoints

9.10.3.1 Statistical Analysis Methods for Primary Efficacy Endpoints

The following analyses will be performed for both of ITT and PP populations.

For each of percentage of parabasal cells, percentage of superficial cells and vaginal pH, Mixed-effects Model Repeated Measures (MMRM) approach will be used. In the model, repeated measurements of the change from baseline at Week 4, Week 8 and Week 12 will be the response variable. Baseline value and study center will be modeled as covariates. Significance test to compare the ospemifene group with the placebo group will be based on the mean difference between the two groups at Week 12.

For the MBS of vaginal dryness, Generalized Estimating Equations (GEE) model will be used to fit a marginal proportional odds model to the longitudinal ordered categorical data (Fitzmaurice et al., 2011). In the model, repeated measurements of the change from baseline in MBS of vaginal dryness at Week 4, Week 8 and Week 12 will be the response variable. Baseline severity of dryness and study center will be modeled as covariates. Significance test to compare ospemifene group to placebo group will be based on the mean of cumulative log odds ratio (over ordered category responses) at Week 12.

9.10.3.2 Other Statistical Analysis Methods for Secondary Endpoints

For secondary efficacy endpoints, Analysis of Covariance (ANCOVA) will be used for observed case data, where baseline will be included as covariate.

9.10.3.3 Sensitivity Analyses for the GEE analysis

In order to evaluate the robustness of the GEE analysis for the MBS of vaginal dryness, a sensitivity analyses using the MMRM method will be performed.

In this analysis, ordered categorical data will be treated as continuous data.

9.11 Safety Analyses

9.11.1 Adverse Events

AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). Of the AEs reported in the eCRF, TEAEs will be used for safety analyses. The definition of TEAE is described in Section 7.6.11.10.

The number of subjects who experience ≥1 TEAE, non-fatal treatment-emergent SAEs, significant TEAEs, TEAEs leading to withdrawal, and TEAEs with an outcome of death will be counted for each treatment group. The incidences and their 95% confidence intervals (CIs) will be calculated using the Clopper-Pearson method. The number of TEAEs counted by cases reported will also be presented. Treatment-related TEAEs will be summarized by the same category as TEAEs in the overall summary.

A summary of TEAEs by MedDRA system organ class and preferred term will be presented for each treatment group with the number and percent of subjects. A summary of severity and outcome will be presented by system organ class and preferred term.

All AEs, including AEs that existed prior to or after the first dose of the study drug, will be listed. AEs reported with an onset date prior to randomization of study drug will be listed separately.

9.11.2 Vital Signs

Summary statistics for vital signs will be presented for each scheduled time point measured after randomization and for the change from baseline to each time point. Baseline will be the last value obtained before initial dose.

9.11.3 Clinical Laboratory Analyses

Summary statistics for laboratory test data will be presented for each scheduled time point measured after randomization and for the change from baseline to each time point. Baseline will be the last value obtained before initial dose.

Qualitative laboratory test data at baseline and at planned visits will be classified according to test category.

9.11.4 Endometrial Safety

Summary statistics for endometrial thickness and endometrial histology will be presented for each scheduled time point measured after randomization and for the change from baseline to each time point. Baseline will be the last value obtained before initial dose.

9.11.5 Other Safety Variables

Other clinical safety variables (e.g., gynecological examination, ECG and weight) will be summarized with descriptive statistics for each scheduled time point measured after randomization and for the change from baseline to each time point. Baseline will be the last value obtained before initial dose.

9.12 Interim Analysis

No interim analysis is planned for this study.

10. ADMINISTRATIVE CONSIDERATIONS

10.1 Study Administrative Structure

Sponsor:	Shionogi Inc. 300 Campus Drive Florham Park, NJ 07932 USA
Sponsor's Contact:	PPO Shionogi Inc. 300 Campus Drive, Florham Park, NJ 07932 USA TEL: PPO FAX:
Sponsor's PPO	PPO
Sponsor's Medical Expert:	PPO Shionogi Inc. 300 Campus Drive Florham Park, NJ 07932 USA TEL: PPO
Medical Monitor:	PPO Project Physician UBC 920 Harvest Drive Blue Bell, PA 19422 TEL: PPO
Investigator and Study Center:	Multicenter (United States)
Study Monitoring:	UBC 920 Harvest Drive, Suite 200 Blue Bell, PA 19422 TEL: PPO
Emergency Contact:	PPO TEL: PPO PPO TEL: PPO
Clinical Laboratory:	CENTRAL LABORATORY: EUROFINS 2430 New Holland Pike Lancaster, PA 17601 VAGINAL IMAGING AND CENTRAL READER: Canfield Scientific, Inc. 4 Wood Hollow Road Parsippany, NJ 07054

CENTRAL ULTRASOUND:
BioClinica
100 Overlook Center, 3rd Floor
Princeton, NJ 08540

CENTRAL ENDOMETRIAL HISTOLOGY READER:
EUROFINS
2430 New Holland Pike
Lancaster, PA 17601

ELECTRONIC DIARIES:
New England Survey Systems
1415 Beacon Street
Brookline, MA 02446

*CENTRAL (DXA) BMD READER:
BioClinica
100 Overlook Center, 3rd Floor
Princeton, NJ 08540

*CENTRAL BREAST DENSITY READER:
BioClinica
100 Overlook Center, 3rd Floor
Princeton, NJ 08540

**Central Readers were utilized for Protocol versions 06 October 2015 and 11 March 2016*

10.2 Institutional Review Board Approval

The IRB will safeguard the rights, safety, and well-being of the subjects by reviewing the following study documents: the protocol, ICF, written information about subject recruitment procedures (if applicable), other written information given to the subjects, Investigator's Brochure, safety updates, annual progress reports (if applicable), and any significant revisions to these documents. The Investigator or the Sponsor will provide these study documents to the IRB. The IRB will be appropriately constituted in accordance with ICH good clinical practice (GCP), and local requirements, as applicable. The study will be undertaken only after IRB has given full approval and the Sponsor has received a copy of the approval.

