AN OPEN-LABEL PILOT PROSPECTIVE VULVOSCOPY WITH PHOTOGRAPHY STUDY OF THE VISIBLE CHANGES IN THE VULVA, VESTIBULE AND VAGINA PRE- AND POST- TWENTY WEEKS OF DAILY ADMINISTRATION OF 60 MG OSPEMIFENE IN POST-MENOPAUSAL WOMEN WITH DYSPAREUNIA FROM VULVAR VAGINAL ATROPHY

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SUMMARY

This study is Investigator initiated research (IIR) supported by a grant and study medication from Shionogi.

1. INTRODUCTION

Ospemifene is indicated for post-menopausal women diagnosed with vulvar vaginal atrophy (VVA) and dyspareunia. While ospemifene clinically significantly reduces pain associated with dyspareunia, there has been little prospective documentation using vulvoscopy with detailed photography of the visible changes to the vulva, vestibule and vaginal region with daily administration of 60 mg ospemifene in post-menopausal women with VVA and dyspareunia. This study will include a total of 6 prospective photographic sessions of the vulva, vestibule and vagina over the 20 weeks administration of 60 mg ospemifene in the study. Comparisons will be made of baseline photography (vulvoscopy session 0) with photography at 4 weeks (vulvoscopy session 1), 8 weeks (vulvoscopy session 2), 12 weeks (vulvoscopy session 3), 16 weeks (vulvoscopy session 4) and 20 weeks (vulvoscopy session 5).

2. TRIAL OBJECTIVE

The primary objective of this study is to prospectively document, using vulvoscopy with detailed photography, the visible changes to the vulva, vestibule and vaginal region in post-menopausal women with dyspareunia taking 60 mg daily ospemifene for twenty weeks at 6 timepoints: baseline, 4 weeks, 8 weeks, 12 weeks,16 weeks and 20 weeks.

Secondary objectives include changes in pain as noted on the pain scale (appendix 2) and the q-tip test, in the vestibule on visual scale (appendix 3) by the clinician and sexual function by subject diary (appendix 4).

3. DESCRIPTION OF RESEARCH DESIGN

3.1 Overall Study Plan

This is an unblinded study to be conducted at a single research center, San Diego Sexual Medicine. Subjects meeting inclusion and exclusion criteria will receive 60 mg ospemifene daily for twenty weeks. After the informed consent is

signed, a baseline physical examination, and vulvoscopy with detailed photography of the vulva, vestibule and vagina, will be performed. Physical examination and vulvoscopy with detailed photography of the vulva, vestibule and vagina, will be repeated prospectively every 4 weeks for a total of 20 weeks. Therefore, physical examination and vulvoscopy with detailed photography of the vulva, vestibule and vagina will be performed prospectively at baseline (vulvoscopy session 1), 4 weeks (vulvoscopy session 2), 8 weeks (vulvoscopy session 3), 12, weeks (vulvoscopy session 4), 16 weeks (vulvoscopy session 5) and 20 weeks (vulvoscopy session 6) following daily administration of 60 mg ospemifene.

3.2 Study Duration

Each eligible subject will participate in the study for approximately 20 weeks. It is expected this single site investigator-initiated research study will be completed approximately 8 months following initial approval by the Independent Review Board.

3.3 Independent Review Board (IRB) Approval

Prior to conducting any study-related procedures, the Principal Investigator will obtain written approval from Aspire Independent Review Board for the informed consent form, protocol, recruitment materials, and any written information provided to Subjects pertaining to the procedure.

3.4 Rationale for Study Design and Subject Selection

Currently there have been limited prospective studies using vulvoscopy with detailed photography demonstrating visible changes to the vulva, vestibule and vagina following oral administration of 60 mg ospemifene in post-menopausal women with VVA and dyspareunia. Information regarding visible changes to the vulva, vestibule and vagina may be very important to the patient and to the health care provider to best understand the beneficial effects of ospemifene and to ensure patient compliance with treatment.

This study is being conducted in an unblinded fashion because the primary endpoint is a collection of photographs. All subjects will receive the same active drug at the same dosage.

