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APPLICATION NUMBER:

203505Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	203505
Priority or Standard	Standard
Submit Date(s)	April 26, 2012
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Division / Office	Division of Reproductive and Urologic Products (DRUP)/Office of Drug Evaluation III (ODE III)
Reviewer Name(s)	Theresa H. van der Vlugt, M.D.
Review Completion Date	February 4, 2013
Established Name	Ospemifene
(Proposed) Trade Name	Osphena™
Therapeutic Class	Selective Estrogen Receptor Agonist/Antagonist
Applicant	Shionogi Inc.
Formulation(s)	Tablet
Dosing Regimen	One Oral Tablet Daily
Proposed Indication(s)	Treatment of Vulvar and Vaginal Atrophy due to Menopause, Including Moderate to Severe Symptoms of Dyspareunia and/or Vaginal Dryness and Physiological Changes (Parabasal Cells, Superficial Cells and pH) in Postmenopausal Women
Intended Population(s)	Postmenopausal Women

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of 60 mg Osphena™ (ospemifene) tablets, taken orally daily, for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. Recommendation for approval for the treatment of moderate to severe dyspareunia is based on:

1. The safety and efficacy data presented in the Clinical Study Report (CSR) for the primary 12-week Study 15-50310 included in the application (received on April 26, 2012), and the addendum to the final CSR for Study 15-50310 received on July 9, 2012.
2. The safety and efficacy data presented in the CSR for the second 12-week Study 15-50821 included in the application (received on April 26, 2012), and the addendum to the final CSR for Study 15-50821 received on July 9, 2012.
3. The safety data presented in the CSR for the long-term 52-week safety Study 15-50718 included in the application.
4. The additional safety data presented in the CSR for the 40-week extension Study 15-50310X conducted in women with intact uteri who completed the parent Study 15-50310 included in the application.
5. The additional safety data presented in the CSR for the 52-week extension Study 15-50312 conducted in women without an intact uterus (hysterectomized women) who completed the parent Study 15-50310 included in the application
6. The 120-Day Safety Update received on August 24, 2012.
7. Additional safety data received on November 2, 2012 (requested on October 15, 2012) for actual copies of local and central transvaginal ultrasound reports and local and central endometrial biopsy histology reports.
8. No outstanding Chemistry, Manufacturing and Controls (CMC) or nonclinical pharmacology/toxicology issues.

This reviewer does not recommend approval of 60 mg Osphena™ for the treatment of moderate to severe vaginal dryness, a symptom of vulvar and vaginal atrophy, due to menopause. The data submitted in the application for moderate to severe vaginal dryness is not supportive of approval.

The safety of 60 mg ospemifene tablets, taken orally daily, is not a concern. The review of the original safety data in the application, the Safety Update Report received on August 24, 2012, and the additional safety data received on November 2, 2012 did not demonstrate any overall safety concerns for 60 mg ospemifene.

1.2 Risk Benefit Assessment

Osphena (ospemifene) 60 mg is a non-steroid estrogen agonist/antagonist, also referred to in published literature as a selective estrogen receptor modulator (SERM). Other members of the pharmacological class currently on the market include clomiphene, tamoxifen, raloxifene and toremifene. The pharmacological class has been in extensive use for at least 30 years for a number of varying indications. Different estrogen agonists/antagonists have different tissue effects, depending on their relative estrogenic and anti-estrogenic activity on those tissues. Clomiphene is used predominantly in premenopausal women as an inducer of ovulation; tamoxifen and toremifene are used for the treatment of breast cancer; and raloxifene is used for the treatment and prevention of osteoporosis and for reducing the risk of invasive breast cancer.

The safety information on this class has been established with special attention to the uterus (increased incidence of adenocarcinoma of the endometrium, endometrial hyperplasia, endometrial polyps, endometrial stromal glandular proliferation, and uterine sarcoma), venous thromboembolic events (increased incidence of deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis) in addition to a possible increase in the incidence of thrombotic stroke.

At the time of this review, no structurally non-estrogen product is approved for the proposed indication.

Osphena™ (ospemifene) 60 mg is not currently marketed in the United States or internationally.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarketing risk evaluation and mitigation strategies (REMS) are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarketing requirements and commitments are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Per the Applicant, ospemifene is a non-steroid estrogen agonist/antagonist. The Applicant states that ospemifene exerts an agonistic effect on estrogen receptors in the vagina and bone, is neutral on the uterus, and has anti-estrogenic effect in breast tissue.

Vulvar and vaginal atrophy (VVA) is a condition associated with declining postmenopausal estrogen levels, and is often symptomatic and can be progressive.

The vaginal wall has estrogen receptors, mainly in the basal layers of the epithelium, but also in stromal cells and smooth muscle fibers. Estrogen affects the epithelium, connective tissue and vaginal wall elasticity. Physiologic estrogen concentrations are associated with a thickened and mature vaginal mucosa and increased vaginal blood flow, lubrication, and mechanical sensitivity. Estrogen stimulation produces glycogen used by lactobacilli. Lactic acid produced by the bacteria keeps vaginal pH levels low (from 3.5 to 4.5), which is essential for the body's natural defense against vaginal infections.

The purpose of this application is to obtain marketing authorization for ospemifene in the treatment of moderate to severe vaginal dryness and moderate to severe dyspareunia, both symptoms of vulvar and vaginal atrophy, due to menopause. The proposed dose is 60 mg once daily administered orally.

Per the Applicant, the approval of ospemifene would offer an alternative to estrogens for the management of postmenopausal VVA and provide the only non-estrogen approved treatment for this population.

2.2 Tables of Currently Available Treatments for Proposed Indications

Several estrogen-alone and estrogen plus progestin products are approved for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA) due to menopause. See Section 9 Appendices, Subsection 9.4, Tables of Currently Available Treatments for a VVA Indication for information on currently approved estrogen-alone and estrogen plus progestin products.

At the time of this review, no structurally non-estrogen product is approved for the proposed indication.

2.3 Availability of Proposed Active Ingredient in the United States

Ospemifene is not approved in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Ospemifene is a member of the class of estrogen agonists/antagonists. Other members of the pharmacological class currently on the market include clomiphene, tamoxifen, toremifene and raloxifene. The pharmacological class has been in extensive use for at least 30 years for a number of varying indications, as different SERMs have different tissue effects, depending on their relative estrogenic and anti-estrogenic activity. Clomiphene is used predominantly in premenopausal women as an inducer of ovulation; tamoxifen and toremifene are used for the treatment of breast cancer; and raloxifene is used for the treatment and prevention of osteoporosis and for the prevention of invasive breast cancer.

The safety information on this class has been established with special attention to the uterus (increased incidence of adenocarcinoma of the endometrium, endometrial hyperplasia, endometrial polyps, endometrial stromal glandular proliferation, and uterine sarcoma), venous thromboembolic events (increased incidence of deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis) in addition to a possible increase in the incidence of thrombotic stroke.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

IND 67216 for ospemifene was initially filed on March 25, 2003 by Hormos Medical Corp (Finland). The initial IND submission included a proposed Phase 3, 12-week, double-blind, placebo-controlled study to assess the safety and efficacy of 60 mg and 90 mg ospemifene doses in 450 healthy postmenopausal women. The Sponsor was advised, 1) that ospemifene was as new molecular entity (NME), 2) that clinical trials with ospemifene would need to demonstrate the lowest effective dose, and 3) that the Division of Reproductive and Urologic Products (DRUP) recommends the inclusion of 30 mg, 45 mg, and 60 mg ospemifene doses versus placebo in the initial Phase 3 study.

On October 4, 2005, an End-of-Phase 2 (EOP2) meeting was completed with the Sponsor to discuss the ospemifene development plans. DRUP recommended that:

- The initial Phase 3 study (Study 15-50310) include the 30 mg, 45 mg, and 60 mg ospemifene treatment groups.
- The oral active treatment groups and the placebo treatment group be administered with a vaginal lubricant. DRUP recommended that the Phase 3 study should be double-blinded and double-dummied to demonstrate whether or not an oral drug

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product treatment in combination with a placebo vaginal lubricant showed statistically significant improvement beyond that of either oral placebo drug product or placebo vaginal lubricant alone.

- A Thorough QT_c study be conducted.
- *In-vivo* induction-based interaction studies may be necessary depending on the results of in-vitro studies.
- Effects of ospemifene on CYP2B6 and CYP2D6 substrates, and CYP2C9, CYP2C19 and CYP2B6 inhibitors should be addressed.
- A multi-generational reproductive and development study in at least one species would be required at the time of the NDA application.

A revised Phase 3 protocol for Study 15-50310 was submitted on March 10, 2006 (amended on October 4, 2006), and included the 30 mg and 60 mg ospemifene doses only versus placebo.

A DRUP Advice/Information Request letter, dated January 9, 2007, recommended that subjects be enrolled who met the following inclusion criteria:

- a vaginal pH greater than 5.0.
- no greater than 5% superficial cells on a vaginal smear, and
- at least one moderate to severe symptom of vulvar and vaginal atrophy that the subject has self-identified as most bothersome to her.

In addition, DRUP recommended that:

- each moderate to severe symptom self-identified as most bothersome by the subject be analyzed separately (the Sponsor had proposed to submit a composite analysis of all symptoms).

In a teleconference on April 29, 2008:

- The Sponsor advised DRUP that a PRN vaginal lubricant had been added to all three treatment groups in Study 15-50310. Study 15-50310 was not double-dummied as previously recommended by DRUP. DRUP advised that the proposed study be conducted, as originally proposed for Study 15-50310, to include lubricant in all subjects in a double-blind, double-dummy approach. DRUP indicated that the intent is to demonstrate whether or not oral drug treatment in combination with placebo vaginal lubricant demonstrated statistically significant improvement beyond that of either oral placebo drug product or placebo vaginal lubricant.

The Sponsor stated their belief that allowing use of lubricant as needed represented more of a real world application and that information could be extracted to address the Division's concerns. Based on this discussion, the Division concurred with lubricant use on an as needed basis in the second study as well (Study 15-50821).

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- DRUP advised the Sponsor that the proposed method of analyzing two independent strata (dryness stratum and dyspareunia stratum) was acceptable for the 60 mg ospemifene dose in the second 12-week study (Study 15-50821).
- DRUP recommended that the effects of ospemifene on CYP2B6 be examined *in vivo*.
- DRUP advised the Sponsor that the CMC process change between the Study 15-50310 formulation and the to-be-marketed formulation would require a bioequivalence study.

In the pre-NDA meeting completed on September 29, 2009, the Sponsor was advised that:

- The proposed Integrated Summary of Efficacy (ISE) outline and datasets formats were acceptable.
- The Integrated Summary of Safety (ISS) and the selection of adverse events of particular interest both appeared to be satisfactory. The Sponsor was requested to also present the safety data separately for each Phase 3 study.
- The results of the Thorough QT_c study could not be submitted after the NDA application.
- The results of the *in vivo* study of the effects of ospemifene on substrates for CYP2B6 should be submitted with the NDA.
- The absence of data on the effects of ospemifene in patients with renal impairment would be a review issue (the sponsor confirmed that they did not plan to conduct a renal impairment study).
- The bioequivalence study bridging two formulations should be conducted as a single dose study under fasted conditions. This is generally considered to be the most sensitive *in vivo* setting to test similarity of immediate release formulations. The data from this study should be available in the NDA application.

In a teleconference on April 12, 2011, DRUP re-iterated the recommendations previously provided and confirmed that:

- The Penn 5 formulation used in Study 15-50310 and the (b) (4) 5 formulation used in Study 15-50821 both need to show bioequivalence with the (b) (4) commercial formulation in order to adequately bridge the formulations.
- It is acceptable to submit additional stability data by the 12-Day Safety Update. It is a review issue as to whether your stability package will support a 2-year expiry.
- Additional information on drug product batches manufactured with different (b) (4) content needs to be provided to help determine whether a specification should be set.

2.6 Other Relevant Background Information

No additional relevant background information is available.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Applicant conducted numerous internal audits at participating centers during the ospemifene development program. Study-specific audit certificates are available in the application for 5 Phase 1 pharmacokinetic studies (Studies 15-51030, 15-51031, 15-50716, 15-50719, and 15-50823). Study-specific audit certificates are also available for the following clinical studies: Study 15-50310 (four clinical sites audited including Site # 4633 [R. Garn Mabey, MD], Site # 4617 [Judith Taylor, MD], Site # 4614 [William Koltun, MD], and Site # 3144 [Douglas Young, MD]); Study 15-50821 (9 separate sites including 3 sites visited for compliance audits); and Study 15-50718 conducted in Europe (Site # 16 in Belgium, Site # 23 in Denmark, Site # 43 in Sweden, and Site # 37 in Finland). No corrective action appears to have resulted from these internal audits.

DRUP requested an inspection by the Office of Scientific Investigations (OSI) for the following clinical sites in the U.S. which participated in both of the primary 12-week studies:

1. Site # 1002 for Study 15-50310 and Site # 152 for Study 15-50821; Marina Rackhel, MD, Torrance Clinical Research, Lomita, CA.
2. Site # 4633 for Study 15-50310 and Site # 108 for Study 15-50821; Garn Mabey, MD, Affiliated Clinical Research, Inc., Las Vegas, NV.
3. Site # 1009 for Study 15-50310 and Site # 183 for Study 15-50821; R. Hal Younglove, MD, Radiant Research, Overlook Park, KS.

Medical Officer's Comments:

On December 18, 2012, OSI provided an evaluation of clinical inspections for Dr. Marina Rackhel (Site # 1002 for Study 15-50310 and Site # 152 for Study 15-50821), Dr. R. Hal Younglove (Site # 1009 for Study 15-50310 and Site # 183 for Study 15-50821), and Dr. Garn Mabey (Site # 4633 for Study 15-50310 and Site # 108 for Study 15-50821). A Form FDA 483 was not issued at the conclusion of the inspection of Dr. Marina Rackhel and Dr. R. Hal Younglove. A review of the respective records revealed no significant discrepancies or regulatory violations. For Dr. Marina Rackhel, the inspection report indicates, "The study appears to have been conducted adequately,

and the data submitted by this site may be used in support of the respective indication.” For Dr. R. Hal Younglove, the inspection report indicates, “The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.”

A Form FDA 483 was issued at the conclusion of the inspection of Dr. Garn Mabey. Per the OSI inspection report, observations for Study 15-50310 included:

- *Five (5) subjects (Subjects 002, 005, 007, 008, and 009) with transvaginal ultrasound (TVU) examinations that were initially confirmed by a local radiology group rather than by the protocol-required central read facility. Subsequently, the central reader confirmed that these subjects met appropriate inclusion criteria.*
- *Ten (10) subjects with visits 3 to 15 days out-of-window of the protocol specified time-period due to delayed diagnostic results with respect to TVU findings.*
- *Seven (7) subjects did not sign the most recent version (4/27/06) of the informed consent form at the time of their visits.*

A Form FDA 483 was also issued at the conclusion of the inspection of Dr. Garn Mabey for Study 15-50821:

- *Subject 026 did not meet inclusion criterion # 10 requiring moderate to severe vaginal dryness or dyspareunia as the self-reported MBS at screening and randomization. She was randomized and completed Study 15-50821.*
- *Subject 057 was randomized to the study prior to the receipt of documentation of a negative endometrial biopsy, a criterion for study entry.*

Per the OSI inspection report, Dr. Mabey responded adequately to the inspection findings in a letter dated October 24, 2012, in which he committed to the implementation of additional staff training and study practices to eliminate the recurrence of the findings noted above. Per the OSI Assessment of Data Integrity:

“The observations noted above for Dr. Mabey’s clinical site are pending a final review of the Establishment Inspection Report (EIR) and sign-off on the letter to Dr. Mabey. An inspection summary addendum will be generated if conclusions change upon review of the EIR.”

“The review division may wish to consider the exclusion of the data for Subject 026 in Protocol 15-50821 as this subject met an exclusion criterion but was randomized anyway and completed the study; otherwise, the deviations noted above would not appear to have significant effect on data quality or subject safety. Other than the deviations noted above, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.”

This reviewer does not recommend exclusion of the data for Subject 026 in Study 15-50821. VVA effectiveness is evaluated by mean change from baseline in the self-reported MBS. A review of the efficacy data reported for Subject 026 does not raise any concerns.

No addendum to the EIR was received as of the date of this review.

OSI also completed an inspection of Shionogi USA, Inc., particularly the Applicant's oversight over the clinical trials and the monitoring practices over the investigator sites. The monitoring files for Sites 1002, 4633, and 1009 for Study 15-50310 and Sites 152, 108, and 183 for Study 15-50821 were reviewed. Adverse event reporting, electronic data capture (used only for Study 15-50821), and documentation of the final disposition of the investigational product (IP) were also reviewed.

A Form FDA 483 was issued at the conclusion of the inspection for the following observation:

- Failure of the Applicant to obtain in writing the final disposition of all returned and unused IP. There was no documentation regarding the final disposition of approximately 1124 bottles of the IP for Study 15050310 and approximately 1296 bottles of IP for Study 15-50821.

Per the OSI Clinical Inspection Summary, the Applicant responded in writing in a letter dated November 13, 2012. Per the Applicant, "the previous sponsor did not obtain a written statement regarding the disposition of IP from the responsible CRO." Updated SOPs have been submitted by the Applicant that "should address the need for written documentation of IP disposition for future studies." "Other than the deficiency regarding documentation of the disposition of IP as noted above, the studies appear to have been conducted adequately, and the data submitted by the sponsor appear acceptable in support of the respective indication. The observations noted above for Shionogi are pending a final review of the Establishment Inspection Report (EIR) and sign-off on the letter to the firm. An inspection addendum will be generated if conclusions change upon review of the EIR."

Medical Officer's Comments:

No addendum to the EIR was received as of the date of this review.

3.2 Compliance with Good Clinical Practices

Twelve-week Study 15-50310 and Study 15-50821, 52-week Study 15-50718, 40-week extension study 15-50310X and 52 weeks, open-label extension Study 15-50312 all appear to have been conducted in accordance with the ethical principles originating

from the Declaration of Helsinki and undertaken in accordance with the principles of Good Clinical Practice (GCP) as set forth in the International Conference on Harmonization Guidelines for GCP (ICH-E6). Written informed consent, approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), was obtained for all subjects.

Three sites were visited, during the development program, for compliance audits: IMPACT Clinical Trials, Los Angeles, CA (Study 15-50821), Columbia Center for Women's Health Research, Inc., Columbus, OH (Study 15-50821), and Radiant Research, Chicago, IL (Study 15-50310).

The Debarment Certification dated April 17, 2012, available in the application states, "Shionogi Inc., hereby certifies that it did and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application for Ospemifene."

3.3 Financial Disclosures

Per the application, each listed Principal Investigator and Sub-Investigator for Studies 15-50310, 15-50310X, 15-50718, 15-50821, and 15-50312 did not disclose any "proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b)", dated April 26, 2012. There were, however, missing financial certifications and disclosures for 4 Principal Investigators and 8 Sub-Investigators.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Ospemifene is an estrogen agonist/antagonist that belongs to the substituted triphenyl chloroethane class, and is a white to off-white, crystalline powder. Per the Applicant, ospemifene is a Class II drug substance with low solubility-high permeability (per the Biopharmaceuticals Classification System). Ospemifene is manufactured by (b) (4)

Per the Applicant, the aim of formulation development was to develop an immediate release film-coated tablet containing 60 mg ospemifene as drug substance. Film-coating of the tablets was preferred because of the unpleasant taste of the drug substance. A capsule formulation was used in Phase 1 and Phase 2 clinical studies (Studies 1506001 and 156002). A tablet formulation was used in Phase 2 Study 15-

50717 and in all Phase 3 Studies. The *in vitro* dissolution profile of the tablet formulation is comparable to the capsule formulation.

The drug product, 60 mg ospemifene tablets, is a white to off-white, oval, film-coated, biconvex tablet, with one side engraved “60”. Penn Pharmaceuticals Services Ltd., located in the United Kingdom, will manufacture the to-be-marketed drug product.