Amendments to the protocol will be subject to the same requirements as the initial review. The Investigator will submit all periodic reports and updates as required by the IRB. The Investigator will inform the IRB of any reportable AEs.

10.3 Ethical Conduct of the Study

This study will be conducted in accordance with all appropriate regulatory requirements and under the protocol approved by an IRB. The study will be conducted in accordance with current ICH GCP, all appropriate subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki.

10.4 Subject Information and Consent

The Sponsor will provide the Investigators with a proposed ICF that complies with ICH GCP guidelines and regulatory requirements. The Sponsor must agree to any changes to the proposed consent form suggested by the Investigator prior to submission to the IRB, and the IRB approved version must be provided to the site monitor after IRB approval.

The Investigator will generate a site-specific ICF for the study. The consent form will include all the elements required by ICH GCP and any additional elements required by local regulations; this will be reviewed and approved by the appropriate IRB before use. The Investigator or Sub-investigator will explain the nature, purpose and methods, reasonable anticipated benefits, and potential hazards of the study to the subject in simple terms by using the consent form before the subject is entered into the study. The method of obtaining and documenting informed consent will comply with ICH GCP and all applicable regulatory requirements.

10.5 Subject Confidentiality

Procedures for protecting subject privacy must adhere to applicable data privacy laws and regulations. In order to maintain subject privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the subject by the subject number. The Investigator will grant the site monitors and auditors of the Sponsor or designee and regulatory authorities access to all source documents for verification of data collected in the eCRFs and for verification of the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations. The Investigator and the Sponsor will be responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, Health Insurance Portability and Accountability Act [HIPAA]). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

Data about subjects collected on eCRFs during the study will be documented in an anonymous manner and the subject will only be identified by subject number. In the emergent or rare event that for safety or regulatory reasons it is necessary to identify a subject, the Sponsor and the Investigator are bound to keep this information confidential.

10.6 Study Monitoring

The Sponsor or designee will monitor the study to ensure the study is conducted in accordance with GCP requirements and the protocol. Study monitoring will be performed by a representative of the Sponsor (site monitor) through on-site monitoring

visits as frequently as necessary and frequent communications (e-mail, letter, telephone, and fax). The site monitor will review data recorded in the eCRFs, verify the eCRF entries with direct access to source documents, collect any safety/efficacy information about subjects, verify that amounts of unused study drug are accurate, and check retention of source documents and essential documents.

The Investigator agrees to permit such monitoring as well as audits or reviews by regulatory authorities, the IRB, or the Sponsor.

10.7 Electronic Case Report Forms and Source Documents

10.7.1 Electronic Case Report Forms

The eCRFs for each subject who signed informed consent will be provided and historic information and study data, which are specified by the protocol, will be recorded on eCRFs by the Investigator or designee. All subject data from study visits must be collected on source documents and are promptly entered in the eCRFs in accordance with the specific instructions given. All eCRF entries will be performed by an Investigator, Sub-investigator, or study coordinator who is authorized for documentation. Data should be entered within 72 hours after each subject's visit.

When queries are generated to the participating medical institutions for resolution by the Sponsor or designee, eCRF data will be changed or a response will be recorded in accordance with the specific instructions given. The Investigator must ensure that data reported in the eCRF is accurate, complete, legible, and timely and must sign the eCRFs to verify the integrity of the data recorded.

A list of the reference ranges for all laboratory tests to be undertaken will be a part of the documentation to be collected prior to the initiation of study. The list of reference ranges for all laboratory tests should be updated if they are changed during the study. If a central laboratory has been selected to perform any or all tests, it is essential that all reference ranges for the laboratory tests to be analyzed at the laboratory should also be collected.

10.7.2 Source Data and Source Documents

Source documentation supporting eCRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status. However, the following data can be directly recorded on an eCRF as source data:

- Reason for use of prior therapy or concomitant therapy
- Severity, seriousness, causal relationship to the study drug of AE
- Any comments inserted into eCRF
- Automatically-calculated data in eCRF (age, BMI)

The Investigator must maintain source documents such as laboratory reports, and complete medical history and physical examination reports. All the source documents are accessible for verification by the site monitor, auditor, the IRB, inspections of regulatory authority. Direct access to these documents must be guaranteed by the Investigator, Sub-investigator, or study coordinator, who must provide support at all times for these activities. For all sources of original data required to complete the eCRF, the nature and location of the source documents will be identified by the Sponsor and the site staff. If electronic records are maintained at the medical institution, the method of verification must be specified in document within the medical institution.

10.7.3 External Data

The following data will be reported in documents/data bases separate from eCRFs.

- eDiary
- Results of cervical cytology (PAP) smear
- Results of vaginal smear
- Results of vaginal imaging
- Results of TVU
- Results of DXA scan
- Results of breast mammogram
- Results of biopsy for endometrial histology
- Results of clinical laboratory tests including serum hormone levels and markers of bone metabolism

10.8 Committees

10.8.1 Visual Imaging Independent Panel Review (IPR)

An Independent Panel Review (IPR) will be established and will be composed by three experts in obstetrics and gynecology. This panel will independently review vulvo-vaginal photographs of all subjects at all scheduled time points in a random and blinded fashion. Details of IPR composition, roles and responsibilities, and processes will be documented in a separate IPR charter.