4. Selection and Withdrawal of Subjects

The study population will include menopausal females with vulvar vaginal atrophy (VVA) causing dyspareunia.

4.1 Subject Inclusion Criteria

All criteria below must be met in order for a Subject to be eligible for study participation.

1. Subject provides written informed consent and HIPAA authorization before any study procedures are conducted;

2. Subject is female;
3. Subject is aged 21-80 years;
4. Subject has a body mass index (BMI) < 37 kg/m^2
5. Subject is menopausal either naturally (at least 12 months amenorrheic) or 6 weeks after a bilateral salpingo-oophorectomy prior to natural menopause; subjects with hysterectomy only must have a serum FSH > 40 mIU/mL;
6. Subject has vulvovaginal atrophy with dyspareunia;
   Subject agrees to comply with the study procedures and visits.

4.2 Subject Exclusion Criteria

Subjects who meet any of the following criteria shall be excluded:

1. Subject has a hypersensitivity to any of the ingredients of ospemifene;
2. Subject has used ospemifene in the past;
3. Subject has documented or suspected breast cancer, history of heart attack or stroke;
4. Subject has clinically significant findings on physical examination;
5. Subject has uncontrolled hypertension;
6. Subject has any chronic medical condition or psychologic disorder that the Principal Investigator feels makes her ineligible for the study;
7. Subject is currently on local or systemic androgen therapy including local or systemic testosterone (washout 14 days for local or topical androgen or non-depot injection, 1 month for depot, 6 months for pellet;
8. Subject is currently on local or systemic estrogen therapy or androgen therapy (washout 14 days for vaginal estrogen, 60 days for oral/transdermal therapy);
9. Subject is currently using a SERM or products that have estrogenic or anti-estrogenic effects within last month;
10. Subject currently using itraconzole, ketoconazole, digitalis or alkaloids heparin or strong cytochrome P 450 3A4 inhibitors;
11. Subject has a history of substance abuse within 12 months prior, or consuming > 14 alcoholic drinks per week;
12. Subject has received an investigational drug within 30 days prior to signing consent;
13. Subject has any condition or exhibits behavior that indicates to the Principal Investigator that the Subject is unlikely to be compliant with study procedures and visits.

4.3 Subject Withdrawal Criteria

The Principal Investigator may discontinue a subject's participation in the study at any time if it is considered in the subject's best interest to do so. Such a decision may be precipitated by adverse events, new onset illness, clinically important changes in vital signs, physical examinations, or laboratory tests. Subjects who

are noncompliant with study procedures and visits may also be withdrawn by the Principal Investigator.

Subjects may withdraw from participation in the study at any time for any reason. A subject's decision to withdraw will not cause the subject to lose any benefits to which she is entitled. A subject who withdraws prematurely from the study will return to the clinic as soon as possible and before any further ospemifene treatment of any kind, to undergo the final visit evaluations.

If a subject prematurely withdraws or is withdrawn from study participation, the reason for the withdrawal must be recorded on the case report form (CRF). Record the primary reason for premature withdrawal according to the following categories:

- **Adverse Event**: Subject experiences an intolerable event, which may or may not be related to the study medication;
- **Withdrawn Consent**: Subject withdraws from study participation for personal reasons (exclude adverse experience before indicating this category);
- **Concomitant Medication Violation**: Subject initiates, discontinues, or changes dosing regimen of concomitant medication in violation of the protocol, which, in the judgment of the Principal Investigator, may adversely affect evaluation of safety;
- **Lost-to-Follow-up**: Subject does not return for evaluation and no further contact is made by the Subject after three documented phone or email attempts and a final attempt by certified mail.
- **Other**: Any reason that does not fit in the above 4 categories: the reason will also be recorded on the CRF.

5. Clinical Procedures

Clinical procedures throughout the study are described in the sections below, and summarized briefly in **Appendix 1**.

5.1 Informed Consent and HIPAA

Each potential study Subject must provide written informed consent and authorize release of her protected health information before any study procedure is conducted.