The excipients in 60 mg ospemifene tablets are pregelatinized starch (b) (4), mannitol (b) (4), povidone (b) (4), sodium starch glycolate (b) (4), microcrystalline cellulose (b) (4), colloidal silicon dioxide (b) (4), magnesium stearate (b) (4). The ospemifene tablets are coated (b) (4) hypromellose, titanium dioxide, lactose monohydrate, (b) (4), (b) (4).

(b) (4) The active and placebo tablets were identical in size, weight, taste, and color.

See the Chemistry, Manufacturing, and Controls (CMC) Review for additional CMC information.

4.2 Clinical Microbiology

No Clinical Microbiology review was conducted for the NDA application. The ospemifene drug product does not contain anti-microbial preservatives. Per the Chemistry Review, dated December 12, 2012, the microbial testing of the registration batches of ospemifene was performed according to USP <61> and USP <62>.

4.3 Preclinical Pharmacology/Toxicology

Ospemifene was first documented as a metabolite of toremifene which is approved for the treatment of advanced ER-positive breast cancer. Per the Applicant, “the pharmacodynamics of ospemifene resembles other approved estrogen agonist/antagonist including raloxifene and tamoxifen.” Per the Applicant, ospemifene has an “estrogen-like effect on the vaginal mucosa”, “estrogen-like effect on bone”, and “partial agonist-antagonist estrogen-like effects are seen in the uterus”. Per the Applicant, ospemifene “appears to profile as a full antiestrogen” in the mammary gland.

Ospemifene has two pharmacologically active main human metabolites M-1 (4-hydroxyospemifene) and M-2 (4'-hydroxyospemifene). M-1 is considered to be a major and M-2 a minor metabolite (exposures 25% and 7%, respectively, of the parent drug). Ospemifene binds to human ER α and ER β with essentially comparable affinity.

Per the application, a full program of toxicology studies were completed in mouse, rat, rabbit, hamster, minipig, dog, and monkey, with the focus on rat and monkey. “Ospemifene was well tolerated in all toxicology studies.”

Medical Officer’s Comments:

Per the Pharmacology/Toxicology Review, dated January 15, 2013, in “rats, mice, female dogs, and female monkeys, there were no unexpected toxicities noted. The main effects noted were related to the exaggerated pharmacological effect of ospemifene on reproductive organs”:

- *“The ovary, uterus, mammary gland, and male reproductive organs showed a predominantly antagonistic profile, whereas the vagina and liver showed agonism.”*
- *“Vaginal mucification was noted in rats and monkeys.”*
- *“The mammary gland showed sex- and species-specific effects, considered to be pharmacological and predominantly antagonistic in female rats and monkeys.”*
- *“In rats and female monkeys, increased liver weight correlated with centrilobular hepatocyte hypertrophy and enzyme changes. These findings are consistent with induction of CYP enzymes that metabolize ospemifene and M1.”*

Per the application, the embryo-fetal studies with ospemifene “did not reveal any teratogenic effects and no evidence of mutagenicity, clastogenicity, or genotoxicity *in vitro* or *in vivo* was detected in the studies performed.”

Medical Officer’s Comments:

Per the Pharmacology/Toxicology Review, “Ospemifene was embryotoxic and adversely affected parturition. There were development effects noted in the offspring of pregnant rats. These effects were noted at exposures significantly lower than human exposures. In rabbits, the exposure was 10-fold over proposed clinical dose based on body surface area.”

“Embryofetal toxicity (EFT) studies were conducted with rats and rabbits. In rats, an increase in placental weight and an increased number of testicular displacements among pups was noted. In rabbits, an increase in total resorption was noted that correlated with decreased number of live fetuses and an increase in post-implantation loss.” In a pre- and post-natal development study conducted in rats:

- *“There was increased maternal mortality and total litter loss preceded by clinical signs of difficult parturition such as dystocia, vaginal bleeding, ruffled fur, lethargy, hypothermia, and/or uterine prolapse.”*
- *“Gestational duration increased, consistent with mortality, prolapse, and dystocia.”*

- *“There was a significant decrease mean viable pups born and increased post-implantation loss (total and %), and non-significant increase in number of litters with dead pups compared to control.”*

Per the Pharmacology/Toxicology Review, “The weight of the evidence suggests that ospemifene is not genotoxic. Ospemifene was negative on the in vitro Ames and mouse lymphoma cell assay and in the in vivo mouse micronucleus and rat liver DNA adduct assays. There were no structural alerts for ospemifene or the M1 and M2 metabolites.”

Per the application, “In the 2-year carcinogenicity study in mice and rats, the male mice developed scrotal herniation and severe abdominal swelling during the first months of dosing. This resulted in unscheduled study termination at 27 weeks in the male mice. Female mice and rats (both genders) tolerated ospemifene well for 104 weeks. Survival rate was slightly higher in ospemifene-treated rats than in controls. Type of tumors and their incidences were comparable to those seen in the oncogenicity studies with other SERMs. The exception were thymic tumors (most benign), which were often seen in ospemifene-treated rats. The toxicological and oncogenic profiles indicate that ospemifene is unlikely to cause any major untoward pathological findings in any organs or tissues in clinical use in postmenopausal women.”

Medical Officer’s Comments:

Per the Pharmacology/Toxicology Review, “ospemifene is tumorigenic to rodents based on the findings from the rat and mouse 2-year carcinogenicity studies.” “The exposure multiples in rats and mice was 1- and 5-fold, respectively, over clinical exposure at the proposed dose.” “In general, there was only a minimal dose-relationship in the tumor findings”:

- *“In both rats and female mice, there were significant neoplastic increases in the liver and ovary.”*
- *“Mice had significant neoplastic increases in adrenal and liver.”*
- *“Rats had significant increases in liver, spleen and thymus neoplasms.”*

“Except for skin, both neoplastic and non-neoplastic treatment-related effects in estrogen target organs” “were consistent with the established ospemifene pharmacology/toxicology or other mixed estrogen agonist/antagonist”.

Per the Pharmacology/Toxicology Review, “The nonclinical findings support Approval from a pharm/tox perspective for the treatment of moderate to severe VVA in postmenopausal women at a daily dose of 60 mg.” See the Pharmacology/Toxicology Review, dated January 15, 2013, for additional preclinical information.

Medical Officer's Comments:

This reviewer agrees with the Pharmacology/Toxicology reviewer's recommendation that nonclinical findings support the approval of 60 mg ospemifene.

4.4 Clinical Pharmacology

Per the application, the ospemifene development program is comprised of 21 Phase 1 studies that included healthy male subjects, healthy postmenopausal female subjects, subjects with hepatic impairment, and subjects with renal impairment.

4.4.1 Mechanism of Action

Ospemifene is an estrogen agonist/antagonist. Its biological actions are largely mediated through binding to the estrogen receptors ER α and ER β . This binding results in activation of estrogenic pathways in some tissues (agonist effect) and blockage of estrogenic pathways in other tissues (antagonist effect).

Per the application, ospemifene is a biopharmaceutical class II compound with low solubility and high permeability. This profile is not mediated by P-glycoprotein active transport in the cell membranes. The human absolute bioavailability is not known, due to poor solubility of ospemifene in intravenous formulations. Per the Applicant, "concomitant food intake will increase the bioavailability of ospemifene tablets approximately 2-fold, most likely due to the dissolving effect of the biliary secretion." In the primary Phase 3 clinical trials, ospemifene was administered with food.

4.4.2 Pharmacodynamics

Study 15-50921 evaluated the PK of ospemifene in the presence of renal insufficiency in postmenopausal women. Study 15-50921 was a Phase 1, open-label, single dose (60 mg ospemifene) PK study that included 8 subjects with severe renal impairment (creatinine clearance < 30 mL/min) and 8 matched healthy control subjects. The mean (SD) AUC_{0-inf} in subjects with severe renal impairment versus healthy control subjects were 10141 (4144) ng.hr/mL and 8073 (2296) ng.hr/mL, respectively. The geometric mean ratio (severe renal impaired/healthy controls) for ospemifene AUC_{0-inf} was 119.6% with a corresponding 90% CI of 81.4% to 175.9%; for ospemifene C_{max} was 79.3% with a corresponding 90% CI of 52.9% to 119.0%. There was an approximate 16% increase in the AUC_{0-inf} ratio of 4-hydroxyospemifene (major metabolite) to ospemifene in subjects with severe renal impairment.

Medical Officer's Comments:

Study 15-50921 results show no clinically important PK differences between subjects with severe renal impairment and control subjects with normal function. Per the Applicant, "These results suggest that no modification of dosing in patients with renal impairment should be required."

Per the Clinical Pharmacology Review, dated January 12, 2013, "Several renal impairment and End-Stage Renal Disease (ESRD) did not significantly impact the systemic exposure of a single 60 mg dose of ospemifene. In subjects with severe renal impairment and ESRD, mean C_{max} , AUC_{0-t} , and AUC_{0-inf} for ospemifene were lower by 21%, higher by 19%, and higher by 20%, respectively. Half-life was the same at about 34 hrs in patients with severe renal impairment and ESRD and normal renal function subjects. These results are expected based upon the known clearance pathway for ospemifene, which is primarily through hepatic metabolism, and fecal and urinary excretion."

Two Phase 1 studies were conducted to evaluate hepatic insufficiency on the PK of ospemifene in postmenopausal women (Study 15-50820 and Study 15-50920).

Study 15-50820 was a Phase 1, open-label, single-dose (60 mg ospemifene), PK study that included 7 subjects with mild hepatic impairment (Child-Pugh Class A), 2 subjects with moderate hepatic impairment (Child-Pugh Class B), and 7 healthy control subjects with normal hepatic function. The mean (SD) AUC_{0-inf} was reported as:

- 6650 (1840) ng.hr/mL in subjects with mild hepatic impairment versus 7190 (1650) ng.hr/mL in healthy subjects.

The individual AUC_{0-inf} for the 2 subjects with moderate hepatic impairment was 10400 ng.hr/mL and 16100 ng.hr/mL. Based on this very limited sample of individuals with moderate hepatic impairment, results suggest that the AUC_{0-inf} in subjects with moderate hepatic impairment was about 50% higher than in healthy control subjects with normal hepatic function or mild hepatic impairment.

Study 15-50920 was a Phase 1, open-label, single-dose (60 mg ospemifene), PK study that included 8 subjects with moderate hepatic impairment (Child-Pugh Class B) and 8 healthy control subjects with normal hepatic function. The mean (SD) AUC_{0-inf} was reported as:

- 9765 (4592) ng.hr/mL in subjects with moderate hepatic impairment versus 6893 (1677) ng.hr/mL in healthy subjects.

Medical Officers Comments:

Only a total of 16 subjects participated in each study (Study 15-50820 and 15-50920). This number is too small to draw any conclusions regarding 60 mg ospemifene and hepatic impairment.

In Study 15-50920, the AUC_{0-inf} of ospemifene in subjects with moderate hepatic impairment was higher than in the control subjects. Based on this information, however, the Applicant concludes that the changes observed in Study 15-50920 are “not considered to be clinically significant in consideration of large pharmacokinetic variability of ospemifene in addition to safety data from subjects studied up to 90 mg”, and that “no dose adjustment is necessary in patients with mild to moderate (Child-Pugh Class A and B) hepatic impairment.”

Per the Clinical Pharmacology Review, subjects with normal hepatic function and patients with mild hepatic impairment had similar mean C_{max} , AUC_{0-t} , and AUC_{0-inf} for ospemifene. In patients with mild hepatic impairment, mean C_{max} , AUC_{0-t} , and AUC_{0-inf} for ospemifene were lower by 21%, 6.1%, and 9.1%, respectively. Moderate hepatic impairment had a slightly greater effect on ospemifene exposure compared to mild hepatic impairment. Overall, the effect of moderate hepatic impairment was not significant following a single 60 mg dose of ospemifene. In patients with moderate hepatic impairment, mean C_{max} was essentially the same. AUC_{0-t} and AUC_{0-inf} for ospemifene were higher by ~28%, compared to subjects with normal hepatic function. In the context of inter-subject variability of approximately 30%, the change in AUC_{0-inf} in patients with moderate hepatic impairment is not significant.”

The proposed labeling submitted for 60 mg ospemifene includes the following information,

 (b) (4)

Clinical Pharmacology recommends proposed labeling for 60 mg ospemifene that includes the following under Section 8 USE IN SPECIFIC POPULATIONS, Subsection 8.7 Hepatic Impairment:

“Do not use in women with severe hepatic impairment. The pharmacokinetics of ospemifene has not been studied in women with severe hepatic impairment (Child-Pugh Class C).”

“No clinically important pharmacokinetic differences with OSPHENA were observed between women with mild to moderate hepatic impairment and healthy women [see Clinical Pharmacology (12.3)].”

“No dose adjustment of OSPHENA is required in women with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.”

4.4.3 Pharmacokinetics

Seven (7) clinical pharmacokinetic (PK) studies were conducted to characterize the biopharmaceutic properties of ospemifene:

1. Study 1506004, a formulation comparison study, was conducted to assess the relative bioavailability of tablet ((b) (4) formulation) compared to capsule (b) (4)
2. Study 15-50208, investigated the effect of food (fasted; fed with high fat) on ospemifene pharmacokinetics of the (b) (4) formulation after a single dose of 60 mg of ospemifene,
3. Study 15-51030 evaluated the comparative bioavailability of five 60 mg ospemifene tablets manufactured at two different manufacturing sites (1 formulation from Penn Pharmaceuticals, UK, and 4 formulations from (b) (4)) under the fasted state.
4. Study 15-50926 evaluated the bioequivalence of 60 mg ospemifene tablets manufactured at two different manufacturing sites (Penn Pharmaceuticals, UK [batch number 0249A] and (b) (4) [batch number 85518] in the fasted state.
5. Study 15-51028 determined the bioequivalence of 60 mg ospemifene tablets manufactured at two different manufacturing sites (Penn Pharmaceuticals, UK [batch number 0249A used in Study 15-50310] and (b) (4) [batch number 85481 intended for commercial use]) in the fasted state.
6. Study 15-51029 determined the bioequivalence of 60 mg ospemifene tablets manufactured at two different manufacturing sites (Penn Pharmaceuticals, UK [batch number 0249A used in Study 15-50310] and (b) (4) [batch number 85481] in the fed state.
7. Study 15-51031 determined the bioequivalence of two 60 mg ospemifene tablets used in the pivotal Phase 3 clinical trial (Study 15-50310) and (b) (4) (batch number A07006 used in Study 15-50821) in the fasted state.

Medical Officer’s Comments:

Studies 15-50926, 15-51028, and 15-51029 did not meet the criteria to establish bioequivalence.

Study 15-51031 showed that the (b) (4) 60 mg ospemifene tablet (batch number A07006) was bioequivalent to the Penn Pharmaceuticals 60 mg ospemifene tablet (batch number 0249A) after administration under fasted conditions.

The tablets used in the two Phase 3 studies were manufactured at different sites (Study 15-50310 used the Penn Pharmaceuticals tablet; Study 15-50821 used the (b) (4) tablet).

The Applicant concludes that the tablet manufactured by Penn Pharmaceuticals used in Study 15-50310 (intended for commercial use) was shown to be bioequivalent to the (b) (4) tablet used in Study 15-50821. Per the Applicant, in Study 15-50310 and Study 15-50821, “ospemifene was administered with food without regard to the type of food (although the fat content of food would affect the bioavailability of ospemifene). It would be appropriate to label ospemifene, if approved, for administration with food without regard to the type of food.”

Per the Clinical Pharmacology Review, dated January 12, 2013, “Pharmacokinetic results show that Penn and (b) (4) ospemifene formulations are comparable. The mean C_{max} for Penn formulation and (b) (4) formulation was 533 and 501 ng/mL, respectively. The mean AUC_{0-t} for Penn formulation and (b) (4) formulation was 3781 and 4661 ng.hr/mL, respectively. The mean AUC_{0-inf} for Penn formulation and (b) (4) formulation was 4165 and 3982 ng.hr/mL, respectively. Median T_{max} for Penn formulation and (b) (4) formulation was 2.0 hrs. Mean $T_{1/2}$ for Penn and (b) (4) formulations was 26.4 hrs. Although the C_{max} for Penn tablets is higher than for (b) (4) tablets, the associated 90% CIs for C_{max} , AUC_{0-t} , and AUC_{0-inf} all fell within 80% to 125%. Penn ospemifene 60 mg tablets (Lot No. 0249A) and (b) (4) ospemifene 60 mg tablets (Lot No. A07006) are bioequivalent.” See the Clinical Pharmacology Review for additional information.

Clinical Pharmacology recommends proposed labeling for 60 mg ospemifene that includes the following under Section 12 CLINICAL PHARMACOLOGY, Subsection 12.3 Pharmacokinetics, Food Effect:

“In general, food increased the bioavailability of ospemifene by approximately 2-3 fold. In a cross-study comparison, single dose OSPHENA 60 mg tablet administered with a high fat/high calorie meal (860 kcal) in postmenopausal women increased C_{max} and AUC_{0-inf} by 2.4- and 2.1-fold, respectively, compared to fasted condition. Elimination half-life and time to maximum concentration (T_{max}) were unchanged in the presence of food. In two food effect studies in healthy males using different ospemifene tablet formulations C_{max} and AUC_{0-inf} increased by 2.3- and 1.9-fold, respectively, with a low fat/low calorie meal (300 kcal) and increased by 3.5- and 2.6-fold, respectively, with a high fat/high calorie meal (860 kcal), compared to fasted condition. OSPHENA should be taken with food [see Dosage and Administration (2.1)].”

Other Clinical Studies Assessing Pharmacokinetics:

The safety, tolerability and pharmacokinetics of ospemifene capsules was investigated, initially in males in a single dose study within the dose range of 10 mg to 800 mg, and subsequently in a 12-week once daily repeat dose study (doses of 25 mg, 50 mg, 100 mg and 200 mg versus placebo) in healthy postmenopausal women (8 subjects on active drug and 2 subjects on placebo at each dose level) in the fasted state (Study 1506003 conducted in Finland) and fed state (Study 15-50927).

On the average, 2.1-fold accumulation of ospemifene was observed after once daily administration in Study 1506003. Steady state was attained within 6 weeks (the next sampling after the first dose) and persisted until week 12.

Medical Officer's Comments:

Ospemifene pharmacodynamic effects on the endometrium were evaluated via endometrial biopsy in 12-week Study 1506003. The reported results demonstrate the following:

- *25 mg ospemifene dose; endometrial biopsy for all subjects reported as atrophic at Baseline and Week 12*
- *50 mg ospemifene dose; endometrial biopsy for Subject # 20 reported as proliferative endometrium Class I (perceptible estrogen effect) at Week 12*
- *100 mg ospemifene dose; endometrial biopsy for Subject # 33 and Subject # 38 reported as proliferative endometrium Class I (perceptible estrogen effect) at Week 12*
- *200 mg ospemifene dose; endometrial biopsy for Subject # 40 and Subject # 44 reported as proliferative endometrium Class II (moderate estrogen effect) at Week 12*
- *Placebo group; endometrial biopsy for Subject # 48 reported as proliferative endometrium Class I (perceptible estrogen effect) at Week 12*

Two (2) of the 40 subjects in Study 1506003 discontinued treatment. One (1) subject was hospitalized for gallbladder stones and pancreatitis (Subject # 25 at the 200 mg ospemifene dose; causality unlikely), and 1 subject discontinued due to severe hot flushes, dizziness and chest pain (Subject # 43; causality probable; ECG normal).

Study 15-50927 was an open-label, single dose (60 mg ospemifene tablets) and steady state PK study conducted in Finland. Twelve (12) healthy postmenopausal women received 60 mg ospemifene tablets once daily after a meal for 9 days. The single dose and steady state PK of ospemifene and its 2 main metabolites (4-hydroxyospemifene and 4'-hydroxyospemifene) were assessed. On days 7, 8, 9 and 10, no statistically significant difference was seen in the mean pre-dose concentration for ospemifene and its 2 metabolites, indicating that steady state was reached by day 7. The systemic

exposure of 4-hydroxyospemifene was 25% of that of ospemifene, and the corresponding systemic exposure of 4'-hydroxyospemifene was 7%.