10.9 Termination or Suspension of the Study

10.9.1 Termination or Suspension of the Entire Study

The Sponsor may prematurely terminate or suspend the study at any time for the following reasons:

- Ensuring safety of the study is difficult due to safety concerns (eg, occurrence of many serious treatment-related TEAEs)
- Achieving the purpose of the study is considered impossible (eg, interim data suggesting lack of efficacy/safety, inadequate recruitment of subjects)

If the study is prematurely terminated or suspended, the Sponsor should promptly inform the Investigators. The Investigator or Sub-investigator should promptly inform the participating subjects and change the study treatment to other appropriate therapy(ies).

For withdrawal criteria for individual subjects, see Section 7.7.

10.9.2 Termination or Suspension of the Study by Medical Institution

The Investigator may prematurely terminate or suspend the study in the medical institution with agreement of the Sponsor at any time when the Investigator considers that ensuring safety of the study is difficult due to safety concerns (eg, occurrence of many SAEs).

The Sponsor may request the Investigator to prematurely terminate or suspend the study in the medical institution at any time when major violations/deviations of protocol, other procedures, and GCP guidelines were not improved.

If the study is prematurely terminated or suspended, the Investigator or Sub-investigator should promptly inform the corresponding IRB and participating subjects and change the study treatment to other appropriate therapy(ies).

The entire study may be discontinued at the discretion of the Sponsor based on the occurrence of the following:

- AEs unknown to date with respect to their nature, severity, and duration;
- Increased frequency and/or severity and/or duration of known AEs;
- Medical or ethical reasons affecting the continued performance of the study;
- Difficulties in recruitment of subjects; or
- Cancellation of drug development by the Sponsor

10.10 Protocol Modifications and Deviations

The Investigator will conduct the study in compliance with the protocol provided by the Sponsor and approval/favorable opinion given by the IRB and the regulatory authority(ies). Modifications to the protocol should not be performed without agreement of both the Investigator and the Sponsor. Changes to the protocol will require written IRB approval/favorable opinion prior to implementation, except when the modification is needed to eliminate immediate hazard(s) to subjects.

The Investigator or Sub-investigator should document any deviation from the protocol and the reason. If the Investigator deviates from the protocol or make a change of the protocol to eliminate an immediate hazard(s) to subjects, the record should be immediately submitted to the Sponsor, the medical institution, and the IRB by the Investigator and the IRB will provide expedited review and approval/favorable opinion. After the Investigator obtained approval/favorable opinion of the IRB, the Investigator should obtain a written agreement of the Sponsor through the medical institution. The

Sponsor will submit all protocol modifications to the regulatory authority (ies) via an Amendment in accordance with the governing regulations.

When deviation from the protocol is required to eliminate immediate hazard(s) to subjects, the Investigator will contact the Sponsor, if circumstances permit, to discuss the planned course of action. Any deviations from the protocol must be fully documented on source documentation.

10.11 Access to Source Documentation

The site monitors, the auditors, the IRB, and regulatory authorities are able to directly access all source documents and other study documentation for study monitoring, on-site audit, or inspection. Direct access to these documents must be guaranteed by the Investigator, Sub-investigator, or study coordinator, who must provide support at all times for these activities.

The Investigator must inform the study subject that his/her study-related records may be reviewed by the above individuals without violating the subject's privacy of personal health information in compliance with HIPAA of 1996 US regulations.

10.12 Data Management

The Sponsor or designee will be responsible for data management and data analysis. These procedures are specified in a separate document.

10.13 Retention of Data

The study documents must be maintained as specified in the ICH GCP and as required by the applicable regulatory requirements. The Investigator and study center should take measures to prevent accidental or premature destruction of these documents.

If the Sponsor is granted manufacturing and marketing approval for the drug, the Sponsor will promptly notify the head of the study center in writing.

Records will be retained for the longest of the following periods:

- At least 2 years after the last marketing application approval
- 2 years after formal discontinuation of the clinical development of the investigational product
- Other period according to applicable local laws, regulations, and other regulatory requirements, whichever is latest

However, the duration of retention may be prolonged in accordance with an agreement with the Sponsor.

These records will be available for copying and inspection if requested by a properly authorized employee of the Food and Drug Administration (FDA) or other government regulatory agency, in accordance with federal regulations. The Investigator must notify

the Sponsor prior to transfer or in cases of accidental loss or destruction of any study records. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

10.14 Quality Control and Assurance

The Sponsor or designee will implement and maintain quality control and quality assurance procedures with written standard operating procedures to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

This study will be conducted in accordance with the provisions of the Declaration of Helsinki and all revisions thereof; in accordance with the ICH GCP and as required by the applicable regulatory requirements.

Necessary training for the study will be provided to investigator's meeting and study center personnel prior to the initiation of the study.

10.15 Publication and Disclosure Policy

All information regarding ospemifene supplied by the Sponsor to the Investigator is privileged and confidential. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical trial will be used toward the development of ospemifene and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

The Sponsor will retain ownership of all data. All proposed publications based on the study will be subject to the Sponsor's approval requirements.

The key design elements of this protocol will be posted in a publicly accessible database, eg, ClinicalTrials.gov.

10.16 Financial Disclosure

Information concerning financial disclosure for Investigators will be addressed in a separate agreement between the Sponsor and the Investigator.