5.1.1 Informed Consent

An Informed Consent Form (ICF) and California Bill of Rights will be written in accordance with established criteria of the Aspire IRB and the appropriate federal regulations to describe the study plan, procedures, and risks. The Aspire IRB must approve the ICF and any ICF amendments or administrative revisions before they are used.

Potential subjects will be informed of the study plan and schedule and will provide written informed consent prior to the initiation of any study-related procedures. Each subject will be afforded the opportunity to ask any questions about the study plan, procedures, or possible risks. The date the consent form was signed by the subject and the Principal Investigator or his designee will be documented. The screening procedures will be performed and recorded on the source documents. No screening procedures may be initiated prior to the Subject signing the ICF.

The original, signed ICF will be retained in the Principal Investigator's study files. A copy of the signed and dated consent form will be given to each potential Subject.

5.1.2 HIPAA

In accordance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, the Subject has the right to determine who has access to protected health information.

Potential subjects will provide written authorization for the Principal Investigator to access the subject's personal health information (PHI) for the purposes of the study. Personal health information relevant to the study includes medical records and the results of tests and procedures. The subject's written authorization also allows sharing this information with the Food and Drug Administration (FDA), other regulatory agencies and the Aspire IRB. The Subject may cancel the authorization in writing at any time, but will then be withdrawn from the study.

An authorization form must include the following elements:

- A description of the information to be used or disclosed;
- Identification of the persons or class of persons authorized to make the disclosure(s);
- Identification of the persons or class of persons authorized to receive the PHI;
- A description of the purposes for the uses or disclosures;
- Expiration date or event triggering expiration;
- Individual's signature and date;
- A statement of the individual's right to revoke his/her authorization;
- A statement of consequences to the individual for refusing to sign the authorization;
- A statement of the potential for the information to be re-disclosed by recipients and no longer protected by the Privacy Rule; and
- If the individual will be denied access to records during the study, a statement that the Subject agrees to temporarily waive access to records during the research.

The original, signed HIPAA authorization form will be retained in the Principal Investigator's study files. A copy of the signed and dated form will be given to each potential Subject.

5.2 Subject Screening (Visit 1)

Candidates for enrollment will be screened within 28 days prior to enrollment. Before initiation of any test procedures, Subjects will be fully informed of the study plan, procedures, and risks involved in participating in the study. Each potential Subject will be required to read and to indicate her understanding by signing and dating the ICF prior to initiation of any screening procedures.

The site will maintain an ongoing screening log of all subjects who provide written informed consent. The screening log will include each Subject's initials, date of birth, and screening number (assigned sequentially), including reason for exclusion if the subject is determined to be ineligible for the study. If the subject does not have a middle name, a dash will be used instead of that initial (e.g., J-S). The subject will be identified on source documents by initials and the assigned Subject number.

Screening procedures will consist of the following:

- Medical history, including surgical procedures, tobacco, alcohol, and medication use (prescription and non-prescription drugs, nutritional supplements, herbals, or investigational drugs);
- Measurement of height (inches) and weight (pounds) in indoor clothing without shoes; recorded to the nearest whole unit;
- Vital signs (blood pressure, pulse, respiration rate, and oral temperature);
- Pain scale;
- Urinalysis;
- Clinical laboratory tests estradiol, LH, FSH (the same clinical laboratory will be used throughout the study):
- Physical examination including review of systems and breast and gynecologic exam;
- Vulvoscopy including detailed photograph(s) of the vulva, vestibule and vagina region and pain scale/Q-tip testing;
- Visual scale.

The Principal Investigator will review all screening assessments and sign and date all reports. Any clinically significant abnormalities will be indicated by the abbreviation CS on the report. Results that are not clinically significant will be identified as NCS. The Principal Investigator will review all inclusion and exclusion requirements and document the eligibility of each Subject to participate further.

5.3 Study Restrictions

The restrictions listed below will be applied from study drug administration through study termination. The Principal Investigator will determine if a deviation from the restrictions warrants Subject withdrawal from the study.