To investigate the absorption, distribution, metabolism and excretion of ospemifene, a mass balance study was conducted with (³H)-radiolabeled ospemifene (Study 15-50206). Per the reported results, ospemifene was rapidly absorbed (T_{max} of 0.75 to 3 hours) and eliminated (plasma, urine and feces) with a mean apparent terminal elimination half-life ($t_{1/2}$) of approximately 25 hours.

A Thorough Q_t/Q_{T_c} study was conducted to assess the effect of repeated doses of therapeutic or supra-therapeutic doses (4x) of ospemifene on Q_T/Q_{T_c} interval prolongation (Study 15-50824). See Subsection 7.4.5 Special Safety Studies/Clinical Trials for a discussion of Study 15-50824.

Medical Officer's Comments:

See the Clinical Pharmacology Review for additional information on clinical pharmacology studies conducted during the development program for NDA 203505.

The Division of Cardiovascular and Renal Products, QT Interdisciplinary Team, was requested to review the final study report for Study 15-50824 included in the NDA application. See the consultation response regarding Study 15-50824 in Subsection 7.4.4 Electrocardiograms (ECGs) of this review

Per the Clinical Pharmacology review, "The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3) has reviewed NDA 203505 for ospemifene 60 mg oral tablets submitted to the Agency on April 26, 2012. We found this NDA Acceptable from a Clinical Pharmacology perspective provided that an agreement is reached between the sponsor and the Division regarding the labeling language." See the Clinical Pharmacology Review, dated January 12, 2013, for additional clinical pharmacology information.

Medical Officer's Comments:

This reviewer agrees with the Clinical Pharmacology reviewer's recommendation that NDA 203505 is acceptable from a clinical pharmacology perspective. This reviewer also agrees with the Clinical Pharmacology reviewer's recommendations for 60 mg ospemifene labeling.

5 Sources of Clinical Data

5.1 Listing of Studies/Clinical Trials

The Applicant completed one Phase 2 dose-ranging 12-week study (Study 15-50717). The Applicant completed three Phase 3 clinical studies to support the use of the once-daily 60 mg ospemifene dose for the treatment of moderate to severe vaginal dryness and moderate to severe dyspareunia, symptoms of vulvar and vaginal atrophy (VVA), due to menopause. The three completed Phase 3 studies are:

1. Study 15-50310
2. Study 15-50821
3. Study 15-50718

In addition, the Applicant completed 2 safety extension study following completion of the parent 12-week Study 15-50310:

- Study 15-50310X included women with uteri in a 40-week safety extension study (total of 52 weeks), and
- Study 15-50312 included women without uteri in a 52-week safety extension study (total of 64 weeks).

5.2 Review Strategy

The available clinical data for 12-week Phase 2 Study 15-50717, 12-week Phase 3 Studies 15-50310 and 15-50821, 52-week Phase 3 Study 15-50718, the 40-week safety extension Study 15-50310X, and the 52-week safety extension Study 15-50312 provides the basis for consideration regarding the safety and efficacy of 60 mg ospemifene for the treatment of moderate to severe vaginal dryness and dyspareunia, symptoms of vulvar and vaginal atrophy, due to menopause.

5.3 Discussion of Individual Studies/Clinical Trials

Phase 2 Study 15-50717:

Study 15-50717 entitled, “Efficacy and Safety of Ospemifene in the Treatment of Vulvar and Vaginal Atrophy (VVA) in Postmenopausal Women: A Phase II Dose-Ranging, 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing Oral Ospemifene 5 mg, 15 mg and 30 mg Daily Doses With Placebo” was

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initiated on August 9, 2007 and completed February 11, 2008. Study 15-50717 was conducted at 9 centers in Finland. The mean age of study participants was 62.4 years of age (range 49 to 79 years of age); all were Caucasian.

The primary objectives of Study 15-50717 were to assess efficacy, safety, and tolerability of 5, 15, and 30 mg of ospemifene in the treatment of VVA in postmenopausal women. The primary efficacy endpoints included:

- changes in superficial and parabasal cells at week 12,
- change in vaginal pH at week 12.

The secondary efficacy endpoints included:

- changes in superficial and parabasal cells at week 4,
- change in vaginal pH at week 4,
- changes in visual evaluation of the vaginal at weeks 4 and 12, and
- changes in serum hormone concentrations at week 12.

A total of 126 subjects were randomized to 1 of 4 treatment groups:

- Ospemifene 5 mg per day (manufactured by (b) (4))
- Ospemifene 15 mg per day (manufactured by Penn Pharmaceutical Services)
- Ospemifene 30 mg per day (manufactured by Penn Pharmaceuticals Services)
- Placebo per day (manufactured by Penn Pharmaceuticals Services)

Suitable subjects who gave written informed consent were screened for eligibility for the study. Subjects were eligible for the study if they met all of the following inclusion criteria at Screening and before Randomization:

1. Provided written informed consent to participate in the study, and agreed to follow the dosing instructions and complete all required study visits.
2. A woman 40 to 80 years of age at randomization.
3. Postmenopausal defined as:
 - at least 12 months since the previous spontaneous menstrual bleeding. If there was any uncertainty about the time of the last spontaneous bleeding, the postmenopausal status was confirmed with FSH levels > 40 IU/L and estradiol levels < 0.20 nmol/L, or
 - had a hysterectomy with intact ovaries and a serum FSH level > 40 IU/L and an estradiol level < 0.20 nmol/L, or
 - was at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy.
4. Hysterectomized, or had an intact uterus with an endometrial thickness < 4 mm determined by the Screening transvaginal ultrasound (TVU).

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5. Hysterectomized, or had no evidence of hyperplasia, cancer or other pathology from the endometrial biopsy at Screening.
6. Documented negative (for malignancy) mammogram that was obtained at Screening or within 9 months prior to randomization. Normal clinical breast examination at Screening.
7. Documented negative PAP test result at Screening, or within 9 months prior to Randomization or no intact cervix.
8. Five percent (5%) or fewer superficial cells on the vaginal smear.
9. Vaginal pH > 5.0.

Subjects were excluded from the study if they met any of the following criteria:

1. Clinically significant abnormal findings in physical examination at Screening.
2. BMI ≥ 37 mg/m².
3. Systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 100 mmHg.
4. Clinically significant abnormal gynecological findings other than signs of vaginal atrophy (e.g., uterine or vaginal prolapse of Grade 2 or higher).
5. Uterine bleeding of unknown origin.
6. Uterine polyps.
7. Symptomatic or large uterine fibroids (estimated size > 3 cm).
8. Vaginal infection requiring medication.
9. Clinically significant abnormal findings on the Screening ECG, as assessed by the investigator.
10. Intake of any of the following hormonal medications:
 - vaginal hormonal products (rings, creams, gels) within 14 days prior to Screening procedures, or
 - oral or transdermal estrogen and/or progestin therapy within 60 days prior to screening procedures, or
 - intrauterine progestin therapy within 60 days prior to screening procedures.
 - progestin implants or estrogen-alone injectable drug therapy within 90 days prior to Screening procedures, or
 - progestin injectable drug therapy within 6 months prior to screening procedures.
11. Intake of a SERM (e.g., raloxifene, tamoxifen, toremifene, or clomiphene), tibolone or any other medications that were expected to have clinically significant estrogenic or antiestrogenic vaginal effects, within 60 days prior to Screening procedures.
12. Regular use of herbal or dietary supplements, including black cohosh, soy (including the use of soy milk), phytoestrogens or over-the-counter agents thought to have estrogenic vaginal effects, within 30 days prior to Screening procedures.
13. Current use of heparin, itraconazole, ketoconazole or digitalis alkaloids.
14. Clinically relevant abnormal findings in any safety laboratory tests.
15. Liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) more than twice the upper limit of normal for the testing laboratory.
16. Heterozygous or homozygous for Factor V Leiden test at Screening.

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17. Suspicion of malignancy on mammography, clinical suspicion of any other kind of malignancy, or history of malignancy within 10 years. A history of basal cell carcinoma was allowed.
18. Consumption of more than 14 drinks containing alcohol per week.
19. Current or history of severe renal or hepatic impairment.
20. Current or history of thromboembolic or blood coagulation disorder.
21. Current or history of cerebrovascular incident (e.g., bleeding, stroke or transient ischemic attack).
22. Physical or mental condition that, in the opinion of the investigator, might have interfered with the subject's ability to comply with the study procedures.
23. Participation in another clinical intervention study within 30 days of Screening.
24. Previous participation in any clinical study of ospemifene.

Medical Officer's Comments:

Limited efficacy data was generated from Study 15-50717, based on the enrollment criteria utilized, which did not include all of the Agency's recommended co-primary endpoints for a VVA indication.

For a subject to be included in the efficacy analysis for a VVA indication, the Agency's 2003 draft Guidance for Industry entitled "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation" recommends that she have identified at baseline at least one individual moderate to severe symptom of vulvar and vaginal atrophy that is most bothersome to her and have a baseline percentage of superficial cells that does not exceed 5% and have a vaginal pH greater than 5.0. In Study 15-50717, only two of the three recommended inclusion criteria were included - 5% or fewer superficial cells on the vaginal smear and a vaginal pH > 5.0.

Subjects were screened for Factor V Leiden in this study. If documented heterozygous or homozygous positive, these subjects were excluded. Because routine screening for Factor V Leiden is not currently recommended, the exclusion of heterozygous or homozygous positive may have influenced the study outcome relative to the general population.

Per the application, no subject was positive for Factor V Leiden at Screening in Study 15-50717.

At the Screening visit (Visit 1), demography, medical history and concomitant medications were recorded, vital signs (blood pressure and pulse), weight and height were recorded, body mass index (BMI) was calculated, and subjects underwent a full physical examination, breast examination, gynecological examination (evaluation of uterine prolapse [Grade 0, normally positioned cervix to Grade 4, halfway or greater outside the hymenal ring], evaluation of vaginal prolapse [Grade 0, normal to Grade 4,

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clearly visible outside]), visual evaluation of the vagina (petechiae, pallor, friability, vaginal dryness, and redness seen in the vaginal mucosa), vaginal pH measurement (pH indicator strip), vaginal smear (sample from the lateral vaginal wall evaluated at the central pathology laboratory who performed the cell count to determine the proportions of parabasal, intermediate, and superficial cells), cervical Papanicolaou (PAP) smear (analyzed by a pathologist at the central pathology laboratory), transvaginal ultrasound (TVU performed locally) for endometrial thickness, endometrial biopsy (normal or atrophic endometrial histology were eligible for randomization; insufficient tissue specimen and TVU thickness < 4 mm were eligible for randomization), mammography (unless normal mammogram documented in the previous 9 months), 12-lead electrocardiogram (ECG), blood sample for assay of hormone levels (estradiol, FSH, LH, and SHBG), and clinical laboratory safety screen (clinical chemistry, hematology, urinalysis, and Factor V Leiden).

Visit 2 (Day 1) was the Baseline visit and took place within 14 days of the Screening visit. Eligibility checked, and suitable subjects were randomized in equal proportions to 1 of 4 treatment groups: ospemifene 5 mg, ospemifene 15 mg, ospemifene 30 mg, and placebo. Study participants were instructed to take study medication in the morning with food. Per the application, both low and high fat foods increase the absorption of ospemifene.

An interim visit was conducted 23-33 days after the Baseline visit (Week 4)

Twelve (12) weeks after the start of treatment, or sooner if the subject withdrew from the study prematurely, (Visit 4, conducted 79-89 days after the Baseline visit), subjects had their BMI determined, a full physical examination, breast examination, gynecological examination (same as Screening visit), visual evaluation of the vagina (same as Screening visit), vaginal pH measurement (same as Screening visit), vaginal smear (same as Screening visit), TVU for endometrial thickness, endometrial biopsy (if TVU endometrial thickness \geq 4 mm), 12-lead ECG, blood sample for assay of hormone levels (same as Screening visit), clinical laboratory safety screen (same as Screening visit minus Factor V Leiden), drug serum concentration, compliance check and return of study medication.

Two weeks after the end of the treatment (or withdrawal), at Visit 5 (conducted 9-19 days after the last dose of study medication), subjects underwent a follow-up assessment including physical examination, breast examination, and gynecological examination.

Adverse events (AEs), changes in concomitant medications, vital signs (blood pressure and pulse) were monitored throughout the study. If a subject reported vaginal bleeding, a TVU was performed. If the endometrium was \geq 4 mm, a hysteroscopy and guided biopsy were performed.

Statistical analysis for primary efficacy data was performed on the intent-to-treat (ITT) population, which included all treated subjects. Last Observation Carried Forward (LOCF) was used for incomplete data for the primary efficacy endpoints and the associated Week 4 secondary endpoints. An additional analysis of primary efficacy was performed on the per protocol (PP) population. Safety data were reported in the population of all treated subjects (i.e., safety population), which in this study included the same subjects as the ITT population.

The primary method of analysis for the efficacy data was analysis of covariance (ANCOVA) with treatment and center as fixed factor and screening value as covariate. Where the assumptions of ANCOVA were not met, the Cochran-Mantel-Haenszel (CMH) statistic was used.

Of the 126 subjects enrolled in the study, 117 (92.9%) subjects completed it. Seven (5.6%) subjects withdrew because of adverse events (AEs) and 2 (1.6%) subjects withdrew their consent. See Table 1.

Table 1: Disposition of Subjects in Study 15-50717

Subject Disposition	Placebo N = 34 n %	Ospemifene 5 mg N = 33 n %	Ospemifene 15 mg N = 29 n %	Ospemifene 30 mg N = 30 n %
Completion of Study	33 (97.1%)	20 (87.9%)	28 (96.6%)	27 (90.0%)
Reason for Withdrawal				
Adverse event	1 (2.9%)	3 (9.1%)	1 (3.4%)	2 (6.7%)
Subject request	0 (0.0%)	1 (3.0%)	0 (0.0%)	1 (3.3%)
Protocol violation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Adapted from NDA 203505, Study 15-50717 Clinical Study Report, page 43 of 79.

All except 4 subjects (3.2%, 4 of 126 treated subjects) were compliant with the study treatment (took a dose of study medication on \geq 85% of treatment days: 2 in the placebo treatment group and 2 in the 5 mg ospemifene treatment group).

Primary Efficacy Results in Study 15-50717:

Per the Phase 2 Study 15-50717 reported findings for vaginal superficial cells (ITT population), “the difference in median change from Screening to Week 12 between the active ospemifene groups and the placebo group was not statistically significant for the 5 mg ospemifene treatment group (p=0.198) but was statistically significant for the 15 mg ospemifene treatment group (p=0.002) and the 30 mg ospemifene treatment group (p=0.018).” For parabasal cells (ITT population), “the difference in mean change from screening to Week 12 between the active ospemifene groups and the placebo group

was not statistically significant for the 5 mg treatment group ($p=0.695$) but was statistically significant for the 15 mg ospemifene treatment group ($p=0.003$) and the 30 mg ospemifene treatment group ($p<0.001$)."

"The difference in mean change from Screening to Week 12 for vaginal pH in Study 15-50717 was not statistically significant for the 5 mg ospemifene treatment group ($p=0.464$) but was statistically significant for the 15 mg ospemifene treatment group ($p=0.002$) and the 30 mg ospemifene treatment group ($p<0.001$)."

Medical Officer's Comments:

The following observations are made from the reported results of the increase in the proportion of superficial cells and the decrease in the proportion of parabasal cells, and the decrease in vaginal pH between Baseline and Week 12:

- *the 5 mg ospemifene dose is an ineffective dose,*
- *the 15 mg ospemifene dose is an effective dose, and*
- *the 30 mg ospemifene doses is an effective dose and produced a stronger response than the 15 mg ospemifene dose.*

Secondary Efficacy Results in Study 15-50717:

Of the 4 stated secondary efficacy endpoints in Study 15-50717, only the changes in visual evaluation of the vaginal at weeks 4 and 12 will be discussed.

Per the application, there was a clear effect of dose on visual evaluation findings, with the changes in the 5 mg ospemifene treatment group being similar to the placebo treatment group, changes in the 15 mg ospemifene treatment group reported as greater than those in the 5 mg ospemifene group, and changes in the 30 mg ospemifene treatment group being the greatest compared with the other 3 groups. At week 12:

- petechiae were absent in 12 (35.3%) subjects in the placebo group, and from 12 (36.4%), 16 (55.2%) and 18 (60.0%) subjects in the 5 mg, 15 mg and 30 mg ospemifene groups, respectively. Nine (9) subjects presented with severe petechiae at Week 12: 3 (8.8%) in the placebo group, 5 (15.2%) in the 5 mg ospemifene group, and 1 (3.3%) in the 30 mg group.
- pallor was absent in 5 (14.7%) subjects in the placebo group, and from 5 (15.2%), 11 (37.9%) and 14 (46.7%) subjects in the 5 mg, 15 mg and 30 mg ospemifene groups, respectively. Only 2 subjects had severe pallor at Week 12 (1 (2.9%) in the placebo group and 1 (3.0%) in the 5 mg ospemifene group).
- friability was absent in 7 (20.6%) subjects in the placebo group, and from 10 (30.3%), 13 (44.8%) and 18 (60.0%) subjects in the 5 mg, 15 mg and 30 mg ospemifene groups, respectively. At Week 12, 3 subjects presented with severe friability (2 [5.9%] in the placebo group and 1 [3.0%] in the 5 mg ospemifene group).

- vaginal dryness was absent in 8 (23.5%) subjects in the placebo group, and from 9 (27.3%), 15 (51.7%) and 22 (73.3%) subjects in the 5 mg, 15 mg and 30 mg ospemifene groups, respectively. Severe dryness was present at Week 12 in only 2 subjects: 1 (2.9%) in the placebo group and 1 (3.0%) in the 5 mg ospemifene group.
- vaginal redness was absent in 7 (20.6%) subjects in the placebo group, and from 13 (39.4%), 15 (51.7%) and 16 (53.3%) subjects in the 5 mg, 15 mg and 30 mg ospemifene groups, respectively. Severe redness was present at Week 12 in 10 subjects: 4 (11.8%) in the placebo group, 5 (15.2%) in the 5 mg ospemifene group, and 1 (3.3%) in the 30 mg ospemifene group.

Medical Officer's Comments:

The visual inspection of the vaginal mucosa is not a substitute for the self-identified moderate to severe most bothersome symptom of VVA. Nonetheless, these reported results show an effect of dose with the 5 mg ospemifene dose being similar to placebo, changes in the 15 mg ospemifene dose greater than the 5 mg ospemifene dose, and the greatest changes being present in the 30 mg ospemifene dose.

Safety Evaluation in Study 15-50717:

An overview of adverse events occurring in Study 15-50717 are shown in Table 2.

Table 2: Overview of Adverse Events in Study 15-50717: Safety Population

Disposition	Placebo N = 34 n %	Ospemifene 5 mg N = 33 n %	Ospemifene 15 mg N = 29 n %	Ospemifene 30 mg N = 30 n %
Subjects with AEs	22 (64.7%)	15 (45.5%)	13 (44.8%)	15 (50.0%)
Subjects with SAEs	2 (5.9%)	0 (0.0%)	1 (3.4%)	1 (3.3%)
Subjects with TEAEs ¹	6 (17.6%)	9 (27.3%)	10 (34.5%)	11 (36.7%)

Source: Adapted from NDA 203505, Study 15-50717 Clinical Study Report, page 60 of 79.

¹ Causality assessment possible, probable, definite, missing.

Definitions: AEs = adverse events, SAEs = serious adverse events, and TEAEs = treatment-emergent adverse events.

No deaths occurred in Study 15-50717.