In accordance with the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860), the Sponsor will provide the FDA with: Certification, that no financial arrangements with an Investigator or Sub-investigator have been made where compensation could affect study outcome; that the Investigator or Sub-investigator has no proprietary interest in the tested product; that the Investigator or Sub-investigator does not have a significant equity interest in the Sponsor of the covered study; and that the Investigator has not received significant payments of other sorts, and/or disclosure of specified financial arrangements and any steps taken to minimize the potential for bias.

11. REFERENCE LIST

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Appendix 1 Restricted Dietary and Herbal Therapies

Soy (*Glycine max*)

Flaxseed (*Linum usitatissimum*)

Nettle root (*Urtica dioica*)

Pygeum (*Pygeum africanum*)

Beta-sitosterol

Licorice (*Glycyrrhiza glabra*)

Ginseng

Tribulus (*Tribulus terrestris*)

Red clover (*Trifolium pretense*)

Chasteberry (*Vitex agnus-castus*)

Japanese knotweed (*Polygonum cuspidatum*)

Black Cohosh (*Cimicifuga racemosa*)

Hops (*Humulus lupulus*)

Dong Quai (*Angelica sinensis*)

Fo-Ti (*Polygonum multiflorum*)

Kudzu (*Pueraria lobata*)

Alfalfa (*Medicago sativa*)

Mung bean sprout (*Vigna radiate*)

Sicklepod (*Cassia obtusifolia*)

Turkish rhubarb root (*Rheum palmatum*)

Phytoestrogens:

- Isoflavones (biochanin A, daidzein, genistein)
- Resveratrol
- Coumestrol

Appendix 2 Patient Self-Assessment of Vulvar and Vaginal Atrophy Questionnaire

Have you had the following symptoms in the past month? (or since the last visit?)

If yes, please indicate if the most severe episode of the symptom was mild, moderate or severe.

Please choose one option per question.

Symptom	*None*	*Mild*	*Moderate*	*Severe*
Vaginal Dryness?				
Vaginal and/or Vulvar Irritation or Itching?				
Difficult or Painful Urination?				
Vaginal Pain Associated with Sexual Activity?				
Vaginal Bleeding Associated with Sexual Activity?				

Which symptom is the most bothersome to you? Please choose one symptom that was indicated above as moderate or severe. (Ask at Visits 1 and 2 [Screening & Randomization])

Vaginal Dryness?	
Vaginal and/or Vulvar Irritation or Itching?	
Difficult or Painful Urination?	
Vaginal Pain Associated with Sexual Activity?	
Vaginal Bleeding Associated with Sexual Activity?	

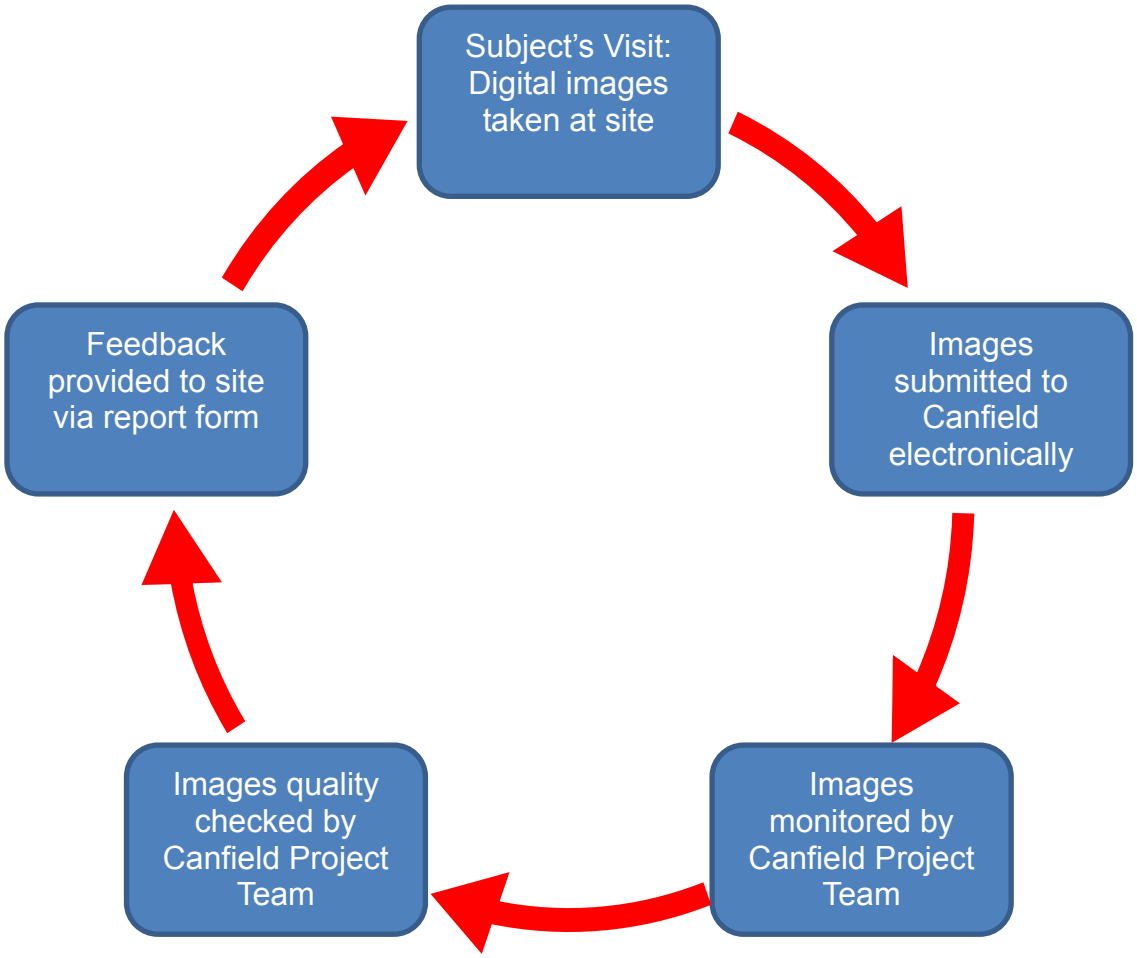
Appendix 3 Vaginal Health Index (VHI)