From screening through completion of the last study procedures, Subjects may not do the following:

- use of any prescription hormone (any administration);
- change any prescription medication without notifying the Principal Investigator;
- use any over-the-counter products, vitamins or herbal and/or nutritional supplements;
- use any investigational drug or medical device products;
- use any drugs of abuse.

5.4 Study Day 0 (Visit 2)

Subject meeting inclusion and exclusion criteria may enroll any time after screening up to 28 days after consent is signed:

- Measure vital signs (blood pressure, pulse, respiration rate, and oral temperature);
- Assess any change in concomitant medication since screening visit;
- Complete pain scale;
- Vulvoscopy including detailed photograph(s) of the vulva, vestibule and vagina region and pain scale/Q-tip testing;
- Complete visual scale;
- Educate subject as to how study medication is administered (taken each morning);
- Dispense study medication (35 tabs), diaries (10) and lubricant;
- Assess adverse events.

5.5 Study Days 28 ± 7, 56 ± 7, 84 ± 7, 112 ± 7 (Visits 3, 4, 5, 6)

Each Subject will report to the Principal Investigator's office on study Days 28, 56, 84 and 112 ± 7 for the following procedures at each visit:

- Measure vital signs (blood pressure, pulse, respiration rate, and oral temperature);
- Assess any change in concomitant medication;
- Complete pain scale;
- Vulvoscopy including photograph(s) of the vulvar vestibule region and pain scale/Q-tip testing;
- Complete visual scale;

- Collect medication and calculate compliance (reeducate Subject on medication administration if compliance is <80% or >120%);
- Collect diaries;
- Dispense study medication (35 tabs), new diaries and new lubricant;
- Assess adverse events.

5.6 Study Day 140 ± 7 (Visit 7) or Early Termination Visit

On Study Day 140 ± 7 each Subject will report to the Principal Investigator's office for the following procedures:

- Measure vital signs (blood pressure, pulse, respiration rate, and oral temperature);
- Assess any change in concomitant medication;
- Complete pain scale;
- Perform physical examination including review of systems and breast and gynecologic exam;
- Vulvoscopy including photograph(s) of the vulva, vestibule and vagina region and pain scale/Q-tip testing;
- Complete visual scale;
- Collect medication and calculate compliance;
- Collect diaries;
- Assess adverse events.

If a Subject terminates study participation or is withdrawn from the study by the Principal Investigator before visit 7, the Subject should return to the Principal Investigator's office as soon as possible for the following procedures:

- Measure vital signs (blood pressure, pulse, respiration rate, and oral temperature);
- Assess any change in concomitant medication;
- Complete pain scale;
- Assess any change in concomitant medication since screening visit;
- Perform physical examination including review of systems and breast and gynecologic exam;
- Vulvoscopy including photograph(s) of the vulva, vestibule and vagina region and pain scale/Q-tip testing;
- Complete visual scale;
- Collect medication and calculate compliance;
- Collect diaries;
- Assess adverse events.

6 Adverse Event Assessment

6.1 Adverse Events

An adverse event (AE) is any undesirable sign, symptom, medical condition, or laboratory abnormality occurring after the Subject has taken the first dose of study medication, whether the event is considered study medication-related or not. Medical conditions or diseases present before starting study medication are only considered adverse events if they worsen after starting study medication. The Principal Investigator will follow all Subjects who experience an adverse event until the Subject's medical condition returns to normal or until a clinically satisfactory resolution is obtained.

Adverse events are classified in several ways: as either serious or non-serious, and either expected or unexpected. Serious adverse events (SAEs) include those that result in death, are life threatening, require inpatient hospitalization or result in prolongation of an existing hospitalization, result in persistent or significant disability or incapacity, require medical or surgical intervention to prevent one of the outcomes described above, are congenital anomalies or birth defects, or are medically important events or reactions (see Section 7.2). Non-serious adverse events are those adverse events that do not meet the above criteria for serious adverse events. Expected adverse events are those events that have been previously observed and are described in the current prescribing information for the study medication. Unexpected adverse events are those events that are not listed in the prescribing information, or are not consistent with the specificity or severity described in the current prescribing information.