Seven (7) subjects discontinued study participation due to an adverse event:

- Placebo group = irritability (Subject 01-114; unlikely related)
- 5 mg ospemifene group = rash (Subject 02-102; possible related)
- 5 mg ospemifene group = herpes zoster (Subject 02-104; unlikely related)
- 5 mg ospemifene group = pain in extremity (Subject 09-112); unlikely related)
- 15 mg ospemifene group = headache (Subject 06-104; possible related)

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- 30 mg ospemifene group = sleep disorder (Subject 04-103; possible related)
- 30 mg ospemifene group = dizziness (Subject 05-104; possible related)

Four (4) subjects (3.2%) each experienced 1 AE classified as serious as follows:

- Placebo group = lower abdominal pain
- Placebo group = tension headache
- 15 mg ospemifene = headache
- 30 mg ospemifene = dizziness

The most common adverse event in Study 15-50717 was hot flush, occurring in a total of 11 subjects (8.7%): 2 (5.9%) in the placebo treatment group, 3 subjects in each of the ospemifene treatment groups (5 mg ospemifene [9.1%], 15 mg ospemifene [10.3%], and 30 mg ospemifene [10.0%]). Headache was the second most common AE occurring in a total of 8 subjects (6.3%): 5 subjects in the 15 mg ospemifene treatment group (17.2%), and in 1 subject each in the placebo (2.9%), 5 mg ospemifene (3.0%), and 30 mg ospemifene (3.3%) treatment groups. Influenza, urinary tract infection, and back pain each occurred in 5 (4.0%) subjects overall but in not more than 2 subjects in any treatment group.

There were no clinically meaningful or dose-related changes from Baseline to Week 12 in vital signs, laboratory tests, ECGs, physical and gynecological examinations, including TVUs. One (1) subjects had an endometrial thickness > 4 mm at Week 12 (4.5 mm; change from 3.8 mm at Baseline to 4.5 mm at Week 12). The endometrium was found to be atrophic on endometrial biopsy in this subject.

Medical Officer's Comments:

The overall conclusions for Phase 2 Study 15-50717 are:

- *5 mg ospemifene taken once daily was not statistically better than placebo.*
- *15 mg and 30 mg ospemifene taken once daily improved the objective measures of VVA (proportion of superficial and parabasal cells and vaginal pH).*
- *The effects of the 30 mg ospemifene dose was greater than the 15 mg ospemifene dose for the mean change in the proportion of superficial and parabasal cells and vaginal pH.*
- *The most common adverse event was hot flushes.*

Phase 3 Study 15-50310:

Study 15-50310 entitled, "Efficacy and Safety of Ospemifene in the Treatment of Vulvar and Vaginal Atrophy (VVA) in Postmenopausal Women: A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing Oral Ospemifene 30 mg and 60 mg Daily Doses with Placebo" was initiated on January 16, 2006 and

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completed November 19, 2007. Subjects were enrolled who had at least one most-bothersome moderate to severe symptom of VVA. The original study design was to include all subjects and combine them for analysis regardless of the most bothersome symptom reported at randomization (composite analysis of all most bothersome symptoms). Following advice from DRUP, QuatRX Pharmaceuticals (now the U.S. Agent for Hormos Medical Corporation) amended the study protocol to analyze the most bothersome symptom by each symptom, resulting in two substantial most bothersome symptom groups (vaginal dryness and dyspareunia) with very small groups for other symptoms (vaginal irritation/itching, dysuria, and vaginal bleeding associated with sexual activity) (Amendment # 5 dated April 24, 2007).

Subjects were randomly assigned in a 1:1:1 ratio to one of the following three treatment groups, stratified by uterine status (intact or hysterectomized):

- Ospemifene 30 mg tablets and nonhormonal vaginal lubricant
- Ospemifene 60 mg tablets and nonhormonal vaginal lubricant
- Placebo tablets and nonhormonal vaginal lubricant

The study was conducted at 83 centers (76 of 83 centers randomized at least 1 subject; 7 centers screened but did not randomize any subjects) in the U.S. The mean age of study participants was 58.6 years of age (range 41 to 80 years of age); 90.1% were Caucasians.

The primary objectives were to assess the efficacy, safety, and tolerability of 30 mg of ospemifene and 60 mg of ospemifene versus placebo in the treatment of VVA in postmenopausal women. The primary efficacy endpoints included:

1. Change from Baseline (Screening) to Week 12 in the percentage of parabasal cells in maturation index of the vaginal smear.
2. Change from Baseline (Screening) to Week 12 in the percentage of superficial cells in maturation index of the vaginal smear.
3. Change from Baseline (Screening) to Week 12 in vaginal pH.
4. Change from Baseline (Randomization) to Week 12 in most bothersome VVA symptom (hereafter referred to as the MBS) of vaginal dryness and vaginal pain associated with sexual activity (hereafter referred to as dyspareunia).

The secondary efficacy endpoints were as follows:

1. Change from Baseline (Screening) to Week 4 in percentage of parabasal cells in the maturation index.
2. Change from Baseline (Screening) to Week 4 in percentage of superficial cells in the maturation index.
3. Change from Baseline (Screening) to Week 4 in vaginal pH.

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4. Change from Baseline (Randomization) to Weeks 4 and 12 in severity of the MBS by symptom (except vaginal dryness and dyspareunia at Week 12).
5. Change from Baseline (Randomization) to Weeks 4 and 12 in severity of the MBS as a composite.
6. Change from Baseline (Randomization) to Weeks 4 and 12 in severity of VVA symptoms (by symptom) in subjects reporting the symptom as moderate or severe at Baseline.
7. Change from Baseline (Randomization) to Weeks 4 and 12 in severity of VVA symptoms.
8. Change from Baseline (Screening) to Weeks 4 and 12 in Maturation Value (MV). The MV was calculated with the following formula:
$$MV = (S \times 1) + (I \times 0.5) + (P \times 0)$$
, where “S” was the percentage of superficial cells, “I” was the percentage of intermediate cells, and “P” was the percentage of parabasal cells.
9. Percentage of subjects who were responders at Week 12. A subject was defined as a “responder” if the following criteria were met:
 - Subject’s MV increased by 10 from Baseline (Screening)
 - Vaginal pH decreased by 0.5 from Baseline (Screening)
 - MBS improved (decrease in severity) by 1 point in the change from Baseline (Randomization)
10. Change from Baseline (Screening) to Weeks 4 and 12 in visual evaluation of vagina (by gynecological examination).
11. Change from Baseline (Screening) to Week 12 in serum hormones.
12. Change from Baseline (Randomization) to Weeks 4 and 12 in urinary symptoms.
13. Frequency of lubricant application.

Subjects were to take 1 tablet of study medication each morning with food for 12 weeks. Subjects were instructed to apply the vaginal lubricant (K-Y® Brand Jelly) as needed and to record its use in the daily medication diary. Per the Applicant, the inclusion of nonhormonal vaginal lubricant for use during Study 15-50310 was at the request of FDA.

Medical Officer’s Comments:

DRUP advised that Study 15-50310 be designed to include vaginal lubricant as part of the study arm in all subjects in a double-blind, double-dummy approach. The Division’s intent was to collect data that would demonstrate whether or not oral drug product treatment in combination with placebo vaginal lubricant demonstrated statistically significant improvement beyond that of either oral placebo drug product or placebo vaginal lubricant.

Suitable subjects who gave written informed consent were screened for eligibility for the study. Subjects who met all of the following criteria at Screening and before Randomization were eligible for participation in Study 15-50310:

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1. Provided written informed consent to participate in the study and agreed to follow dosing instructions and complete all required study visits.
2. A woman 40 to 80 years of age at the time of Randomization.
3. Postmenopausal defined as:
 - at least 12 months since the last spontaneous menstrual bleeding,
 - at least 6 weeks since bilateral oophorectomy with or without hysterectomy, or
 - had a hysterectomy with ovaries intact and a follicle stimulating hormone (FSH) level of ≥ 40 IU/L.
4. Documented negative (for malignancy) mammogram obtained at Screening or within 9 months prior to Randomization. Normal clinical breast examination at Screening.
5. Had the following criteria for VVA: 5% or fewer superficial cells confirmed by maturation index in the vaginal smear, vaginal pH greater than 5.0, and at least one moderate or severe symptom of VVA.

Subjects who met any of the following criteria were not eligible to participate in Study 15-50310:

Subjects with an intact uterus:

1. Double-layer endometrial thickness > 4 mm on endometrial ultrasound at Screening, as determined by the central ultrasound core lab assessment.
2. Evidence of hyperplasia, cancer, or other pathology from the endometrial biopsy at Screening.
3. An abnormal Pap test result at Screening based upon Bethesda System (2001) Classifications: atypical squamous cells of undetermined significance (ASC-US) (human papillomavirus [HPV] high risk positive), atypical squamous cells (cannot exclude high grade squamous intraepithelial lesion), atypical glandular cells (endocervical, endometrial), low and high grade squamous intraepithelial lesion, and carcinoma, and an unsatisfactory specimen. The following abnormal results were not exclusionary: negative for intraepithelial lesion, reactive/reparative changes, and ASC-US (HPV negative).
4. Uterine bleeding of unknown origin.
5. Uterine polyps.

Subjects with or without an intact uterus:

6. Vaginal infection requiring medication.
7. Clinically significant abnormal findings at physical examination.
8. A BMI of ≥ 37 .
9. Used of dietary supplements or herbal therapies with assumed clinically significant estrogenic vaginal effects within 30 days prior to the initial screening visit.

10. Use of local vaginal hormonal products within 14 days prior to the initial screening visit.
11. Use of oral or transdermal estrogen and/or progestin therapy within 60 days prior to the initial screening visit.
12. Use of progestin implants or estrogen alone injectable drug therapy within 90 days prior to the initial screening visit.
13. Use of estrogen pellet therapy or progestin injectable drug therapy within 6 months prior to the initial screening visit.
14. Use of sex hormones or medications that were expected to have a clinically significant effect on sex hormone levels within 60 days prior to the initial screening visit (including oral birth control medications and raloxifene [Evista]).
15. Systolic blood pressure =180 mmHg or diastolic blood pressure =100 mmHg.
16. Clinically relevant abnormal findings in any safety laboratory tests and/or liver enzymes (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) more than twice the upper limit of normal for the testing laboratory.
17. Heterozygous or homozygous for Factor V Leiden (test done at Screening).
18. Had clinically significant abnormal gynecological findings other than signs of vaginal atrophy.
19. Clinically significant abnormal findings on the screening ECG.
20. Suspicion of malignancy on mammography, clinical suspicion of any other kind of malignancy, or history of malignancy within 10 years (basal cell carcinoma in history was allowed).
21. Consumer of more than 14 drinks containing alcohol per week (1 drink = 1.5 oz. of distilled spirits, 12 oz of beer, or 5 oz. of wine).
22. Current or history of severe renal or hepatic impairment.
23. Current or history of thromboembolic or blood coagulation disorder.
24. Currently using heparin, itraconazole, ketoconazole or digitalis alkaloids.
25. Participated in another clinical intervention study within 30 days prior to the planned Randomization.
26. Any physical or mental condition which in the opinion of the Investigator could interfere with the subject's ability to comply with the study procedures.
27. Previously participated in this study or any other study of ospemifene.

Medical Officer's Comments:

In Study 15-50310, subjects were screened for Factor V Leiden. If documented heterozygous or homozygous positive, these subjects were excluded. Because routine screening for Factor V Leiden is not currently recommended, the exclusion of heterozygous or homozygous positive may have influenced the study outcome relative to the general population.

Per the application, 2 subjects heterozygous positive for Factor V Leiden at Screening in Study 15-50310 (1 subject in the 30 mg ospemifene treatment group [Subject 726] and 1 subject in the 60 mg ospemifene treatment group [Subject 173]) were

randomized, received treatment, and completed the study without any reported adverse events.

Per the Office of Clinical Pharmacology (OCP), Genomics Group, Review of NDA 203505, “Factor V Leiden (FVL) is a genetic characteristics marked by poor anticoagulant responses to activated protein C (APC) resulting from a glutamine to arginine substitution at the Arg506 APC cleavage site in the Factor V gene. This single amino acid substitution leads to Factor V resistance to APC and subsequent increased thrombin generation. The FVL polymorphism is common in the U.S. population. The prevalence of carrying at least one allele in whites is 5.3%; the prevalence is lower in other ethnicities (Hispanic Americans: 2.2%, Native Americans 1.3%, African Americans 1.2%, Asian Americans: 0.5 %;). In the US population, homozygosity for FVL polymorphisms is uncommon at a frequency of 0.02%. The absolute risk for developing VTE in the general population is low (<1/1000 patient years) but increased if other risk factors are present. The absolute risk associated with FVL for developing a VTE is comparable to the absolute risk associated with other known risk factors (for example, oral contraceptive (OC) use + increased age). VTE risk is exaggerated in the presence of more than one risk factor.”

Efficacy Assessments in Study 15-50310:

Vaginal smear samples were taken from the middle third of the lateral vaginal wall to determine the proportion of superficial and parabasal cells in the vaginal epithelium. The vaginal smear samples were evaluated at the central pathology laboratory by a qualified pathologist and included the identification of any underlying infection or condition and its impact on the validity of the maturation index. The central pathologist performed the cell count for each sample. The subjects entering the study were required to have 5% or less superficial cells at Screening.

The pH measurement was obtained by pressing a pH indicator strip against the vaginal wall. The subjects entering the study were required to have a vaginal pH value greater than 5.0 at Screening. The subjects were advised not to have sexual intercourse within 24 hours prior to the measurement.

Using a 4-point scale (none [0], mild [1], moderate [2], or severe [3]), subjects self-identified her moderate to severe symptom that was most bothersome to her:

- vaginal dryness
- vaginal pain associated with sexual atrophy (dyspareunia)
- vaginal and/or vulvar irritation/itching
- dysuria
- vaginal bleeding associated with sexual activity

Subjects had to have at least one moderate or severe VVA symptom to be eligible for the study. At Visit 2 (Randomization), subjects recorded which one of the moderate or severe symptoms was the most bothersome.

Medical Officer's Comments:

DRUP currently recommends that the following three symptoms be included in the self-assessment questionnaire used in support of a VVA indication: vaginal dryness, dyspareunia, or vaginal irritation/itching. Based on experience, symptoms such as dysuria and vaginal bleeding associate with sexual activity are infrequently identified as moderate to severe and most bothersome in postmenopausal populations.

Study 15-50310 was amended on April 24, 2007 to analyze only vaginal dryness and dyspareunia of the original 5 moderate to severe vaginal symptoms included in the study protocol.

A visual evaluation of the vagina (petechiae, pallor, friability, vaginal dryness, and redness seen in vaginal mucosa), assessed on a 4-point scale (0 = None, 1 = Mild, 2 = Moderate, 3 = Severe), was performed as part of the gynecological examination and the findings were documented on the subjects' case report form (CRF).

As previously noted, nonhormonal vaginal lubricant (K-Y® Brand Jelly) was used, as needed, and record in the daily medication diary. The total number of lubricant applications was recorded weekly as 0 = none, 1 = 1-2 times, 2 = 3 or more times.

Safety Assessments in Study 15-50310:

Subjects were asked to spontaneously report all adverse events (AEs) throughout the study period. Additionally, subjects were queried about AEs at each study visit.

A physical examination was performed, including vital signs, height, weight, and BMI. A 12-lead ECG was taken at Screening and at Week 12 (or end-of-treatment). Cervical smear samples were taken at Screening and at Week 12 and analyzed by a central pathologist. The samples were classified according to Bethesda System (2001).

Transvaginal ultrasound (TVU) was performed locally and the endometrial thickness was determined by a central reader. Subjects were to have an endometrial thickness < 4 mm to be eligible for study participation. Endometrial biopsy was obtained for a woman with a uterus. Endometrial biopsy assessments were based on Blaustein's classification. Per the study protocol, subjects with normal or atrophic endometrial histology were eligible for randomization. Subjects with an insufficient tissue biopsy sample were included if the TVU was < 4 mm. At Week 12, if the endometrial biopsy results confirmed insufficient endometrial tissue for diagnosis after a valid attempt was

made to sample the endometrium, a TVU result of < 4 mm was considered as not indicative of endometrial hyperplasia.

All endometrial histological samples were analyzed by two independent pathologists. When there was a disagreement between the evaluations of histology classification by the two independent pathologists, a third independent pathologist evaluated the samples. The concurrence of two of the three independent pathologists was used as the final diagnosis. However, if there was no agreement among the three pathologists, then the most severe pathologic diagnosis was used as the final diagnosis. All pathologists were blinded both to the study treatment and to each other's readings of the histology slides. This process was carried out by [REDACTED] (b) (4)

Medical Officer's Comments:

The Agency's 2003 draft Guidance for Industry entitled, "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation" recommends endometrial monitoring to include, but not limited to, the following:

- *The endometrial tissue obtained by endometrial biopsy at screening, during the conduct of the study, and at the end-of-study be processed in the same manner by a central laboratory.*
- *Three independent expert pathologists, blinded to treatment group and to each other's readings, determine the diagnosis of endometrial biopsy slides during the conduct of the study.*
- *Participating study pathologists be from different institutions with independent fiduciary and organizational reporting, and these pathologists not meet to review slides before or during the conduct of the clinical trial.*
- *The concurrence of two of the three pathologists be accepted as the final diagnosis. If there is no agreement among the three pathologists, the most severe pathologic diagnosis (i.e., atypical hyperplasia > complex hyperplasia, simple hyperplasia > benign endometrium) would be used as the final diagnosis.*

The procedure followed for the pathologists assessments of the endometrial biopsy specimen in Study 15-50310 is not in full compliance with the Agency's 2003 draft Clinical Evaluation Guidance for Industry. Two independent pathologists initially evaluated the endometrial biopsy slides in this study, not three. The third pathologist was consulted only if the initial two pathologists disagreed in their evaluation of the slides. The re-read of endometrial biopsy slides previously evaluated might lead to an introduction of bias in the evaluation conducted by the third pathologist, thus affecting the final diagnosis.

If a subject reported vaginal bleeding during the study, an attempt was to be made to determine the etiology and a visual inspection and gynecological examination was to be

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performed. If no obvious reason was identified and the subject had an intact uterus, a TVU was to be performed to assess possible uterine pathology and the thickness of endometrium. If the endometrial thickness was < 4 mm, an endometrial biopsy was to be performed. If the biopsy yielded an insufficient sample and bleeding persisted, a hysteroscopy and guided biopsy was to be performed. If the endometrial thickness was \geq 4 mm, a hysteroscopy and guided biopsy was to be performed. In addition, the adnexa were to be checked with ultrasonography.

Clinically significant laboratory findings were identified and recorded. Any clinically significant abnormal laboratory findings at the end of the study were followed up until satisfactory resolution or diagnosis could be made.

Safety laboratory assessments included the following:

Visit 1 and Visit 4:

Hematology :	red blood cell (RBC) count, white blood cell count (WBC), differential, platelet count, hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, RBC distribution width, and mean platelet volume.
Chemistry:	albumin, ALT, AST, total bilirubin, creatinine, total protein, glucose, uric acid, blood urea nitrogen, and creatine kinase.
Coagulation:	activated partial thromboplastin time, fibrinogen, antithrombin III antigen, Factor V Leiden (Screening only), protein-C antigen, and protein-S antigen.
Urinalysis	blood, glucose, ketones, protein

Visit 2 and Visit 4:

Lipids:	total cholesterol, direct measurement of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), and triglycerides.
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Statistical and Analytical Plans:

Per the application, the study was conducted under the same protocol at all study centers. To ensure estimable results in the statistical analyses, small centers were pooled by geographical location.

The last-observation-carried-forward (LOCF) approach was used to replace missing values for the efficacy analyses. If the subject had no assessments during treatment, baseline assessments were carried forward.

Per the statistical analysis plan (SAP), changes in superficial cells, parabasal cells, and vaginal pH were to be analyzed using an ANCOVA model where change from Baseline was the response variable, the baseline value was the covariate, and the treatment, uterine status and study center were the fixed effects. Per the application, the ANCOVA assumptions were severely violated in Study 15-50310, thus a nonparametric approach (rank-based analysis of variance method) was used, stratifying by study center and by uterine status separately.

Change in severity of MBS by symptom and as a composite, change in severity of VVA symptoms, change in severity of VVA symptoms reported as moderate to severe at Baseline, and responders at Week 12 were examined using a CMH row mean scores test controlling for study center and uterine status.