	1	2	3	4	5
Overall Elasticity	None	Poor	Fair	Good	Excellent
Fluid Secretion	None	Scant	Superficial	Moderate	Normal
pH	≥6.1	5.6–6.0	5.1–5.5	4.7–5.0	≤4.6
Epithelial Mucosa	Petechiae before contact	Bleeds with light contact	Bleeds with scraping	Not friable, thin mucosa	Not friable, normal mucosa
Moisture	None, mucosa inflamed	None, mucosa not inflamed	Minimal	Moderate	Normal

Appendix 4 Vulvar Health Index (VuHI)

	Normal (0)	Mild (1)	Moderate (2)	Severe (3)
Labia Majora	Normal	Mild loss	Moderate loss	Severe loss or disappeared
Labia Minora	Normal	Mild loss	Moderate loss	Severe loss or disappeared
Clitoris	Normal size	Mild decrease in size	Moderate decrease in size	Severe decrease or undetected
Introitus & Elasticity	Normal	Mild decrease or stenosis	Moderate decrease or stenosis	Severe decrease or stenosis
Color	Normal	Mild pallor	Moderate pallor	Severe pallor
Discomfort & Pain	None	Mild during intercourse	Moderate during intercourse	Moderate during intercourse and any discomfort intensity beyond intercourse
Other Findings (Petechiae, Excoriation, Ulceration, etc.)	None	Mild	Moderate	Severe

Appendix 5 Process for Capturing Vulvar and Vaginal Photography



Appendix 6 Female Sexual Function Index (FSFI) Questionnaire

Subject ID _____ Date _____

INSTRUCTIONS: These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation and vaginal intercourse. Sexual intercourse is defined as penile penetration (entry) of the vagina.

Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CHECK ONLY ONE BOX PER QUESTION.

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how **often** did you feel sexual desire or interest?

   ☐ Almost always or always
   ☐ Most times (more than half the time)
   ☐ Sometimes (about half the time)
   ☐ A few times (less than half the time)
   ☐ Almost never or never

2. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?

   ☐ Very high
   ☐ High
   ☐ Moderate
   ☐ Low
   ☐ Very low or none at all

Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how **often** did you feel sexually aroused ("turned on") during sexual activity or intercourse?

   ☐ No sexual activity
   ☐ Almost always or always
   ☐ Most times (more than half the time)
   ☐ Sometimes (about half the time)
   ☐ A few times (less than half the time)
   ☐ Almost never or never

4. Over the past 4 weeks, how would you rate your **level** of sexual arousal ("turn on") during sexual activity or intercourse?

   ☐ No sexual activity
   ☐ Very high
   ☐ High
   ☐ Moderate
   ☐ Low
   ☐ Very low or none at all

5. Over the past 4 weeks, how **confident** were you about becoming sexually aroused during sexual activity or intercourse?

   ☐ No sexual activity
   ☐ Very high confidence
   ☐ High confidence
   ☐ Moderate confidence
   ☐ Low confidence
   ☐ Very low or no confidence

6. Over the past 4 weeks, how **often** have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

   ☐ No sexual activity
   ☐ Almost always or always
   ☐ Most times (more than half the time)
   ☐ Sometimes (about half the time)
   ☐ A few times (less than half the time)
   ☐ Almost never or never

7. Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

8. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

9. Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

10. Over the past 4 weeks, how **difficult** was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **often** did you reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **difficult** was it for you to reach orgasm (climax)?

- ☐ No sexual activity
- ☐ Extremely difficult or impossible
- ☐ Very difficult
- ☐ Difficult
- ☐ Slightly difficult
- ☐ Not difficult

13. Over the past 4 weeks, how **satisfied** were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

14. Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner?

- ☐ No sexual activity
- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

15. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner?

- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life?

- ☐ Very satisfied
- ☐ Moderately satisfied
- ☐ About equally satisfied and dissatisfied
- ☐ Moderately dissatisfied
- ☐ Very dissatisfied

17. Over the past 4 weeks, how **often** did you experience discomfort or pain during vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

18. Over the past 4 weeks, how **often** did you experience discomfort or pain following vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Almost always or always
- ☐ Most times (more than half the time)
- ☐ Sometimes (about half the time)
- ☐ A few times (less than half the time)
- ☐ Almost never or never

19. Over the past 4 weeks, how would you rate your **level** (degree) of discomfort or pain during or following vaginal penetration?