Any abnormality that, in the judgment of the Principal Investigator or a physician identified on Form FDA 1572, impacts the health, safety, or well-being of the study participant such that immediate follow-up (e.g., additional testing or treatment intervention) is warranted is considered a clinically significant abnormality. A determination of clinical significance is independent of whether or not the abnormality is considered causally related to the use of the study medication.

6.2 Serious Adverse Events

A SAE is defined by federal regulation as any AE that results in any of the following outcomes:

1. Death
2. Life threatening (Subject is at risk of death at the time the event occurs)
3. Persistent/significant disability or incapacity (substantial disruption of a person's ability to conduct normal life functions)
4. Inpatient hospitalization or prolongation of an existing hospitalization.

5. Congenital anomaly or birth defect.

Additionally, important medical events that may not result in death, be life threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the Subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Any SAE occurring in a Subject after providing informed consent and until 30 days after completing the study must be reported to the Aspire IRB. The reporting period may be extended if there is a strong suspicion of a study medication reaction. Reports of overdosage must be monitored and reported as an SAE.

6.3 Adverse Event Reporting

All adverse events, whether volunteered by the Subject, discovered during general questioning by the Principal investigator, or detected through a physical examination or other means, will be recorded in the clinic chart (source document) and on the Adverse Events CFR. Each description of an adverse event will include:

1. Duration: start and stop dates
2. Expectedness
3. Severity: events will be classified as either *mild* (causing no limitation in normal activities), *moderate* (causing some limitation in normal activities), or *severe* (causing significant limitation in or the inability to perform normal activities)
4. Action taken
5. Relationship to the study medication: not related, possibly related, or probably related
6. Outcome: resolved, continuing requiring no treatment, continuing requiring treatment, hospitalization, or death

Whenever possible, adverse events causing premature study discontinuation should be followed to resolution.

All SAEs occurring during the study and up to 28 days after the Subject completes the study (visit on Day 84 or earlier) *must be reported to the Aspire IRB within 1 week of learning of the event with the exception of death which must be reported within 24 hours*. Additionally, the Principal investigator must provide any other AE notification required by the IRB. Each SAE is to be recorded on a SAE worksheet along with follow-up records. Examples of follow-up records may include photocopies of hospital records, consultation reports, autopsy findings, laboratory reports, and a summary of the outcome of the reaction.

6.4 Risks

The risks to Subjects in this study are those associated with in the package insert for ospemifene: hot flashes, vaginal discharge, muscle spasms and increased sweating. Less common but serious side effects include stroke, blood clots and cancer of the lining of the uterus.

7. Study Medication and Accountability

The Principal Investigator is responsible for study medication at the investigational site, including storage, accountability, record keeping, and reconciliation.

7.1 Study Medication

Ospemifene (Osphena®) 60 mg tablets will be provided by Shionogi Pharmaceuticals, in sufficient quantity to dose all Subjects.

The ospemifene tablets provided for this study will be taken from commercial drug supply.

7.2 Study Medication Blinding

This is an open-label (unblinded) study and no blinding of study medication is required.

7.3 Study Medication Labeling

Each envelope of medication provided to each Subject will be marked as to subject (initials and subject number), visit number and date of dispensing.

7.4 Study Medication Storage

Ospemifene will be stored in a cool, dry place. The study medication shall be stored in a securely locked, substantially constructed enclosure to which access is limited. The Principal Investigator shall take adequate precautions, including locked storage, to prevent theft or diversion of the study medication, consistent with CFR Title 21, part 312.69.

7.5 Study Medication Handling

Study medication will be shipped to the investigational site after the granting agency (Shionogi Pharmaceuticals) has received the required study documents in accordance with regulatory requirements.

All study medication is to be administered in accordance with the protocol and only to enrolled Subjects. Only authorized personnel may supply the study medication to each Subject.

7.6 Study Medication Accountability

All study medications will be Subject to inventory upon receipt, and stored in accordance with Section 8.4. Applicable regulatory requirements for this study will be enforced by the Principal Investigator or designated site personnel through the study. The Principal Investigator (or designee) will document the date, Subject identification, and lot number used each time drug is dispensed for Subject use.