Descriptive summaries that include change from Baseline were created for the visual evaluation of the vagina (by gynecological examination), serum hormones, and urinary symptoms and were based on observed values for each appropriate time point.

A descriptive summary of the frequency of lubricant application by week was created.

Two subjects populations were analyzed: 1) An ITT subject was any individual who was randomized into the study and received at least one dose of study drug; and 2) A PP subject was an ITT subject who completed at least 10 weeks of treatment, completed the end of study assessments, took at least 85% of the study drug, did not have any major protocol violations, and did not have a vaginal infection (as assessed with the vaginal smear used to measure the MI) or any other medical condition that confounded the primary efficacy assessment. Both the efficacy and safety analyses were conducted on the ITT population.

Changes in the Conduct of Study 15-50310:

Five amendments were applied to the original protocol dated November 18, 2005:

Amendment 1, dated January 4, 2006, was finalized before the first subject entered the study, and included the following changes:

- Clarification that Pap test results were based upon Bethesda System 2001 and specified a classification of low-grade squamous intraepithelial lesion (LSIL) was exclusionary.
- Change of the targeted location of the vaginal smear from the upper third to the middle third of the lateral vaginal wall.

Amendment 2, dated January 20, 2006, was finalized before any subject reached Visit 4 (Week 12), and included the following change:

- Inclusion of an additional serum sample to be collected at Visit 4 (Week 12) to assess steady state trough ospemifene levels.

Amendment 3, dated April 14, 2006, included the following changes:

- Extension of the acceptable time window for screening to 42 days.
- Specification that the TVU was to be performed before the endometrial biopsy.
- Clarification that the endometrial biopsy was to be read by at least two pathologists before randomization.
- Clarification that the endometrial thickness measurement from the central reader was to confirm eligibility.
- Change of the requirements for the washout of products that have estrogenic vaginal effect to be relative to the beginning of screening rather than randomization.

Amendment 4, dated July 13, 2006, included the following changes:

- Lowering of the age limit for inclusion to 40 years.
- Specification of raloxifene as an exclusionary medication.
- Addition of instructions on how to manage subjects with urinary tract infections.
- Revision of the statistical analysis section in response to FDA review and advice.

Amendment 5, dated April 24, 2007, included the following changes:

- Allowed subjects to participate if they consumed up to 14 alcoholic beverages a week
- Allowed subjects to participate if they completed involvement in another clinical study 30 days or more before Screening.
- Eliminated the expectation that at least 50% of the subjects would have an intact uterus
- Revised the statistical analysis sections in response to FDA recommendations, including the sample size and power consideration sections

Phase 3 Study 15-50821:

Study 15-50821 entitled, “Efficacy and Safety of Ospemifene in the Treatment of Moderate to Severe Vaginal Dryness and Vaginal Pain Associated With Sexual Activity, Symptoms of Vulvar and Vaginal Atrophy (VVA), Associated With Menopause: A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing Oral Ospemifene 60 mg Daily Dose With Placebo in Postmenopausal Women” was initiated on August 4, 2008 and completed July 30, 2009. Hormus Medical Ltd. was the Sponsor for Study 15-50821, and QuatRX Pharmaceutical Company acted as its U.S. representative.

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Study 15-50821 was a second 12-week study designed to evaluate the effects of 60 mg ospemifene per day versus placebo (randomized 1:1). Eligible subjects entered one of two randomization strata based on their self-reported MBS; 1) dryness strata, or 2) dyspareunia strata. Each stratum was analyzed as an independent study group.

The study was conducted at 119 centers (112 of 119 centers randomized at least 1 subject) in the U.S. Subjects were randomized to 60 mg ospemifene per day or placebo in a 1:1 fashion. The mean age of study participants was 58.6 years of age (range 40 to 79 years of age); 87.6% were Caucasians and 6.9% were African-American.

The primary objectives were to assess the efficacy, safety, and tolerability of 60 mg of ospemifene in the treatment of VVA associated with menopause:

- moderate to severe vaginal dryness, and
- moderate to severe dyspareunia.

The 4 co-primary efficacy endpoints included:

- percentage of superficial cells in the maturation index of the vaginal smear,
- percentage of parabasal cells in the maturation index of the vaginal smear.
- vaginal pH, and
- severity of the MBS of VVA of vaginal dryness (Dryness Stratum) and dyspareunia (Dyspareunia Stratum)

The secondary efficacy endpoints included:

1. Change from Baseline in percentage of parabasal cells in the maturation index – Week 4.
2. Change from Baseline in percentage of superficial cells in the maturation index – Week 4.
3. Change from Baseline in vaginal pH – Week 4.
4. Change from Baseline in severity of the MBS of vaginal dryness and dyspareunia – Week 4.
5. Change from Baseline in severity of VVA symptom (by symptom) in subjects reporting the symptom as moderate to severe at Baseline – Weeks 4 and 12.
6. Change from Baseline in severity of VVA symptoms (by symptom) – Weeks 4 and 12.
7. Change from Baseline in maturation value (MV) – Weeks 4 and 12.
8. Percentage of subjects who are responders - Week 12.
9. Change from Baseline in visual evaluation of vagina – Weeks 4 and 12.
10. Change from Baseline in serum hormones – Week 12.
11. Change from Baseline in total score and the domains of the Female Sexual Function Index (FSFI) – Weeks 4 and 12.

12. Change from Baseline in urinary symptoms as assessed by the Urinary Distress Inventory – Short Form (UDI-6) – Weeks 4 and 12.
13. Frequency of lubricant use and sexual activity.

A total of 750 subjects were planned for randomization into Study 15-50821, stratified based on the self-reported MBS (vaginal dryness or dyspareunia) and randomized 1:1 within each stratum of the study to 2 treatment groups (60 mg ospemifene or placebo) as follows:

- Approximately 250 subjects (125 subjects per treatment group) were to be enrolled in the stratum for subjects reporting moderate to severe vaginal dryness as the MBS (Dryness Stratum).
- Approximately 500 subjects (250 subjects per treatment group) were to be enrolled in the stratum for subjects reporting moderate to severe vaginal pain associated with sexual activity as the MBS (Dyspareunia Stratum).

Each stratum was analyzed as an independent study.

Subjects were to take 1 tablet of study medication each morning with food for 12 weeks. Subjects were instructed to apply the vaginal lubricant (K-Y® Brand Jelly) as needed and to record its use in the daily medication diary.

Suitable subjects who gave written informed consent were screened for eligibility for the study. For inclusion into Study 15-50821, subjects were required to fulfill all of the following criteria:

1. Sign a written informed consent to participate in the study and agreed to follow dosing instructions and complete all required study visits.
2. A woman 40 to 80 years of age at the time of Randomization.
3. Postmenopausal defined as:
 - at least 12 months since the last spontaneous menstrual bleeding (if uncertain, confirmed with FSH level > 40 IU/L)
 - had a hysterectomy with ovaries intact and a FSH level of > 40 IU/L
 - at least 6 weeks since bilateral oophorectomy with or without hysterectomy
4. Hysterectomized or had an intact uterus with double-layer endometrial thickness < 4 mm at Screening, as determined by the central ultrasound core laboratory assessment.
5. Hysterectomized or had no evidence of hyperplasia, cancer, or other pathology from the endometrial biopsy at Screening.
6. A negative Pap test result at Screening or no cervix. Excluded Bethesda System (2001) Classifications included: ASC-US ([atypical squamous cells of undetermined significance] human papillomavirus [HPV] High Risk Positive), ASC-H (atypical squamous cells-couldn't exclude high-grade squamous intraepithelial lesion [SIL]),

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Atypical Glandular Cells (Endocervical, Endometrial, not otherwise specified [NOS]), Low Grade SIL, High Grade SIL, Carcinoma, Unsatisfactory specimen.

7. Documented negative (for malignancy) mammogram obtained at Screening or within 9 months prior to randomization. Normal clinical breast examination at Screening.
8. Had the following criteria for VVA: 5% or fewer superficial cells confirmed by maturation index in the vaginal smear, vaginal pH greater than 5.0, and moderate to severe vaginal dryness or dyspareunia as the self-reported MBS.

Any of the following was regarded as a criterion for exclusion from the trial:

1. Clinically significant abnormal findings in the physical examination at Screening.
2. BMI of ≥ 37 .
3. Systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 100 mmHg.
4. Clinically significant abnormal gynecological findings other than signs of vaginal atrophy (e.g., uterine or vaginal prolapse of Grade 2 or higher).
5. Uterine bleeding of unknown origin.
6. Uterine polyps.
7. Symptomatic and/or large uterine fibroids (estimated size > 3 cm).
8. Vaginal infection requiring medication.
9. Clinically significant abnormal findings (as determined by the investigator) on the screening ECG.
10. Taken any of the following hormonal medications:
 - Vaginal hormonal products (rings, creams, gels) within 14 days prior to any screening procedures
 - Oral or transdermal estrogen and/or progestin therapy within 60 days prior to screening procedures
 - Intrauterine progestin therapy within 60 days prior to screening procedures
 - Progestin implants or estrogen alone injectable drug therapy within 90 days prior to screening procedures
 - Estrogen pellet therapy or progestin injectable drug therapy within 6 months prior to screening procedures
11. Taken a SERM (e.g., raloxifene, tamoxifen, toremifene, or clomiphene), tibolone, or any other medications that were expected to have clinically significant estrogenic and/or antiestrogenic effects within 60 days prior to screening procedures.
12. Regular use of any dietary supplements or herbal therapies, including black cohosh, soy (including soy milk), phytoestrogens, or over the counter (OTC) agents known to possibly have estrogenic vaginal effects within 30 days prior to screening procedures.
13. Use of:
 - Heparin or,
 - Digitalis alkaloids or,
 - Strong inhibitors of cytochrome P450 (CYP) 3A4: systemic itraconazole, systemic ketoconazole, human immunodeficiency virus (HIV) antivirals (indinavir, nelfinavir, ritonavir or saquinavir), clarithromycin, telithromycin or nefazodone.

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14. Clinically relevant abnormal findings in any safety laboratory tests.
15. Liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) more than twice the upper limit of normal for the testing laboratory.
16. Heterozygous or homozygous for Factor V Leiden (test done at Screening).
17. Suspicion of malignancy on mammography, clinical suspicion of any other kind of malignancy, or history of malignancy within 10 years (basal cell carcinoma in history was allowed).
18. Consumption of more than 14 drinks containing alcohol per Week (1 drink = 1.5 oz of distilled spirits, 12 oz of beer, or 5 oz of wine).
19. Current or history of severe renal or hepatic impairment (including current or history of hepatitis C or hepatitis B surface antigen positive hepatitis B).
20. Current or history of thromboembolic or blood coagulation disorder.
21. Current or history of cerebrovascular incident (e.g., bleeding, stroke, or transient ischemic attack).
22. A participant in another clinical intervention study within 30 days prior to Screening.
23. 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.
24. Previously participated in this study or any other study of ospemifene.

Medical Officer's Comments:

Like Study 15-50310, Study 15-50821 also screened for heterozygous or homozygous Factor V Leiden, and excluded those potential study participants found to be positive. No participants in Study 15-50821 were positive at baseline.

Efficacy Assessments in Study 15-50821:

Vaginal smear samples were taken from the middle third of the lateral vaginal wall to determine the proportion of superficial and parabasal cells in the vaginal epithelium. The vaginal smear samples were evaluated at the central pathology laboratory by a qualified pathologist and included the identification of any underlying infection or condition and its impact on the validity of the Maturation Index. The central pathologist performed the cell count for each sample. The subjects entering the study were required to have 5% or less superficial cells at Screening.

The pH measurement was obtained by pressing a pH indicator strip against the middle third of the vaginal wall. The subjects entering the study were required to have a vaginal pH value greater than 5.0 at Screening. The subjects were advised not to have sexual intercourse and to refrain from using vaginal lubricant within 24 hours prior to the measurement.

Using a 4-point scale (none [0], mild [1], moderate [2], or severe [3]), subjects self-identified her moderate to severe symptom that was most bothersome to her:

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- vaginal dryness
- vaginal pain associated with sexual atrophy (dyspareunia)

Subjects had to self-report moderate or severe vaginal dryness or dyspareunia as her MBS to be eligible for the study.

A visual evaluation of the vagina, assessing petechiae, pallor, friability, vaginal dryness, and redness on a 4-point scale (0 = None, 1 = Mild, 2 = Moderate, 3 = Severe) was performed as part of the gynecological examination.

Subjects also assessed the presence or absence of urinary symptoms using the Urinary Distress Inventory-Short Form (UDI-6) questionnaire. The UDI-6 assesses the following symptoms: frequent urination; urine leakage related to feeling of urgency; urine leakage related to physical activity, coughing, or sneezing; small amount of urine leakage; difficulty emptying bladder; and pain or discomfort in the lower abdominal or genital area (rated on a 4-point scale [not at all, slightly, moderately, and greatly]). Subjects documented the use of vaginal lubricant, as well as sexual activity during treatment.

Safety Assessments in Study 15-50821:

A physical examination was performed, including vital signs, height, weight, and BMI. A 12-lead ECG was taken at Screening and at Week 12 (or end-of-treatment). Cervical smear samples were taken at Screening and at Week 12 and analyzed by a central pathologist. The samples were classified according to Bethesda System (2001).

TVU was performed locally by a trained study staff member and the endometrial thickness was determined by a central reader. Subjects were to have an endometrial thickness < 4 mm to be eligible for study participation. Endometrial biopsy was obtained for a woman with a uterus. Endometrial biopsy assessments were based on Blaustein's classification. Per the study protocol, subjects with normal or atrophic endometrial histology were eligible for randomization. Subjects with an insufficient tissue biopsy sample were included if the TVU was < 4 mm. All endometrial histological samples were analyzed by two independent pathologists. When there was a disagreement between the evaluations of histology class by the two pathologists, a third independent pathologist evaluated the samples. The concurrence of two of the three independent pathologists was used as the final diagnosis. However, if there was no agreement among the three pathologists, then the most severe pathologic diagnosis was used as the final diagnosis. All pathologists were blinded both to the study treatment and to each other's readings of the histology slides. This process was carried out by (b) (4)

Medical Officer's Comments:

See the Medical Officer's Comments on page 44 of this review regarding the Applicant's process for the histologic evaluation of endometrial biopsy specimens.

If a subject reported vaginal bleeding during the study, an attempt was to be made to determine the etiology and a visual inspection and gynecological examination was to be performed. If no obvious reason was identified and the subject had an intact uterus, a transvaginal ultrasound was to be performed to assess possible uterine pathology and the thickness of endometrium. If the endometrial thickness was < 4 mm, an endometrial biopsy was to be performed. If the biopsy yielded an insufficient sample and bleeding persisted, a hysteroscopy and guided biopsy was to be performed. If the endometrial thickness was \geq 4 mm, a hysteroscopy and guided biopsy was to be performed. In addition, the adnexa were to be checked with ultrasonography.

Clinically significant laboratory findings were identified and recorded. Any clinically significant abnormal laboratory findings at the end of the study were followed up until satisfactory resolution or diagnosis could be made.

Subjects were asked to spontaneously report all adverse events (AEs) throughout the study period. Additionally, subjects were queried about AEs at each study visit.

Safety laboratory assessments included the following:

Visit 1 and Visit 4:

Hematology :	red blood cell (RBC) count, white blood cell count (WBC), differential, platelet count, hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, RBC distribution width, and mean platelet volume.
Chemistry:	albumin, ALT, AST, total bilirubin, creatinine, total protein, glucose, uric acid, blood urea nitrogen, and creatine kinase.
Coagulation:	activated partial thromboplastin time, fibrinogen, antithrombin III antigen, Factor V Leiden (Screening only), protein-C antigen, and protein-S antigen.
Urinalysis	blood, glucose, ketones, protein

Visit 2 and Visit 4:

Lipids:	total cholesterol, direct measurement of low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C), and triglycerides.
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Statistical and Analytical Plans:

Per the application, the study was conducted under the same protocol at all study centers. To ensure estimable results in the statistical analyses, small centers were pooled by geographical location.

Each efficacy stratum (dryness or dyspareunia) was analyzed separately. Analyses were conducted on the combined data for the 2 strata for all safety variables.

The LOCF approach was used to replace missing values for the efficacy analyses. If the subject had no post-baseline observations during treatment, baseline observation were used as the last observation in the study and were carried forward.

No imputations were done for missing values for the following efficacy variables: visual examination of the vagina, serum hormones, urinary symptoms, and frequency of lubricant application and sexual activity. These variables were summarized using observed cases only.

Safety endpoints were summarized using Week12/LOCF. Change scores were summarized only for subjects with both baseline and post-baseline measurements.

Two subjects populations were analyzed: 1) An ITT subject was any individual who was randomized into the study and received at least one dose of study medication; and 2) A PP subject was an ITT subject who completed at least 10 weeks of treatment, completed the end of study assessments, took at least 85% of the study drug, did not have any major protocol violations, and did not have a vaginal infection (as assessed with the vaginal smear used to measure the maturation index) or any other medical condition that confounded the primary efficacy assessment. Both the efficacy and safety analyses were conducted on the ITT population.

Per SAP, changes in superficial cells, parabasal cells, and vaginal pH were to be analyzed using an ANCOVA model where change from Baseline to Week 12/LOCF was the response variable, the baseline value was the covariate, and the treatment and study center were the fixed effects.

The change from Baseline to Week 12 in the severity of the MBS (dryness stratum or dyspareunia stratum) was analyzed using a CMH row mean scores test controlling for study center.

Changes in the Conduct of Study 15-50821:

No amendment was received for Study 15-50821.

Phase 3 Study 15-50718:

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Study 15-50718 entitled, “Efficacy and Long-Term Safety of Ospemifene in the Treatment of Vulvar and Vaginal Atrophy (VVA) in Postmenopausal Women: A 52-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Comparing 60 mg Daily Dose of Ospemifene With Placebo” was initiated on November 26, 2007 and completed on June 26, 2009. The study was conducted at 23 centers in Belgium, Denmark, Finland and Sweden. Hormus Medical Ltd., Turku, Finland was the Sponsor for Study 15-50718.

The primary objective of Study 15-50718 was to assess the long-term safety of 60 mg ospemifene, including endometrial biopsies after 52 weeks of treatment, to support the overall safety profile of ospemifene in the treatment of VVA. Study 15-50718 also assessed the percentage of superficial cells and parabasal cells in the Maturation Index and vaginal pH during the first 12 weeks of this double-blind, placebo-controlled Phase 3 study. Per the protocol, the primary efficacy endpoints included:

“Change from baseline to Week 12/LOCF in the following:

- percentage of parabasal cells in the Maturation Index,
- percentage of superficial cells in the Maturation Index, and
- vaginal pH.”

The secondary efficacy endpoints were:

- Change from baseline in percentage of parabasal cells in the Maturation Index at Weeks 12, 26 and 52 (observed cases).
- Change from baseline in percentage of superficial cells in the Maturation Index at Weeks 12, 26 and 52 (observed cases).
- Change from baseline in vaginal pH at Weeks 12, 26 and 52 (observed cases).
- Change from baseline in visual evaluation of the vagina (by gynecological examination) at Weeks 12, 26 and 52 (observed cases).
- Change from baseline in serum hormones at Weeks 12, 26 and 52 (observed cases).

Medical Officer’s Comments:

Because Study 15-50718 did not assessed the change from Baseline to Week 12 in the self-identified most bothersome moderate to severe symptom of vulvar and vaginal atrophy (the third recommended co-primary endpoint for a VVA indication), this study is considered supportive for efficacy consideration. The efficacy results for the proportion of superficial/parabasal cells in the Maturation Index, and vaginal pH reported in Study 15-50718 are not included in this reviewer’s analysis of the efficacy data submitted to support the effectiveness for the 60 mg ospemifene dose to relieve moderate to severe vaginal dryness or dyspareunia. In addition, Study 15-50718 utilized a 6:1

randomization scheme for 60 mg ospemifene and placebo, respectively, which is not acceptable for a primary efficacy study.

Overall, Study 15-50718 reported a statistically significant mean change in the proportion of superficial/parabasal cells and vaginal pH with 60 mg ospemifene versus placebo at Week 12 (all p-values < 0.0001).