- ☐ Did not attempt intercourse
- ☐ Very high
- ☐ High
- ☐ Moderate
- ☐ Low
- ☐ Very low or none at all

Thank you for completing the questionnaire

Appendix 7 Urinary Distress Inventory (UDI-6)

Do you experience, and, if so, how much are you bothered by:

1. Frequent urination?

Yes ☐ No ☐
If Yes, how much does it bother you?
not at all ☐ slightly ☐ moderately ☐ greatly ☐

2. Urine leakage related to the feeling of urgency?

Yes ☐ No ☐
If Yes, how much does it bother you?
not at all ☐ slightly ☐ moderately ☐ greatly ☐

3. Urine leakage related to physical activity, coughing, or sneezing?

Yes ☐ No ☐
If Yes, how much does it bother you?
not at all ☐ slightly ☐ moderately ☐ greatly ☐

4. Small amounts of urine leakage (drops)?

Yes ☐ No ☐
If Yes, how much does it bother you?
not at all ☐ slightly ☐ moderately ☐ greatly ☐

5. Difficulty emptying your bladder?

Yes ☐ No ☐
If Yes, how much does it bother you?
not at all ☐ slightly ☐ moderately ☐ greatly ☐

6. Pain or discomfort in the lower abdominal or genital area?

Yes ☐ No ☐
If Yes, how much does it bother you?
not at all ☐ slightly ☐ moderately ☐ greatly ☐

Appendix 8 Genital Prolapse Grading

The following grading will be used for evaluation at screening
(patient should have an empty bladder and Valsalva strain maximally).

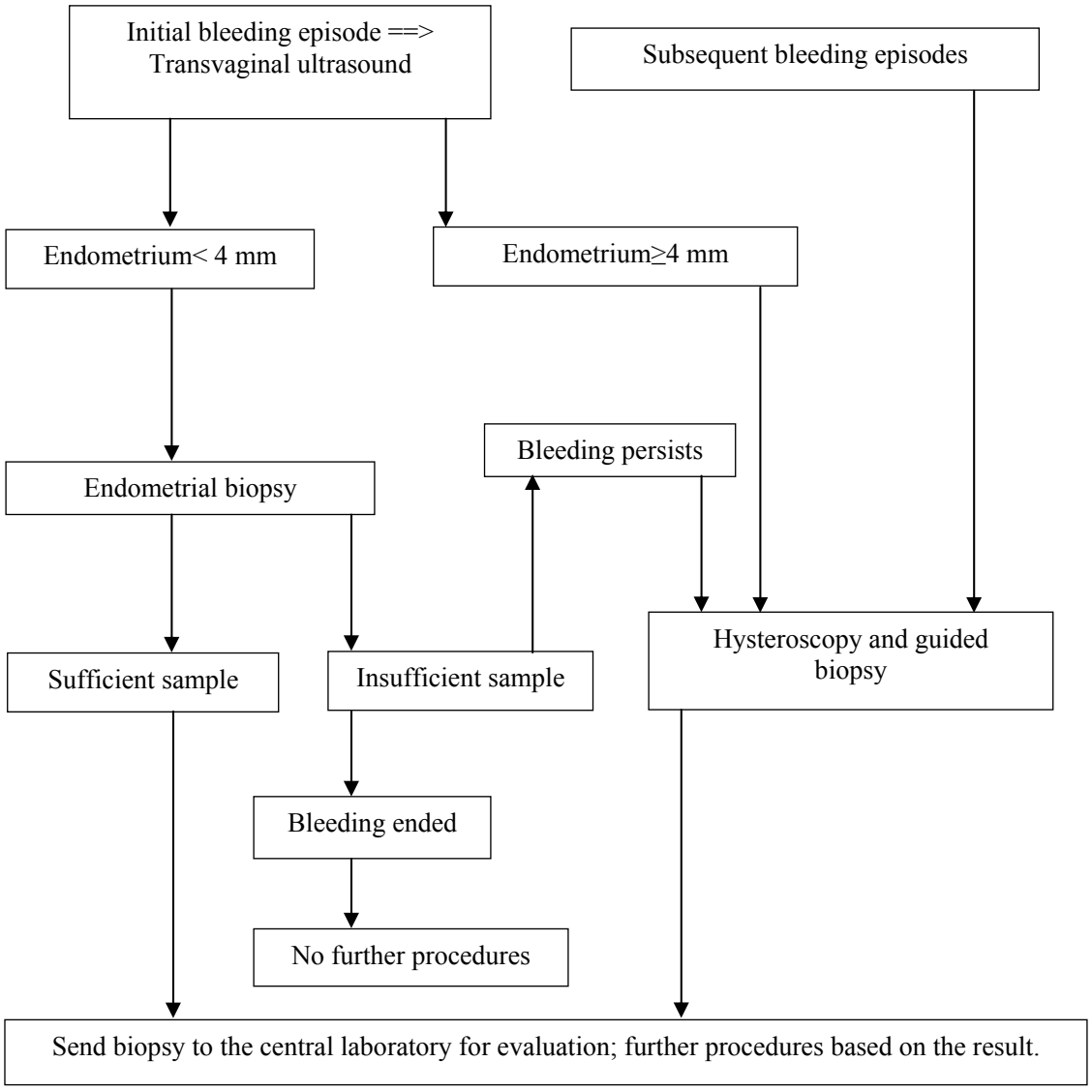
Uterine Prolapse:

Grade 0 - Normally positioned cervix or vaginal apex
Grade 1 - Less than half way to the hymenal ring
Grade 2 - More than half way to the hymenal ring
Grade 3 - At the hymenal ring
Grade 4 - Halfway or greater outside the hymenal ring

Vaginal Prolapse (cysto[urethra]cele or rectocele):

Grade 0 - Normal
Grade 1 - Some bulging during Valsalva, no symptoms
Grade 2 - Size approximately hen`s egg
Grade 3 - Approaching hymenal level, bulging “out”
Grade 4 - Clearly visible outside

Appendix 9 Diagnostic Procedures Required in a Subject with Intact Uterus and Vaginal Bleeding



Appendix 10 Management and Discontinuation Criteria for Abnormal Liver Function Tests

Management and Discontinuation Criteria for Abnormal Liver Function tests have been designed to ensure subject safety and evaluate liver event etiology. (See Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, Food and Drug Administration [FDA]: 2009)