Throughout the study, the Principal Investigator will maintain an accounting of all study medication. The Principal Investigator must not destroy any unused study medication. The Principal Investigator will return all unopened study medication and a copy of the completed drug disposition form to Shionogi Pharmaceuticals.

8. Statistical Methods

8.1 Determination of Sample Size

The sample size of 10 menopausal Subjects was chosen for this study based on this being a pilot study and this sample size will be sufficient to prospectively document visible changes to the vulva, vestibule and vagina in post-menopausal women with VVA and dyspareunia. There will be a total of 6 photographic sessions of the vulva, vestibule and vagina over the 20 weeks of the study. The photograph(s) at baseline (vulvoscopy session 0) will be compared to photographs at 4 weeks (vulvoscopy session 1), 8 weeks (vulvoscopy session 2), 12 weeks (vulvoscopy session 3), 16 weeks (vulvoscopy session 4) and 20 weeks (vulvoscopy session 5).

8.2 Photographic Data

Changes to the vulva, vestibule and vagina will be examined prospectively by comparing photographs of post-menopausal women with VVA and dyspareunia at 4 weeks, 8 weeks, 12 weeks, 16 weeks and 20 weeks while on treatment with 60 mg ospemifene. The proportion of subjects with improvement will be tabulated by scheduled visit.

8.3 Patient Reported Outcomes

Mean pain score will be summarized at each scheduled visit. Subjects will also be categorized at each visit as having more pain, the same pain, or less pain compared to baseline.

Mean scores will be summarized for each item of the visual scale at each scheduled visit. Subjects will also be categorized at each visit as worsened, unchanged, or improved compared to baseline for each item of the visual scale at each scheduled visit.

For each subject, the proportion of total sexual events with a 'yes' response since the last scheduled visit will be calculated for each diary question at each scheduled visit.

8.4 Safety Data

Safety data will be summarized for each Subject enrolled in the study.

9. Administrative Issues

9.1 Changes to the Protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by the Aspire IRB before implementation. Only in the event of an emergency should a deviation from the protocol occur for an individual Subject. Such a deviation will be for the Subject in the emergency situation and for that Subject only. A description of the deviation from the protocol and the reason for it will be recorded in the source documents.

9.2 Monitoring Procedures

The Principal Investigator and site personnel will complete all CRFs in a timely manner following completion of each Subject visit to facilitate documentation of study procedures and review of the CRFs.

9.3 Access to Data Source/Documentation

The Principal Investigator will permit representatives of the Aspire IRB and/or the FDA (or other regulatory authority) to inspect the facilities and records relevant to this study, including Subject charts, either during the study or after its completion.

9.4 Quality Control and Quality Assurance

The Principal Investigator must provide the documents listed below before drug can be shipped and the study initiated:

- Original Form FDA 1572 completed and signed by the Principal Investigator;
- Current medical license for each physician appearing on Form FDA 1572;
- Copy of IRB correspondence documenting approving the protocol, informed consent form, recruitment materials and any instructions for the Subject regarding the procedure, and any other documents reviewed and/or required by the IRB.

9.5 Ethics

This study will be conducted in accordance with current Good Clinical Practice (GCP), with the Code of Federal Regulations (CFR Title 21, Parts 50, 54, 56, 312, and 314). Current GCP is consistent with the ethical principles described in the current version of the Declaration of Helsinki.

Requirements for Independent Review Board (IRB) review and obtaining informed consent are described in Sections 3.3 and 5.1, respectively.

9.6 Case Report Forms, Data Handling, and Recordkeeping

The following procedures will be employed related to recording of data:

- Relevant information determined at each Subject visit is to be recorded on source documents/CRFs.
- Data recorded on CRFs will be documented in an anonymous fashion with the Subject identified only by her Subject number and initials.
- All CRFs are to be completed in a neat, legible manner to ensure accurate communication of data. A black pen is preferred to ensure clarity of any reproduced copies. Any change or corrections made on the CRFs must be dated and initialed by the person making the change. In such cases, the best procedure is to cross out the original entry with a single line. Do not erase, overwrite, or obliterate, by any means, the original entry.
- CRFs and any data queries should accurately reflect Subject data records (source documents).
- The completed CRF set for each Subject is to be reviewed by the Principal Investigator for completeness and accuracy. The Principal Investigator will sign and date the last CRF page to indicate this review was performed.