The safety and tolerability assessment in Study 15-50718 were:

- Frequency and severity of treatment-emergent adverse events (TEAEs)
- Vital signs (systolic and diastolic blood pressure and pulse)
- Physical examination including breast examination
- Weight and height (body mass index [BMI])
- Gynecological examination
- Cervical Papanicolaou smear
- TVU
- Endometrial histology from biopsy.
- Mammography
- 12-lead ECG
- Clinical safety laboratory assessments (hematology, clinical chemistry, urinalysis)
- Coagulation parameters (antithrombin III, protein-C, and protein-S)
- Serum lipid levels
- Treatment compliance
- Frequency and reasons for early discontinuation

Subjects were eligible for Study 15-50718 if they met all of the following inclusion criteria at Screening and before Randomization:

1. Provided written informed consent to participate in the study, and agreed to follow the dosing instructions and to complete all required study visits.
2. A woman aged 40 to 80 years (inclusive) at the time of Randomization.
3. Postmenopausal defined as:
 - at least 12 months since the previous spontaneous menstrual bleeding. If there was any uncertainty about the time of the last spontaneous bleeding, the postmenopausal status was confirmed with FSH levels >40 IU/L and estradiol levels <0.20 nmol/L, or
 - at least 6 weeks post-surgical bilateral oophorectomy.
4. An intact uterus.
5. Documented mammogram within 3 months prior to randomization or performed during Screening that was negative for malignancy, and a normal clinical breast examination at Screening.
6. 5% or fewer superficial cells in the MI.
7. Vaginal pH > 5.0.

Subjects were excluded from Study 15-50718 if they met any of the following criteria:

1. Double-layer endometrial thickness ≥ 4 mm on endometrial ultrasound at Screening, as determined by the central ultrasound core laboratory assessment.
 2. Evidence of hyperplasia, cancer or other pathology from the endometrial biopsy at Screening.
 3. Abnormal Pap test at Screening. Pap smears were analyzed by [REDACTED] (b) (4)
- Excluded Bethesda System (2001) Classifications:
- ASC-US
 - ASC-H
 - Atypical glandular cells
 - Low grade squamous intraepithelial lesions
 - High Grade squamous intraepithelial lesions
 - Carcinoma
 - Unsatisfactory specimen Included:
 - Negative for intraepithelial lesion
 - Reactive/reparative changes
4. Uterine bleeding of unknown origin.
 5. Uterine polyps.
 6. Symptomatic and/or large uterine fibroids (estimated size >3 cm).
 7. Vaginal infection requiring medication.
 8. Clinically significant abnormal gynecological findings other than signs of vaginal atrophy (e.g. uterine or vaginal prolapse of Grade 2 or higher).
 9. Intake of any of the following hormonal medications:
 - vaginal hormonal products (rings, creams, gels) within 14 days prior to Screening procedures,
 - oral or transdermal estrogen and/or progestin therapy within 60 days prior to Screening procedures,
 - intrauterine progestin therapy within 60 days prior to Screening procedures,
 - progestin implants or estrogen-alone injectable drug therapy within 90 days prior to Screening procedures, or
 - estrogen pellet therapy or progestin injectable drug therapy within 6 months prior to Screening procedures.
 10. Intake of a SERM (e.g., raloxifene, tamoxifen, toremifene, or clomiphene), tibolone or any other medications that were expected to have clinically significant estrogenic and/or antiestrogenic effects, within 60 days prior to Screening procedures.
 11. Regular use of herbal or dietary supplements, including black cohosh, soy (including the use of soy milk), phytoestrogens or over-the-counter agents thought to have estrogenic vaginal effects, within 30 days prior to Screening procedures.
 12. Current use of heparin, digitalis alkaloids, or strong inhibitors of CYP 3A4, i.e. systemic itraconazole, systemic ketoconazole, human immunodeficiency virus

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- antivirals (indinavir, nelfinavir, ritonavir or saquinavir), clarithromycin, telithromycin or nefazodone.
13. Clinically significant abnormal findings on physical examination.
 14. BMI \geq 30 kg/m².
 15. Clinically significant abnormal findings, as assessed by the investigator, on ECG at Screening.
 16. Systolic blood pressure \geq 180 mmHg or diastolic blood pressure \geq 100 mmHg.
 17. Clinically relevant abnormal findings in any safety laboratory tests.
 18. Liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [ASAT]) more than twice the upper limit of normal for the testing laboratory.
 19. Heterozygous or homozygous for Factor V Leiden mutation at Screening.
 20. Suspicion of malignancy on mammography, clinical suspicion of any other kind of malignancy, or history of malignancy within 10 years. A history of basal cell carcinoma was allowed.
 21. Consumption of more than 14 drinks containing alcohol per week.
 22. Current or history of severe renal or hepatic impairment (including current or history of hepatitis C or HBsAg-positive hepatitis B).
 23. Current or history of thromboembolic or blood coagulation disorder.
 24. Current or history of cerebrovascular incident (e.g. bleeding, stroke or transient ischemic attack).
 25. Participation in another clinical intervention study within 30 days prior to Screening.
 26. Physical or mental condition that, in the opinion of the investigator, might have interfered with the subject's ability to comply with the study procedures.
 27. Previous participation in any clinical study of ospemifene.

Medical Officer's Comments:

As in 12-week Study 15-50310 and Study 15-50821, Study 15-50718 excluded prospective study participants who were heterozygous or homozygous Factor V Leiden positive.

One (1) subject (Subject 14-107) found to be heterozygous positive was randomized, received treatment for approximately 8 days, and discontinued study medication due to back pain and cystitis.

Dosing of 60 mg ospemifene or placebo was oral, taken once daily, in the morning with food, as both low and high fat food increase the absorption of ospemifene.

The first dose of study drug was administered in the clinic at the Randomization visit. Subjects were instructed to return any unused study drug at the study visits at Weeks 12, 26, 39 and 52 or the early termination visit. At this time, the investigational site staff counted the number of returned tablets to verify subject compliance and to account for all study drugs.

Safety Assessments in Study 15-50718:

A physical examination, including a breast examination, was performed at the Screening visit and at Weeks 12, 26, 52 (end-of-study) or early discontinuation and Week 56 (Follow-up). Vital signs (systolic and diastolic blood pressure, and pulse) were measured and recorded at every visit except Week 39. Height and weight was measured at Screening. Body mass index (BMI) was calculated at Screening, and Weeks 12, 26 and 52 (end-of-study) or early discontinuation. Any clinically significant changes in physical examination, BMI or vital signs after the Screening visit were recorded as adverse events (AEs).

A gynecological examination was performed at the Screening visit and at Weeks 12, 26, 52 (end-of-study) or early discontinuation, and Week 56 (Follow-up). A cervical Pap smear was obtained at the Screening visit and Week 52 (end-of-study) or if the subject discontinued after the Week 12 visit (early discontinuation). The samples were analyzed by a pathologist at (b) (4) and were classified according to the Bethesda 2001 System. Pelvic organ prolapse was evaluated at Screening. Subjects with uterine or vaginal prolapse of Grade 2 or higher at Screening were not included in the study. Subjects had to have an empty bladder for the assessment and were asked to Valsalva strain maximally. The following grading was used for evaluation of eligibility:

Uterine prolapse:

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

Vaginal prolapse (cystocele/urethrocele 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

A TVU was performed locally at the Screening visit and at Weeks 12, 26 and 52 (end-of-study) or early discontinuation. (b) (4) performed the readings of the endometrial biopsies and the TVUs.

TVUs were sent to (b) (4) for the assessment of double-layer endometrial thickness. The subject was not randomized until the centrally-read TVU result indicated that the double-layer endometrial thickness, excluding any

intrauterine fluid, was < 4 mm. (b) (4) provided instructions for the collection, processing, and shipping of the TVUs, as well as the acceptable formats.

Any symptomatic or large fibroids (estimated size >3 cm) or uterine polyps at Screening excluded the subject from the study. Subjects with endometrial polyps were discontinued if diagnosed during treatment.

An endometrial biopsy was performed at the Screening visit to evaluate each subject's eligibility for the study and to document the subject's endometrial findings at baseline. Subjects with normal or atrophic endometrial histology were eligible for randomization. Subjects with an insufficient biopsy sample after a valid attempt could be randomized if the endometrial thickness was < 4 mm. If an endometrial sample could not be obtained due to cervical stenosis (i.e., cervical os could not be penetrated), the subject was not eligible for the study. Women with endometrial polyps, hyperplasia, cancer or other abnormal pathology in the endometrial histology at Screening were not eligible for enrollment in the study.

At Weeks 12 and 26, an endometrial biopsy was performed only when the double-layer endometrial thickness (excluding any intrauterine fluid) was \geq 4 mm. If the investigator determined that the endometrial thickness was < 4 mm, and the central reader determined that the endometrial thickness was \geq 4 mm, an endometrial biopsy was to be performed after the results from the central reader were received at the site. An endometrial biopsy was performed on all subjects at Week 52. If a subject discontinued from the study prematurely, an endometrial biopsy was to be performed if the endometrial thickness was \geq 4 mm. If the subject had an insufficient biopsy sample at the end of the study, and endometrial thickness by TVU was \geq 4 mm, up to 2 repeat attempts were to be made to obtain a new endometrial biopsy sample with sufficient tissue for a diagnosis.

TVU was performed before endometrial biopsy, if possible, to avoid interference of the biopsy with interpretation of the TVU.

(b) (4) prepared the endometrial slides. Per the application, all endometrial histological slides were analyzed by two independent pathologists. When there was disagreement between the evaluations (histology class) of the two pathologists, a third pathologist evaluated these samples. The concurrence of two of the three independent pathologists was used as the final diagnosis. However, if there was no agreement among the three pathologists, then the most severe histopathologic diagnosis was used as the final diagnosis. All pathologists were blinded both to the study treatment and to each other's readings of the histology slides. In addition, per the application, diagnostic-quality digital slides of any treatment-emergent endometrial biopsy samples suggestive of an endometrial polyp were sent to an expert gynecological pathologist (b) (4).

Medical Officer's Comments:

As previously noted in this review, the Applicant's assessment procedure for the histologic evaluation of endometrial biopsy specimens was not in accordance with the recommendations in the Agency's 2003 draft Clinical Evaluation Guidance for Industry. The Clinical Evaluation Guidance for Industry recommends that three independent expert pathologists from different institutions, blinded to treatment group and to each other's readings, be used to determine the diagnosis of endometrial biopsy slides. The concurrence of two of the three pathologists would be accepted as the final diagnosis. When there is no agreement among the three pathologists, the most severe diagnosis would be used as the final diagnosis.

Per Study 15-50718, endometrial biopsy specimen slides were initially read by two pathologists, and only sent to the third pathologist if there was disagreement between the first two pathologists. This step-wise assessment procedure could lead to an introduction of bias in the evaluation conducted by the third pathologists, thus affecting the final diagnosis.

This reviewer is not in agreement the Applicant's procedure for sending "diagnostic-quality digital slides of any treatment-emergent endometrial biopsy sample suggestive of an endometrial polyp" to a selected "expert gynecological pathologist" to determine the diagnosis. The use of an "expert gynecological pathologist" to determine an "endometrial polyp" diagnosis is not in compliance with the Applicant's stated assessment procedure for determining a final diagnosis in the final protocol for Study 15-50718, "The concurrence of two of the three independent pathologists was used as the final diagnosis. However, if there was no agreement among the three pathologists, then the most severe histopathologic diagnosis was used as the final diagnosis."

If a subject reported vaginal bleeding during the study, an attempt was to be made to determine the etiology and a visual inspection and gynecological examination was to be performed. If no obvious reason was identified and the subject had an intact uterus, a TVU was to be performed to assess possible uterine pathology and the thickness of endometrium. If the endometrial thickness was < 4 mm, an endometrial biopsy was to be performed. If the biopsy yielded an insufficient sample and bleeding persisted, a hysteroscopy and guided biopsy was to be performed. If the endometrial thickness was \geq 4 mm, a hysteroscopy and guided biopsy was to be performed. In addition, the adnexa were to be checked with ultrasonography.

Blood and urine samples were collected for the laboratory tests at the Screening Visit and at Weeks 12, 26 and 52 or early discontinuation. Laboratory samples were sent to (b) (4) for testing.

Safety laboratory assessments included the following:

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.

NDA 203505

Osphena™ (ospemifene) tablets, for oral use

Hematology :	red blood cell (RBC) count, white blood cell count (WBC), differential, platelet count, hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume.
Chemistry:	albumin, ALT, AST, total bilirubin, creatinine, total protein, glucose, uric acid, blood urea nitrogen, and creatine kinase.
Coagulation:	activated partial thromboplastin time, fibrinogen, antithrombin III antigen, Factor V Leiden (Screening only), antithrombin III, protein-C antigen, and protein-S antigen.
Urinalysis	blood, glucose, ketones, protein
Lipids:	total cholesterol, LDL-C, HDL-C, and triglycerides.

Clinically significant laboratory findings were identified and recorded. Any clinically significant abnormal laboratory findings at the end of the study were followed up until satisfactory resolution or diagnosis could be made.

Subjects were queried about AEs at every visit after Screening. All clinical events, including either observed or volunteered problems, complaints, or symptoms, were recorded on the AE pages of the CRF. Each AE was evaluated for duration, severity, association with the study drug or other cause, and seriousness. All SAEs that occurred in a subject receiving study drug, or within 30 days after stopping treatment, were reported to Encorium within 24 hours, even if the SAE did not appear to be treatment-related.

Statistical Considerations:

AEs and medical history verbatim terms were encoded using the Medical Dictionary for Regulatory Activities (MedDRA), version 12.0. Concomitant medication verbatim terms were encoded using the World Health Organization Drug Dictionary (WHO DD), version 6.4. Safety data were presented using the safety population of subjects who received at least of study drug. Subjects in this population were presented according to the actual study treatment received. Any subjects who received both treatments were allocated to the active treatment group.

Changes in the Conduct of Study 15-50718:

Two amendments were applied to the original protocol dated May 24, 2007:

Amendment 1, dated October 24, 2007, included the following changes

- Sponsor and vendor contact information was updated.
- Randomization and screening terminology was clarified.

- It was specified that subjects had be in a fasted state for the study visits at Weeks 12, 26, and 52 (or early discontinuation).
- It was specified that subjects were to be advised not to have sexual intercourse within 24 hours prior to vaginal pH measurement.
- It was clarified that subjects with asymptomatic bacterial vaginosis that, according to the investigator, did not require medication could be randomized to the study.
- It was specified that if a subject with endometrial thickness ≥ 4 mm discontinued from the study prematurely, an endometrial biopsy would be performed.
- Mean platelet volume was deleted from the table of hematology variables for analysis.
- It was clarified that pre-planned surgery was not an SAE.
- It was specified that data were collected using electronic CRFs. Other procedural details associated with electronic data capture were clarified.
- Minor typographical errors were corrected and minor procedural details were clarified.

Amendment 2, dated January 10, 2008, included the following changes:

- Clarify exclusion criteria to include additional concomitant medications which are strong inhibitors of CYP3A4.
- Clarify subject restriction to inform investigators that ospemifene may induce the metabolism of substances via cytochrome P4503A4.

Safety Extension Phase 3 Study 15-50310X:

Study 15-50310X entitled, “Long-term Safety of 30 mg and 60 mg Oral Daily Doses of Ospemifene in the Treatment of Vulvar and Vaginal Atrophy (VVA) in Postmenopausal Women with an Intact Uterus: A 40-Week, Randomized, Double-Blind, Placebo-Controlled, Follow-up to Protocol 15-50310” was initiated on May 16, 2006 and completed on September 18, 2008. This study was a 40-week, multi-center, placebo-controlled safety study designed to assess the long-term safety of daily doses of 30 mg ospemifene and 60 mg ospemifene versus placebo. Subjects who completed 12-week Study 15-50310 without any clinically significant abnormal findings at the end-of-study visit, who had a uterus, were eligible to participate in Study 15-50310X. A subject continued on the same treatment that they were randomized to in Study 15-50310, and the treatment blind was maintained. Consent for participation in Study 15-50310X occurred at Week 12 of Study 15-50310. The study was conducted at 51 centers in the U.S., all of which randomized at least 1 subject.

The primary objective of this study was to assess the long-term safety of 30 mg and 60 mg ospemifene daily doses in the treatment of VVA in a postmenopausal woman with a uterus.

The total treatment period across both studies (Study 15-50310 and Study 15-50310X) was 52 weeks followed by a 4-week post-treatment follow-up visit. Consent for Study 15-50310X occurred at the Week 12 visit of the parent study. Subjects were to continue taking a dose of study drug each morning with food. Subsequent study visits took place at Week 26, Week 52, and Week 56 (Follow-up). Telephone contact was made with the subjects at Weeks 20 and 40 to assess adverse events, concomitant medication use, and treatment compliance.

In total, 180 Subjects were enrolled in Study 15-50310X:

- 62 subjects in the 30 mg ospemifene treatment group
- 69 subjects in the 60 mg ospemifene treatment group
- 49 subjects in the placebo treatment group

Inclusion Criteria:

Subjects who met all of the following criteria at Week 12 (Visit 4) of Study 15-50310 were eligible for this extension study:

1. Provided written informed consent to participate in the study and agreed to follow dosing instructions and complete all required study visits.
2. An intact uterus.
3. Met the inclusion and exclusion criteria for Study 15-50310.
4. Completed 12-week Study 15-50310.

Exclusion Criteria:

Subjects with an intact uterus who met any of the following criteria were not eligible to participate in the study:

1. Clinically significant abnormal findings at the Week 12 end-of-study visit for Study 15-50310.
2. Any physical or mental condition which, in the opinion of the investigator, may have interfered with the subject's ability to comply with the study procedures.

Efficacy Assessments:

There were no efficacy assessments conducted in this extension study.

Safety Assessments:

Subjects were asked to continue to spontaneously report all AEs throughout the study period.

Physical and gynecological examinations were performed at Weeks 26, 52, and 56 (Follow-up) to assess the subject's current health status. Visual evaluation of the vagina (petechiae, pallor, friability, vaginal dryness, and redness seen in vaginal mucosa), was assessed on a 4-point scale (0=None, 1=Mild, 2=Moderate, 3=Severe). A Pap smear and mammogram was repeated at Week 52. At weeks 26 and 52, a TVU was performed locally and evaluated by a central reader (or at the time of discontinuation). An endometrial biopsy was performed at Week 26 only if the TVU indicated that the double-wall thickness was ≥ 4 mm. An endometrial biopsy was performed at end-of-study. Subjects found to have endometrial hyperplasia or endometrial adenocarcinoma at any point during the study were removed from the study. If a subject reported vaginal bleeding during the study, similar follow-up procedures were completed as described in Study 15-50310.

Significant changes in health status or current diseases were recorded as AEs.

Statistical Considerations:

Study 15-50310X was conducted under the same protocol at all study centers.

The change from Baseline represents the change from pre-treatment values. Therefore, the Baseline value from Study 15-50310 was used. All analyses were done on the ITT population. The ITT population was defined as any subject who entered the study and received at least one dose of study medication.

The data were analyzed using descriptive statistics unless otherwise noted. Reasons for premature termination were compared between treatments assigned in Study 15-50310 using descriptive statistics.

Changes in the Conduct of Study 15-50310X:

There were no amendments to the original protocol dated January 3, 2006.

Safety Extension Phase 3 Study 15-50312:

Study 14-50312 entitled, "Long-term Safety of Ospemifene 60 mg Oral Daily Dose for the Treatment of Vulvar and Vaginal Atrophy (VVA0 in Postmenopausal Women Without a Uterus: A 52-Week Open-Label Follow-up to Protocol 15-50310" was initiated on May 8, 2006 and completed on December 22, 2008. This study was a 52-week, multi-center, open-label safety study designed to assess the long-term safety of daily doses of 60 mg ospemifene. Subjects who completed 12-week Study 15-50310 without any clinically significant abnormal findings at the end-of-study visit, who did not have a uterus, were eligible to participate in Study 15-50312. Consent for participation in Study 15-50312 occurred at Week 12 of Study 15-50310. Subsequent study visits took place at Weeks 26, 52, and 56 (Follow-up). Phone contact with subjects took place at Weeks

13 and 39 to assess AEs, concomitant medication, and treatment compliance. Study 15-50312 was conducted at 59 centers in the U.S. (48 centers enrolled at least 1 subject).