1. Abnormal Liver Chemistry Criteria:

The Investigator or Sub-investigator must review study subject laboratories to identify if any levels meet the following criteria:

a. AST or ALT >5 × ULN
b. AST or ALT >3 × ULN and total bilirubin (TBL) >2 × ULN (SAE)
c. AST or ALT >3 × ULN with signs or symptoms compatible with hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, eosinophilia [>5%])

2. Action to be Taken by Investigator:

If any abnormal liver chemistry criterion is met, the Investigator or Sub-investigator must do the following:

- Subjects must be instructed to discontinue study medication immediately. The Investigator or Sub-investigator should not re-challenge the subject with the investigational product without consulting the Sponsor.
- Following the initial observed elevation, every effort should be made to have the subject return to the clinic within 72 hours to repeat liver function chemistries and for further hepatic evaluation.
- Every effort should be made to have the subjects must be monitored 2 to 3 times per week until liver function chemistries (ALT, AST, ALP, total bilirubin) resolve, stabilize or return to within the normal range or to baseline levels.
- This event must be reported to the Sponsor as soon as possible but no later than 24 hours of learning after its occurrence on the Liver Event Form.
- Consultation with a specialist such as a hepatologist is considered.
- Liver imaging (ie, ultrasound, magnetic resonance imaging (MRI), computerized tomography) is considered.
- For criteria b, termed “Hy’s law,” the case must be reported as an SAE.

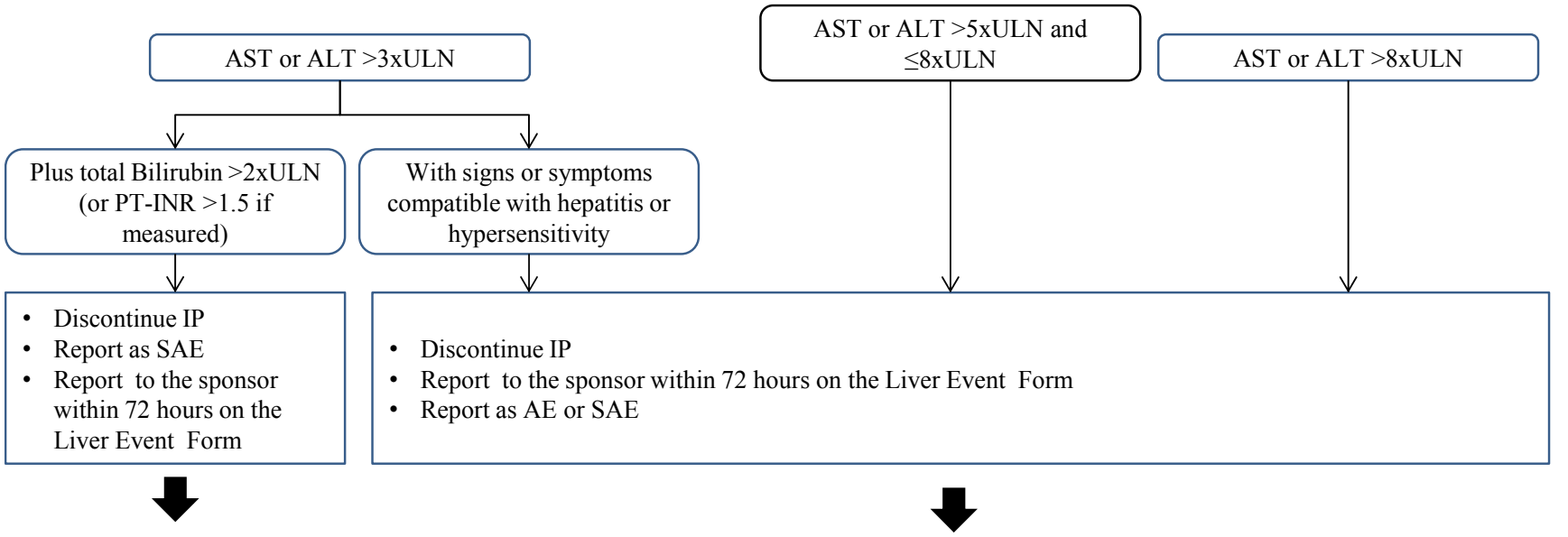
3. Follow-up Examination:

If any of the abnormal liver chemistry criteria are met, the following assessments should be performed at the follow-up visit(s) and documented in the Liver Event Form:

- Clinical symptoms course
  - Concomitant medications: OTC (over-the-counter drug)/herbal/dietary supplements (start and stop dates)
- Alcohol use
- Risk factors for nonalcoholic steatohepatitis (NASH) such as diabetes, obesity and hypertriglyceridemia
- Autoimmune hepatitis/cholangitis
- Wilson's disease
- Laboratory Assessments
  - Viral hepatitis serology
    - Hepatitis A IgM antibody
    - Hepatitis B surface antigen (HBs antigen) and Hepatitis B core antibody (HBc antibody)
    - Hepatitis C RNA
    - Hepatitis E IgM antibody
    - Cytomegalovirus IgM antibody
    - Epstein-Barr viral capsid antigen IgM antibody
  - For subjects with total bilirubin of >1.5 ULN, conjugated bilirubin should be measured.
  - Complete blood count with differential to assess for eosinophilia