9.7 Retention of Data, Documents, and Study Medication

In compliance with CFR Title 21, part 312.57(c), the Principal Investigator will retain all study-related materials for at least 2 years after study completion. Study-related materials include, but are not limited to, medical records (i.e., the

source data), completed case report forms, medication accountability records, and reserve samples of investigational medication. Study medication will be stored securely under the storage conditions described in Section 8.4.

10. References

1. Bachmann GA, Komi JO, Ospemifene Study Group, Ospemifene effectively treats vulvaginal atrophy in postmenopausal women; results from a pivotel phase 3 study. Menopause 2010;17:480-6.
2. Portman DJ, Bachmann GA, Simon JA and Ospemifene Study Group, Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy. Menopause 2013;20:623-30.
3. Goldstein SR, Bachmann GA, Koninckx PR, Lin VH, Portman DJ, Ylikorkala O and Ospemifene Study Group. Climacteric 2014;17:173-82.
4. James A. Simon, MD,1 Vivian H. Lin, MD,2 Cathy Radovich, BS,2 Gloria A. Bachmann, MD,3 and The Ospemifene Study GroupOne-year long-term safety extension study of ospemifene for the treatment of vulvar and vaginal atrophy in postmenopausal women with a uterus, Menopause: The Journal of The North American Menopause Society, Vol. 20, No. 4, pp. 418-427.

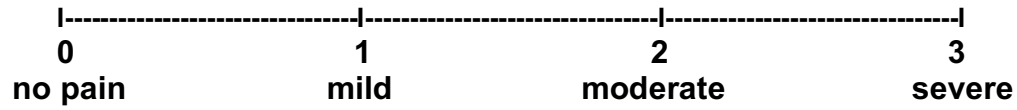
Appendix 1: Schedule of Study Procedures

Study DAY:	**Up to -28**	**0**	**28 ± 7**	**56 ± 7**	**84 ± 7**	**112 ± 7**	**140 ± 7 or ET**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Procedure							
ICF & HIPAA	X						
I/E Criteria	X	X					
Medical history	X	X					
Physical exam	X						X
Breast/Gyn exam	X						X
Vital signs	X	X	X	X	X	X	X
Height & weight	X						X
Concomitant Medications	X	X	X	X	X	X	X
Pain scale	X	X	X	X	X	X	X
Clinical laboratory tests[2]	X						X
Vulvoscopy with photography	X	X	X	X	X	X	X
Visual Scale	X	X	X	X	X	X	X
Q-tip test	X	X	X	X	X	X	X
Dispense study drug		X	X	X	X	X	
Dispense diaries		X	X	X	X	X	
Dispense lubricant		X	X	X	X	X	
Collect/reconcile medication			X	X	X	X	X
Calculate compliance			X	X	X	X	X
Collect diaries			X	X	X	X	X
Collect AE data	X	X	X	X	X	X	X

ET = early termination

For detailed study procedures, see Section 5, Clinical Procedures.

Appendix 2: Pain Scale



Appendix 3: Visual Scale

Observation	0 - none	1 - mild	2 - moderate	3 - severe
Petechiae				
Pallor				
Friability				
Dryness				
Redness				

Appendix 4: Diary

Initials _____ Number _____ Date _____

Please complete after each sexual event, answering all questions.

If you experienced dryness before were you less dry? ☐Yes ☐No ☐N/A

Did you use lubricant during this activity? ☐Yes ☐No

Did you experience pain/discomfort during foreplay? ☐Yes ☐No ☐N/A

Did you experience pain during masturbation? ☐Yes ☐No ☐N/A

Did you experience pain during oral sex? ☐Yes ☐No ☐N/A

Did you experience pain during intercourse? ☐Yes ☐No ☐N/A

Did you stop early because of discomfort? ☐Yes ☐No