In total, 301 subjects were enrolled and included in the ITT population: 97 subjects had received 30 mg ospemifene in Study 15-50310; 97 subjects had received 60 mg ospemifene in Study 15-50310; and 107 subjects had received placebo in Study 15-50310). Subjects took the study medication (60 mg ospemifene) daily each morning with food. The primary emphasis of the safety analyses was to characterize changes from Baseline and flag clinically relevant abnormal findings.

Subjects eligible for participation in Study 15-50312 were screened for entry at Visit 1 (Week 12 in Study 15-50310). The following procedures were performed in addition to the study activities required for Visit 4 of Study 15-50310:

1. The investigator informed the subject both verbally and in writing about the extension study and obtained her written informed consent to participate in the extension study before any study procedures were initiated.
2. Subjects were assessed for eligibility using the inclusion and exclusion criteria for the study. Subjects who did not meet the eligibility criteria were excluded from the study.
3. Each subject maintained the same subject number assigned in the preceding parent study.
4. Subjects were dispensed study drug for the extension study.

Subsequent study visits took place at Weeks 26, 52, and 56 (Follow-up). Phone contact with subjects took place at Weeks 13 and 39 to assess AEs, concomitant medication, and treatment compliance.

Inclusion Criteria:

Subjects who met all of the following criteria at Week 12 (Visit 4) of the preceding parent study (Study 15-50310) were eligible for this extension study:

1. Provided written informed consent to participate in the study and agreed to follow dosing instructions and complete all required study visits.
2. Did not have a uterus.
3. Met the inclusion and exclusion criteria for Study 15-50310.
4. Completed Study 15-50310.

Exclusion Criteria:

Subjects who met any of the following criteria were not eligible to participate in the study:

1. Clinically significant abnormal findings at the Week 12 end-of-study visit for Study 15-50310.
2. Any physical or mental condition which, in the opinion of the investigator, may have interfered with the subject's ability to comply with the study procedures.

Efficacy Assessments:

There were no efficacy assessments conducted in this extension study.

Safety Assessments:

Subjects were asked to continue to spontaneously report all AEs throughout the study period. In addition, subjects were queried regarding adverse events during the scheduled telephone contacts.

Physical and gynecological examinations, and laboratory assessments were performed at Weeks 26, 52, and 56 (Follow-up) to assess the subject's current health status. Visual evaluation of the vagina (petechiae, pallor, friability, vaginal dryness, and redness seen in vaginal mucosa), was assessed on a 4-point scale (0=None, 1=Mild, 2=Moderate, 3=Severe). A Pap smear and mammogram was repeated at Week 52. Significant changes in health status or current diseases were recorded as AEs.

Statistical Considerations:

Study 15-50312 was conducted under the same protocol at all study centers.

The change from Baseline represents the change from pre-treatment values. Therefore, the Baseline value from Study 15-50310 was used. All analyses were done on the ITT population. The ITT population was defined as any subject who entered the study and received at least one dose of study medication.

The data were analyzed using descriptive statistics unless otherwise noted. Reasons for premature termination were compared between treatments assigned in Study 15-50310 using descriptive statistics.

Changes in the Conduct of Study 15-50312:

There were no amendments to the original protocol dated January 3, 2006.

6 Review of Efficacy

6.1 Indication

The proposed indication in the application reads, “OSPENA is an estrogen receptor agonist/antagonist for the treatment of vulvar and vaginal atrophy due to menopause, including moderate to severe symptoms of dyspareunia and/or vaginal dryness and physiological changes (parabasal cells, superficial cells and pH).”

Medical Officer’s Comments:

The proposed indication in NDA 203505 is unacceptable. As proposed, this indication combines the recommended primary clinical outcome of the treatment of moderate to severe symptoms of vulvar and vaginal atrophy, in this case dyspareunia and/or vaginal dryness, with physiologic signs (changes in superficial and parabasal cells, and vaginal pH). The evaluations of these physiologic signs, however, are only supportive of the treatment effect and are not clinically meaningful outcomes in themselves.

Therefore, the indication that would generally be granted for a product approved for the treatment of dyspareunia and vaginal dryness should read, Tradename is indicated for the treatment of moderate to severe dyspareunia and vaginal dryness, symptoms of vulvar and vaginal atrophy, due to menopause.

6.1.1 Methods

The data presented in two 12-week, safety and efficacy Phase 3 clinical studies (Study 15-50310 and Study 15-50821) were reviewed in their entirety.

Phase 3 Study 15-50310:

Eight hundred twenty-six (826) healthy postmenopausal women, with and without an intact uterus, 40 to 80 years of age, were enrolled and included in the ITT population of Study 15-50310. Five hundred and fifty-two (552) subjects were included in the PP population. One hundred thirty-seven (137) subjects discontinued the study. Subjects who completed Study 15-50310 were considered for entrance into long-term safety extension studies (Study 15-50310X for a woman with a uterus; Study 15-50312 for a woman without a uterus).

Phase 3 Study 15-50821:

Nine hundred and nineteen (919) healthy postmenopausal women, with and without an intact uterus, 40 to 80 years of age, were enrolled and included in the ITT population of

Study 15-50821. Seven hundred and seventy (770) subjects were included in the PP population. One hundred (100) subjects discontinued.

Phase 3 Study 15-50718:

Four hundred and twenty-six postmenopausal (426) women with intact uteri, 49 to 79 years of age, were enrolled (363 subjects [85.2%] in the 60 mg ospemifene group and 63 [14.8%] in the placebo group; 6 to 1 ratio). Seventy-seven subjects (77; [18.1%]) discontinued.

The efficacy measurements included in Study 15-50718 were limited to vaginal pH and the percentage of superficial and parabasal cells on the Maturation Index. No data was collected in Study 15-50718 regarding the third recommended co-primary endpoint of the mean change in the self-identified individual most bothersome moderate to severe vulvar and vaginal atrophy symptom between Baseline and Week 12.

Medical Officer's Comments:

Because Study 15-50718 did not assess the change from Baseline to Week 12 in the individual self-identified most bothersome moderate to severe symptom of vulvar and vaginal atrophy, a third recommended co-primary endpoint for a VVA indication, the results for the proportion of superficial/parabasal cells in the Maturation Index, and vaginal pH in Study 15-50718 are not included in this reviewer's decision regarding the effectiveness of the 60 mg ospemifene dose to relieve moderate to severe vaginal dryness or dyspareunia.

6.1.2 Demographics

Phase 3 Study 15-50310:

The demographics and baseline characteristics of the ITT cohort for Study 15-50310 are shown in Table 3.

Table 3: Demographics for Study 15-50310; ITT Population

Parameter and Statistic	Placebo N = 268	Ospemifene 30 mg N = 282	Ospemifene 60 mg N = 276	Total N = 826
Age (Years)				
Mean (SD)	58.9 (6.09)	58.4 (6.27)	58.6 (6.34)	58.6 (6.23)
Median	58.0	58.0	58.0	58.0
(Min, Max)	(43, 79)	(41, 79)	(42, 80)	(41, 80)

Body Mass Index (kg/m²)				
Mean (SD)	26.1 (4.37)	26.4 (4.51)	26.0 (4.44)	26.2 (4.43)
Median	25.3	25.9	25.4	25.6
(Min, Max)	(17.4, 38.0)	(17.2, 41.6)	(15.7, 48.6)	(15.7, 48.6)
Weight (kg)				
Mean (SD)	69.0 (12.90)	69.2 (13.06)	68.4 (12.08)	68.9 (12.68)
Median	67.7	69.5	66.8	67.7
(Min, Max)	(43.1, 113.4)	(41.3, 111.5)	(37.6, 106.6)	(37.6, 113.4)
Race				
African-American	14 (5.2%)	18 (6.4%)	18 (6.5%)	50 (6.1%)
Asian	6 (2.2%)	5 (1.8%)	4 (1.4%)	15 (1.8%)
Caucasian	242 (90.3%)	253 (89.7%)	249 (90.2%)	744 (90.1%)
Hispanic	17 (6.0%)	20 (7.2%)	24 (9.0%)	61 (7.4%)
Other	4 (1.5%)	6 (2.1%)	2 (0.7%)	12 (1.5%)

Source: Adapted from NDA 203505, Study 15-50310 Clinical Study Report, Table 11.2, page 53.
Definitions: ITT = intent-to-treat, SD = standard deviation, Min = minimum, Max = maximum.

Medical Officer's Comments:

The demographics characteristics are similar among the 3 treatment groups in Study 15-50310.

Phase 3 Study 15-50821:

The demographics and baseline characteristics of the ITT cohort for Study 15-50821 are shown in Table 4.

Table 4: Demographics for Study 15-50821 (Dryness and Dyspareunia Strata Combined); ITT Population

Parameter and Statistic	Placebo N = 456	Ospemifene 60 mg N = 463	Total N = 919
Age (Years)			
Mean (SD)	58.5 (6.39)	58.7 (6.56)	58.6 (6.47)
Median	58.0	58.0	58.0
(Min, Max)	(41, 79)	(40, 78)	(40, 79)
Body Mass Index (kg/m²)			
Mean (SD)	26.21 (4.32)	26.16 (4.31)	26.18 (4.31)
Median	25.85	25.70	25.80
(Min, Max)	(16.5, 38.7)	(16.7, 37.0)	(16.5, 38.7)
Weight (kg)			
Mean (SD)	69.38 (12.38)	68.98 (12.38)	69.18 (12.370)
Median	68.35	67.70	68.00
(Min, Max)	(29.6, 111.8)	(40.7, 108.1)	(39.6, 111.8)
Race			
African-American	35 (7.7%)	28 (6.0%)	63 (6.9%)

Asian	3 (0.7%)	8 (1.7%)	11 (1.2%)
Caucasian	396 (86.8%)	409 (88.3%)	805 (87.6%)
Other	22 (4.8%)	16 (3.5%)	38 (4.1%)

Source: Adapted from NDA 203505, Study 15-50821 Clinical Study Report, Table 9, page 59.

Definitions: ITT = intent-to-treat. SD = standard deviation; Min = minimum; Max = maximum.

Medical Officer's Comments:

Table 4 shows the demographic characteristics for the combined strata in Study 15-50821 (Dryness Stratum and Dyspareunia Stratum). The reported demographic characteristics are similar between the 2 treatment groups. In addition, demographic characteristics in Study 15-50821 are similar to Phase 3 Study 15-50310 (see Table 3).

Phase 3 Study 15-50718:

The demographics and baseline characteristics of the ITT cohort for Study 15-50718 are shown in Table 5. This study is the long-term, 52-week safety study conducted in Belgium, Denmark, Finland, and Sweden.

Table 5: Demographics for Study 15-50718: ITT Population

Parameter and Statistic	Placebo N = 63	60 mg Ospemifene N = 363
Age (Years)		
Mean (SD)	62.9 (6.47)	61.7 (6.16)
Range	(50 – 79)	(49 – 78)
Body Mass Index (kg/m²)		
Mean (SD)	24.11 (2.867)	24.65 (2.916)
Range	(17.7 – 29.7)	17.4 – 31.2)
Race		
Caucasian	63 (100.0%)	361 (99.4%)
Black	0 (0.0%)	1 (0.3%)
Asian	0 (0.0%)	1 (0.3%)

Source: Adapted from NDA 203505, Study 15-50718 Clinical Study Report, Table 3, page 59 of 129.

Definitions: ITT = intent-to-treat, SD = standard deviation.

Medical Officer's Comments:

As shown in Table 5, the two treatment groups were closely matched in Study 15-50718. The mean age of study participants in Study 15-50718 was slightly higher (62.3 year of age) than in Studies 15-50310 and 15-50821 (58.6 years of age in both studies). Since the efficacy data reported in Study 15-50718 is considered supportive, these differences in mean age across the three Phase 3 studies are not a review issue.

In all three of these Phase 3 studies completed (Studies 15-50310, 15-50821, and 15-50718), the majority of subjects were Caucasians.

6.1.3 Subject Disposition

Phase 3 Study 15-50310:

The overall disposition of ITT subjects in Study 15-50310 is summarized in Table 6. A total of 826 subjects were enrolled into the study and randomized, 689 (83.4%) subjects completed the study, and 137 (16.6%) subjects discontinued prematurely.

Table 6: Subject Disposition for Study 15-50310: ITT Population

	Placebo N = 268	Ospemifene 30 mg N = 282	Ospemifene 60 mg N = 276	Total N = 826
Number Completed Study	230 (85.8%)	225 (79.8%)	234 (84.8%)	689 (83.4%)
- Continued in Long-Term Safety	156 (58.2%)	160 (56.7%)	167 (60.5%)	483 (58.5%)
Total Discontinued	38 (14.2%)	57 (20.2%)	42 (15.2%)	137 (16.6%)
Reason Discontinued				
- Withdrew Consent	12 (4.5%)	14 (5.0%)	14 (4.5%)	40 (4.8%)
- Lost to Follow-up	4 (1.5%)	8 (2.8%)	6 (2.2%)	18 (2.2%)
- Adverse Event	11 (4.1%)	15 (5.3%)	13 (4.7%)	39 (4.7%)
- Major Protocol Violation	7 (2.6%)	11 (3.9%)	6 (2.2%)	24 (2.9%)
- Used Concomitant Medication	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
- Non-Compliance	1 (0.4%)	3 (1.1%)	1 (0.4%)	5 (0.6%)
- Other	2 (0.7%)	6 (2.1%)	2 (0.7%)	10 (1.2%)

Source: Adapted for NDA 203505, Study 15-50310 Clinical Study Report dated April 20, 2009, page 48.
Definition: ITT = intent-to-treat.

Medical Officer's Comments:

As shown in Table 6, the proportion of subjects who discontinued was greater in the 30 mg ospemifene group (20.2%) than in the 60 mg ospemifene group (15.2%) or the placebo group (14.2%). The slightly higher discontinuation rate for the 30 mg ospemifene treatment group over the 60 mg ospemifene and placebo treatment groups is not fully explained.

The most common reasons for premature discontinuation overall in Study 15-50310 were subject withdrawal of consent (40 subjects, 4.8% of subjects with a slightly higher discontinuation rate in the 30 mg ospemifene treatment group) and adverse events (39 subjects, 4.7% with a higher discontinuation rate in the 30 mg ospemifene treatment group).

See a discussion of adverse events in 12-week Study 15-50310 in Subsection 4.2.1 Common Adverse Events.

Phase 3 Studies 15-50821:

The overall disposition of ITT subjects in Study 15-50821, combining the Dryness Stratum and the Dyspareunia Stratum, is summarized in Table 7. A total of 919 subjects were enrolled into the study and randomized, 819 (89.1%) subjects completed the study, and 100 (10.9%) subjects discontinued prematurely.

Table 7: Subject Disposition for Study 15-50821 (Dryness and Dyspareunia Strata Combined); ITT Population

	Placebo N = 456	Ospemifene 60 mg N = 463	Total N - 919
Number of subjects completed, n (%)	403 (88.4%)	416 (89.8%)	819 (89.1%)
Number of subjects discontinued, n (%)	53 (11.6%)	47 (10.2%)	100 (10.9%)
- Adverse event	14 (3.2%)	25 (5.4%)	39 (4.2%)
- Lost to follow- up	9 (2.0%)	9 (1.9%)	18 (2.0%)
- Protocol violation	2 (0.4%)	1 (0.2%)	3 (0.3%)
- Subject request	19 (4.2%)	8 (1.7%)	27 (2.9%)
- Other	9 (2.9%)	4 (0.9%)	13 (1.4%)

Source: Adapted from NDA 203505, Study 15-50821 Clinical Study Report, Table 6, page 55.

Definition: ITT = intent-to-treat.

Medical Officer's Comments:

As shown in Table 7, the most common reason for discontinuation from Study 15-50821 (strata combined) was due to an adverse event (4.2% of total subjects), occurring in a greater proportion of subjects in the ospemifene group than the placebo group (5.4% versus 3.2%, respectively). However, this reported discontinuation rate in 12-week Study 15-50821 (strata combined) is similar to the reported discontinuation rate due to an adverse event in 12-week Study 15-50310 (4.7%, 39 of 483 subjects).

See a discussion of adverse events in 12-week Study 15-50821 in Subsection 4.2.1 Common Adverse Events.

An analysis of subject disposition by stratum in Study 15-50821 also shows similar completion rates with 87.5% and 89.9% of subjects in the Dryness Stratum and the Dyspareunia Stratum, respectively. See Tables 8 and 9.

Table 8: Subject Disposition for Study 15-50821 (Dryness Stratum); ITT Population

	Placebo N = 154	Ospemifene 60 mg N = 160	Total N = 314
Number of subjects completed, n (%)	137 (89.0%)	138 (86.3%)	275 (87.5%)
Number of subjects discontinued, n (%)	17 (11.0%)	22 (13.8%)	39 (12.4%)
- Adverse event	5 (3.2%)	11 (6.9%)	16 (1.9%)
- Lost to follow- up	3 (1.9%)	3 (1.9%)	6 (1.9%)
- Protocol violation	1 (0.6%)	1 (0.6%)	2 (0.6%)

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- Subject request	6 (3.9%)	4 (2.5%)	10 (3.2%)
- Other	2 (1.3%)	3 (1.9%)	5 (3.2%)

Source: Adapted from NDA 203505, Study 15-50821 Clinical Study Report, Table 14.1.2.1.
Definition: ITT = intent-to-treat.

Table 9: Subject Disposition for Study 15-50821 (Dyspareunia Stratum): ITT Population

	Placebo N = 302	Ospemifene 60 mg N = 303	Total N = 605
Number of subjects completed, n (%)	266 (88.1%)	278 (91.7%)	544(89.9%)
Number of subjects discontinued, n (%)	36 (11.9%)	25 (8.3%)	61 (10.1%)
- Adverse event	9 (3.0%)	14 (4.6%)	23 (3.8%)
- Lost to follow- up	6 (2.0%)	6 (2.0%)	12 (2.0%)
- Protocol violation	1 (0.3%)	0 (0.0%)	1 (0.2%)
- Subject request	13 (4.3%)	4 (1.3%)	17 (2.8%)
- Other	7 (2.3%)	1 (0.3%)	8 (1.3%)

Source: Adapted from NDA 203505, Study 15-50821 Clinical Study Report, Table 14.1.2.2.
Definition: ITT = intent-to-treat.

Phase 3 Study 15-50718:

The overall disposition of ITT subjects in 52-week Study 15-50718 is summarized in Table 10. This study is the long-term, 52-week safety study conducted in Belgium, Denmark, Finland, and Sweden.

Table 10: Subject Disposition for study 15-50718; ITT Population

	Placebo N = 63	60 mg Ospemifene N = 363
Number of subjects completed, n (%)	55 (87.3%)	294 (81.0%)
Number of subjects discontinued, n (%)	8 (12.7%)	69 (19.0%)
- Adverse event	6 (9.5%)	48 (13.2%)
- Subject request	1 (1.6%)	14 (3.9%)
- Protocol violation	1 (1.6%)	4 (1.1%)
- Lost to follow-up	0 (0.0%)	1 (0.3%)
- Other	0 (0.0%)	2 (0.6%)

Source: Adapted from NDA 203505, Study 15-50718 Clinical Study Report, Table 2, page 56 of 129.
Definition: ITT = intent-to-treat.

Medical Officer's Comments:

The proportion of subjects who discontinued Study 15-50718 was higher in the 60 mg ospemifene group compared to the placebo group (19.0% versus 12.7%, respectively), primarily due to discontinuations because of adverse events (13.2% versus 9.5%) and subject request (3.9% versus 1.6%).

See the discussion of adverse events occurring in 52-week Study 15-50718 in Subsection 4.2.1 Common Adverse Events.