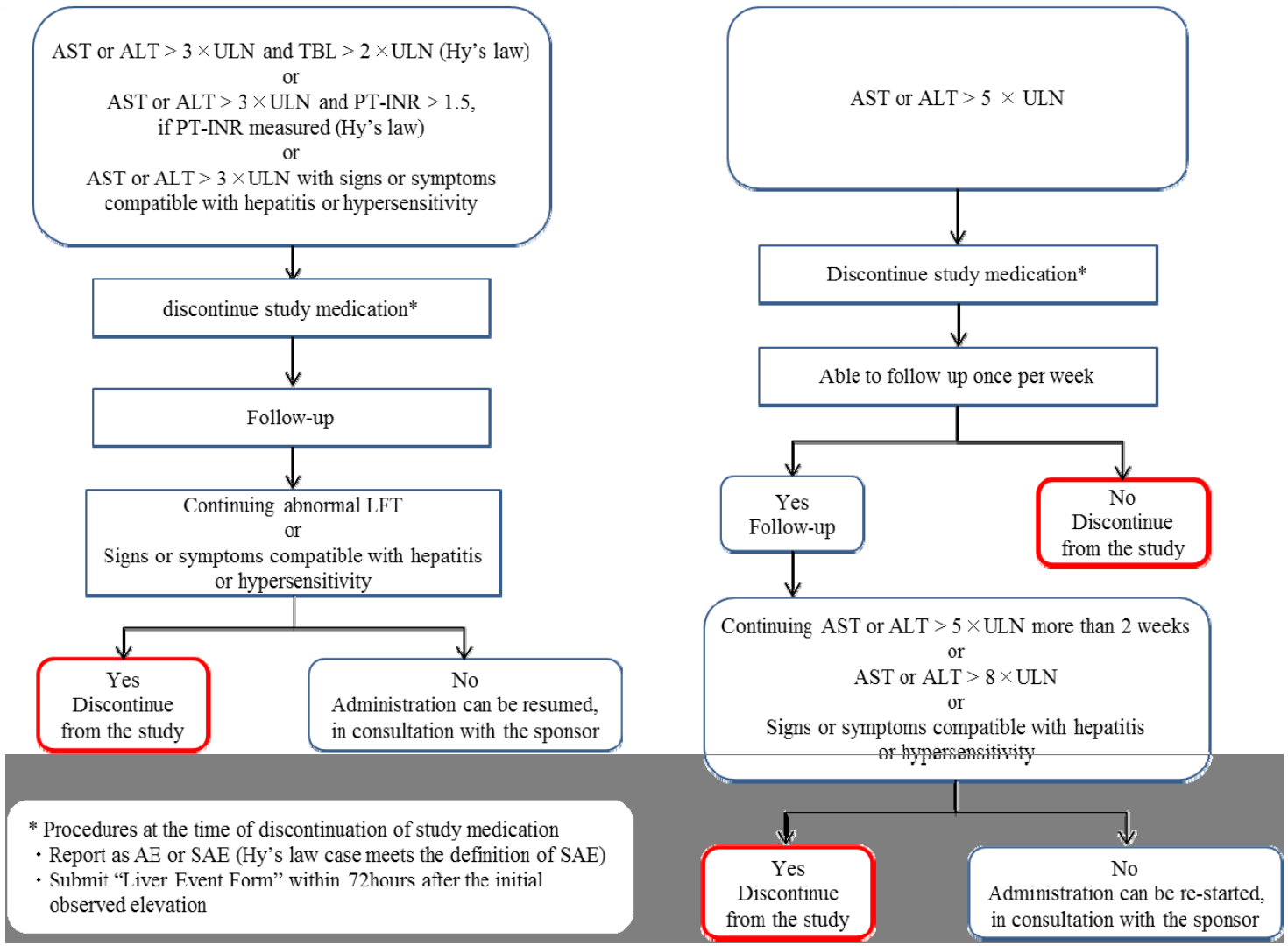
The Investigator or Sub-investigator must not re-challenge the subject with the investigational product without consulting the Sponsor.

Abnormal Liver Chemistry Criteria: Algorithm



- Patients must be instructed to hold study medication immediately.
- The investigator or subinvestigator should not re-challenge the patient with the investigational product without consulting the sponsor.
- Following the initial observed elevation, every effort should be made to have the patient return to the clinic within 72 hours to repeat liver function chemistries and for further hepatic evaluation
- Patients must be monitored 2 to 3 times per week until liver function chemistries (ALT, AST, ALP, total bilirubin) resolve, stabilize or return to within the normal range or to baseline levels.
- Consultation with a specialist such as a hepatologist is considered.
- Liver imaging (ie, ultrasound, magnetic resonance imaging (MRI), computerized tomography) is considered.

Management and Discontinuation Criteria for Abnormal Liver Function Tests (LFT): Algorithm



Appendix 11 Sponsor's Signature

Approval of the Protocol

Product Name: Ospemifene

Study Protocol Title: A Phase 3, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Ospemifene in Patients with Moderate to Severe Vaginal Dryness, a Symptom of Vulvo-vaginal Atrophy (VVA) due to Menopause

Study Protocol Number: 1517I0231

Version/Edition Number: 3

Issue Date of Original (Version 1): 06 October 2015

Issue Date of Version 2: 11 March 2016

Issue Date of Latest Version 3: 02 November 2016

Sponsor signatory:

This clinical study protocol was subject to critical review and has been approved by the Sponsor:

PPO

2 Nov 2016

Date: day-month-year

Appendix 12 Investigator's Signature

Study Title:	A Phase 3, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Ospemifene in Patients with Moderate to Severe Vaginal Dryness, a Symptom of Vulvo-vaginal Atrophy (VVA) due to Menopause
Study Number:	1517I0231
Date of Original:	06 October 2015
Date of Version 2:	11 March 2016
Date of Latest Amendment:	02 November 2016

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____

Printed Name: _____

Title: _____

Affiliation: _____