6.1.4 Analysis of Primary Endpoint(s)

Phase 3 Study 15-50310:

The primary efficacy results obtained for the ITT population from the Clinical Study Report for Study 15-50310, dated April 20, 2009, are shown in Table 11. These reported primary efficacy analyses are not based on subjects who met all three baseline inclusion criteria: $\leq 5\%$ superficial cells on a vaginal smear, a vaginal pH greater than 5.0, and a most bothersome moderate to severe vaginal symptom (vaginal dryness or dyspareunia).

Table 11: Applicant-Reported Primary Efficacy Summary: Mean Change from Baseline to Week 12/LOCF in Study 15-50310; ITT Population

	Ospemifene 30 mg	Ospemifene 60 mg	Placebo
% Superficial Cells	N = 274	N = 272	N = 261
- Baseline Mean (SD)	1.25 (2.907)	1.04 (3.368)	0.91 (2.635)
- Week 12 Mean (SD)	9.30 (12.293)	12.1 (15.85)	3.09 (8.622)
- Mean Change from Baseline (SD)	7.78 (12.136)	10.8 (15.66)	2.18 (8.393)
- P-value for Treatment Comparison ^a	<0.001	<0.001	-
% Parabasal Cells	N = 274	N = 272	N = 261
- Baseline Mean (SD)	40.1 (38.33)	39.3 (38.98)	38.5 (37.60)
- Week 12 Mean (SD)	17.4 (26.54)	8.78 (19.31)	42.7 (37.22)
- Mean Change from Baseline (SD)	-21.9 (32.60)	-30.1 (37.93)	3.98 (35.20)
- P-value for Treatment Comparison ^a	<0.001	<0.001	-
Vaginal pH	N = 282	N = 276	N = 268
- Baseline Mean (SD)	6.35 (0.736)	6.37 (0.763)	6.34 (0.732)
- Week 12 Mean (SD)	5.68 (1.054)	5.36 (0.943)	6.24 (0.911)
- Mean Change from Baseline (SD)	-0.67 (1.054)	-1.01 (1.053)	-0.096 (0.836)
- P-value for Treatment Comparison ^a	<0.001	<0.001	-
Vaginal Dryness	N = 102	N = 118	N = 104
- Baseline Mean (SD)	2.48 (0.558)	2.42 (0.560)	2.38 (0.508)
- Week 12 Mean (SD)	1.26 (0.855)	1.15 (0.975)	1.55 (1.032)
- Mean Change from Baseline (SD)	-1.22 (0.929)	-1.26 (1.025)	-0.84 (0.996)
- P-value for Treatment Comparison ^b	0.040	0.021	-
Dyspareunia	N = 136	N = 120	N = 122
- Baseline Mean (SD)	2.55 (0.653)	2.61 (0.702)	2.66 (0.584)
- Week 12 Mean (SD)	1.53 (1.075)	1.42 (1.17)	1.78 (1.154)
- Mean Change from Baseline (SD)	-1.02 (1.132)	-1.19 (1.292)	-0.89 (1.115)
- P-value for Treatment Comparison ^b	0.200	0.023	-

Source: Adapted from NDA 203505, Study 15-50310 Clinical Study Report, Table 11.8 on page 60, Table 11.7 on page 58, Table 11.9 on page 62, Table 11.10 on page 64, and Table 11.11 on page 66.

- a P-value for treatment comparisons (each active versus placebo) from rank-based analysis of variance stratified by uterine status and pooled center.
- b P-value for treatment comparison (each active versus placebo) from Cochran-Mantel-Haenszel row mean score test controlling for uterine status (intact uterus versus hysterectomized) and pooled center.

Definitions: LOCF = last observation carried forward, ITT = intent-to-treat, SD = standard deviation.

Medical Officer's Comments:

These reported results are not based on subjects who met all three baseline inclusion criteria. However, these ITT reported results for 12-week Study 15-50310 demonstrate mean change differences in the recommended co-primary endpoints of interest.

The difference in mean change from Baseline to Week 12 in the percentage of superficial cells comparing the 2 active treatment groups to placebo showed that both the 30 mg and the 60 mg ospemifene groups were statistically significant compared with placebo group ($p < 0.001$ for both the 30 mg ospemifene group and the 60 mg ospemifene group). With regards to the comparison between the 2 active treatment groups, the 60 mg ospemifene group showed a greater increase in the percentage of superficial cells than the 30 mg ospemifene group.

The difference in mean change from Baseline to Week 12 in the percentage of parabasal cells comparing the 2 active treatment groups to placebo showed that both the 30 mg and the 60 mg ospemifene groups were statistically significant compared with placebo group ($p < 0.001$ for both the 30 mg ospemifene group and the 60 mg ospemifene group). The 60 mg ospemifene group showed a greater decrease in the percentage of parabasal cells than the 30 mg ospemifene group.

The difference in mean change from Baseline to Week 12 in vaginal pH comparing the 2 active treatment groups to placebo showed that both the 30 mg and the 60 mg ospemifene groups were statistically significant compared with the placebo group ($p < 0.001$ for both the 30 mg ospemifene group and the 60 mg ospemifene group). With regards to the comparison between the 2 active treatment groups, the 60 mg ospemifene group showed a greater decrease in vaginal pH than the 30 mg ospemifene group.

The difference in mean change from Baseline to Week 12 in the MBS of vaginal dryness comparing the 2 active treatment groups to placebo showed that both the 30 mg and the 60 mg ospemifene groups were statistically significant compared with the placebo group ($p = 0.040$ for the 30 mg ospemifene group and $p = 0.021$ for the 60 mg ospemifene group).

The difference in mean change from Baseline to Week 12 in the MBS of dyspareunia comparing the 2 active treatment groups to placebo showed that the 60 mg ospemifene group was statistically significant compared with the placebo group ($p = 0.023$), but that

the 30 mg ospemifene was not statistically significant compared with the placebo group (p=0.200).

In a teleconference with the Applicant on June 27, 2012, DRUP repeated its previous advice to the Applicant that the determination of efficacy would be based on data reported in the individual study reports (Study 15-50310 and Study 15-50821) for those subjects who met all of the following inclusion criteria: $\leq 5\%$ superficial cells on a vaginal smear, a vaginal pH > 5.0 , and a most bothersome moderate to severe symptom (vaginal dryness or dyspareunia). The data included in the application in the individual study reports for Study 15-50310 and Study 15-50821 was not based on subjects who met all of the three recommended Baseline inclusion criteria.

One analysis reported in the application in the “Summary of Clinical Efficacy” document and the “Integrated Summary of Efficacy” document, however, appeared to be based on subjects meeting all three of the recommended Baseline inclusion criteria (the modified ITT analysis [mITT]). DRUP requested, therefore, that the Applicant submit an addendum to the Clinical Study Report for Study 15-50310 and Study 15-50821 with the mITT primary analyses (including only subjects who met all three recommended Baseline inclusion criteria) consistent with the mITT analysis presented in the “Summary of Clinical Efficacy” and the “Integrated Summary of Efficacy.” The addendum for Study 15-50310 and for Study 15-50821 was received on July 9, 2012.

The primary efficacy results reported in the addendum to the Study 15-50310 Clinical Study Report, dated July 9, 2012, are shown in Table 12. Per the Applicant, these reported primary efficacy analyses are based on subjects who met all three baseline inclusion criteria: $\leq 5\%$ superficial cells on a vaginal smear, a vaginal pH greater than 5.0, and a most bothersome moderate to severe vaginal symptom (vaginal dryness or dyspareunia).

Table 12: Revised Applicant-Reported Primary Efficacy Summary: Mean Change from Baseline to Week 12/LOCF in Study 15-50310; Modified ITT Population^a

	Ospemifene 30 mg	Ospemifene 60 mg	Placebo
% Superficial Cells	N = 257	N = 254	N = 247
- Baseline Mean (SD)	1.0 (1.53)	0.7 (1.35)	0.7 (1.26)
- Week 12 Mean (SD)	9.1 (11.85)	12.4 (15.63)	2.8 (8.20)
- Mean change from Baseline (SD)	8.1 (11.87)	11.7 (15.72)	2.1 (7.98)
- Lease Squares Mean (SE)	2.3 (0.79)	8.3 (0.78)	2.3 (0.79)
- P-value for Treatment Comparison ^b	<0.0001	<0.0001	-
% Parabasal Cells	N = 257	N = 254	N = 247
- Baseline Mean (SD)	40.2 (38.48)	40.6 (39.07)	38.8 (37.60)
- Week 12 Mean (SD)	16.9 (26.20)	9.0 (19.69)	42.5 (37.25)
- Mean change from Baseline (SD)	-2.3 (33.20)	-31.6 (38.60)	4.7 (35.68)

- Least Squares Mean (SE)	-23.1 (1.62)	-31.6 (38.60)	4.1 (1.64)
- P-value for Treatment Comparison ^b	<0.0001	<0.0001	-
Vaginal pH	N = 257	N = 254	N = 247
- Baseline Mean (SD)	6.36 (0.727)	6.38 (0.751)	6.36 (0.721)
- Week 12 Mean (SD)	5.66 (1.061)	5.37 (0.962)	6.24 (0.908)
- Mean change from Baseline (SD)	-0.67 (1.054)	-0.70 (1.065)	-0.12 (0.831)
- Least Squares Mean (SE)	-0.70 (0.058)	-0.99 (0.058)	-0.11 (0.058)
- P-value for Treatment Comparison ^b	<0.0001	<0.0001	-
Vaginal Dryness	N = 95	N = 113	N = 100
- Baseline Mean (SD)	2.5 (0.50)	2.5 (0.50)	2.4 (0.50)
- Week 12 Mean (SD)	1.3 (0.84)	1.1 (0.98)	1.5 (1.03)
- Mean Change from Baseline (SD)	-1.3 (0.92)	-1.3 (0.99)	-0.9 (0.97)
- P-value for Treatment Comparison ^c	P=0.0407	P=0.0136	-
Dyspareunia	N = 124	N = 110	N = 113
- Baseline Mean (SD)	2.6 (0.48)	2.6 (0.44)	2.7 (0.45)
- Week 12 Mean (SD)	1.5 (1.09)	1.4 (1.17)	1.8 (1.16)
- Mean Change from Baseline (SD)	-1.1 (1.02)	-1.4 (1.14)	-0.9 (1.13)
- P-value for Treatment Comparison ^c	0.0968	0.0012	-

Source: Adapted from NDA 203505, Addendum to Clinical Study Report for Study 15-50310 dated July 9, 2012, Table 14.9.2.1.2, Table 14.9.1.1.2, Table 14.9.3.1.2, Table 14.9.4.1.3, and Table 14.9.4.2.2.

- a Based on subjects who met all three baseline inclusion criteria: $\leq 5\%$ superficial cells on a vaginal smear, a vaginal pH greater than 5.0, and a most bothersome moderate to severe vaginal symptom (vaginal dryness or dyspareunia).
- b P-value was computed using ANCOVA where change from Baseline is response variable, Baseline assessment is the covariate, and treatment, uterus status (intact or not), and center are fixed effects.
- c P-value was computed using Cochran-Mantel-Haenszel row mean score test controlling for uterus status (intact or not) and center.

Definitions: LOCF = last observation carried forward, ITT = intent-to-treat, SD = standard deviation.

Medical Officer's Comments:

As previously noted, a mITT population was defined as including only subjects who met at Baseline the inclusion criteria of $\leq 5\%$ superficial cells on a vaginal smear, had a vaginal pH > 5.0, and at least 1 symptom of VVA (vaginal dryness or dyspareunia) that was designated as moderate or severe and most bothersome. Per the application, most exclusions from the mITT population were due to unmet MBS criteria at Baseline.

From the data shown in Table 12, the 60 mg ospemifene dose demonstrates significantly greater improvement over placebo at Week 12 in the:

- increase of superficial epithelial cells ($p < 0.0001$),
- decrease in parabasal epithelial cells ($p < 0.0001$),
- decrease in vaginal pH ($p < 0.0001$),
- decrease in the severity of the MBS of vaginal dryness ($p = 0.0136$),
- decrease in the severity of the MBS of dyspareunia ($p = 0.0012$).

The 30 mg ospemifene dose demonstrates significantly greater improvement over placebo at Week 12 in the:

- increase of superficial epithelial cells ($p < 0.0001$),
- decrease in parabasal epithelial cells ($p < 0.0001$),
- decrease in vaginal pH ($p < 0.0001$),
- decrease in the severity of the MBS of vaginal dryness ($p = 0.0407$),

but, did not demonstrate significantly greater improvement over placebo at Week 12 in the decrease in the severity of the MBS of dyspareunia ($p = 0.0968$).

Per the Applicant, based on the reported results in Phase 3 Study 15-50310, a second 12-week Phase 3 study (Study 15-50821) was conducted that included only the 60 mg ospemifene dose versus placebo.

Phase 3 Study 15-50821:

The primary efficacy results for the Dryness Stratum reported in the Clinical Study Report for Study 15-50821, dated April 13, 2010, are shown in Table 13. These reported primary efficacy analyses are not based on subjects who met all three baseline inclusion criteria: $\leq 5\%$ superficial cells on a vaginal smear, a vaginal pH greater than 5, and a most bothersome moderate to severe symptom of vaginal dryness.

Table 13: Applicant-Reported Primary Efficacy Summary: Mean Change from Baseline to Week 12/LOCF (Dryness Stratum) in Study 15-50821; ITT Population

	Ospemifene 60 mg N = 160	Placebo N = 154
% Superficial Cells		
- Baseline Mean (SD)	1.2 (3.17)	0.9 (1.69)
- Week 12/LOCF Mean (SD)	13.6 (15.36)	4.3 (9.07)
- Change from Baseline (SD)	12.4 (15.36)	3.3 (9.02)
- P-value for Treatment Comparison ^a	<0.0001	-
% Parabasal Cells		
- Baseline Mean (SD)	45.9 (40.70)	45.6 (40.54)
- Week 12/LOCF Mean (SD)	14.2 (27.27)	42.2 (36.47)
- Change from Baseline (SD)	-31.7 (37.25)	-3.7 (29.97)
- Least Squares Mean (SE)	-31.7 (2.11)	-3.9 (2.18)
- P-value for Treatment Comparison ^b	<0.0001	-
Vaginal pH		
- Baseline Mean (SD)	6.24 (0.802)	6.26 (0.754)
- Week 12 Mean (SD)	5.32 (0.911)	6.02 (0.931)
- Change from Baseline (SD)	-0.92 (1.100)	-0.24 (0.800)
- Least Squares Mean (SE)	-0.95 (0.067)	-0.25 (0.068)
- P-value for Treatment Comparison ^b	<0.0001	-
Vaginal Dryness		
- Baseline Mean (SD)	2.5 (0.50)	2.5 (0.50)
- Week 12 Mean/LOCF (SD)	1.2 (1.03)	1.4 (1.03)
- Change from Baseline (SD)	-1.3 (1.08)	-1.1 (1.02)
- P-value for Treatment Comparison ^c	0.0803	-

Source: Adapted from NDA 203505, Study 15-50821 Clinical Study Report, Table 15 on page 66, Table 16 on page 67, Table 17 on page 68, Table 18 on page 69, Table 14.2.5.1.1, and Table 14.2.5.2.1.

- a P-value was computed using rank-based analysis of covariance (ANCOVA), stratifying by study center.
 - b P-value was computed using ANCOVA where change from Baseline is response variable, Baseline assessment is the covariate, and treatment and center are fixed effects.
 - c P-value was computed using Cochran-Mantel-Haenszel row mean score test controlling for center.
- Definitions: LOCF = last observation carried forward, ITT = intent-to-treat, SD = standard deviation, SE = standard error.

As noted previously, DRUP requested that the Applicant submit an addendum to the Clinical Study Report for Study 15-50821 with the recommended primary analyses (including only subjects who met all three recommended Baseline inclusion criteria; the modified ITT population) consistent with those presented in the “Summary of Clinical Efficacy” and the “Integrated Summary of Efficacy.” The addendum for Study 15-50821 was received on July 9, 2012.

The primary efficacy results for the Dryness Stratum reported in the addendum to the Study 15-50821 Clinical Study Report, dated July 9, 2012, are shown in Tables 14. Per the Applicant, the addendum primary efficacy analyses are based on subjects who met all three baseline inclusion criteria: $\leq 5\%$ superficial cells on a vaginal smear, a vaginal pH greater than 5, and moderate to severe vaginal dryness identified as most bothersome.

Table 14: Applicant-Revised Primary Efficacy Summary: Mean Change from Baseline to Week 12/LOCF (Dryness Stratum) in Study 15-50821; Modified ITT Population^a

	Ospemifene 60 mg	Placebo
% Superficial Cells	n = 157	n = 150
- Baseline Mean (SD)	0.9 (1.44)	0.9 (1.48)
- Week 12/LOCF Mean (SD)	13.4 (15.39)	4.3 (9.12)
- Mean Change from Baseline (SD)	12.5 (15.39)	3.5 (9.02)
- Least Squares Mean (SE)	12.3 (1.03)	3.5 (1.06)
- P-value for Treatment Comparison ^b	<0.0001	-
% Parabasal Cells	n = 157	n = 150
- Baseline Mean (SD)	46.2 (40.63)	45.7 (40.64)
- Week 12/LOCF Mean (SD)	14.5 (27.45)	41.8 (36.55)
- Mean Change from Baseline (SD)	-31.7 (37.16)	-3.9 (30.22)
- Least Squares Mean (SE)	-31.6 (2.13)	-4.1 (2.19)
- P-value for Treatment Comparison ^b	<0.0001	-
Vaginal pH	n = 157	n = 150
- Baseline Mean (SD)	6.25 (0.800)	6.26 (0.755)
- Week 12 Mean (SD)	5.33 (0.917)	6.03 (0.937)
- Mean Change from Baseline (SD)	-0.92 (1.103)	-0.24 (0.808)
- Least Squares Mean (SE)	-0.96 (0.068)	-0.25 (0.070)
- P-value for Treatment Comparison ^b	<0.0001	-

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	n = 157	n = 150
Vaginal Dryness		
- Baseline Mean (SD)	2.5 (0.50)	2.5 (0.50)
- Week 12 Mean (SD)	1.2 (1.02)	1.4 (1.03)
- Mean Change from Baseline (SD)	-1.3 (1.07)	-1.1 (1.01)
- P-value for Treatment Comparison ^c	0.0853	-

Source: Adapted from NDA 203505, Addendum to Study 15-50821 Clinical Study Report dated July 9, 2012, Table 14.9.1.2.2, Table 14.9.2.2.2, Table 14.9.3.2.2, and Table 14.9.4.3.2.

- Based on subjects who met all three baseline inclusion criteria: $\leq 5\%$ superficial cells on a vaginal smear, a vaginal pH greater than 5.0, and a most bothersome moderate to severe vaginal symptom (vaginal dryness or dyspareunia).
 - P-value was computed using ANCOVA where change from Baseline is response variable, Baseline assessment is the covariate, and treatment and center are fixed effects.
 - P-value was computed using Cochran-Mantel-Haenszel row mean score test controlling for center.
- Definitions: LOCF = last observation carried forward, ITT = intent-to-treat, SD = standard deviation, SE = standard error.

Medical Officer's Comments:

As shown in Table 14 in Study 15-50821, the results of the analyses of change from Baseline to Week 12/LOCF in percent superficial cells on a vaginal smear for subjects who met the inclusion criteria for percent superficial cells, vaginal pH, and MBS (mITT population) show that the 60 mg ospemifene treatment group is statistically significantly different versus the placebo group ($p < 0.0001$). Likewise, the results of the analyses of change from Baseline to Week 12/LOCF in percent parabasal cells on a vaginal smear and vaginal pH show that the 60 mg ospemifene treatment group is also statistically significantly different versus the placebo group ($p < 0.0001$ and $p < 0.0001$, respectively).

The results of the analyses of change from Baseline to Week 12/LOCF in the severity of the MBS of vaginal dryness (Dryness Stratum) for subjects who met the inclusion criteria for percent superficial cells, vaginal pH, and MBS of vaginal dryness (mITT population) show, however, that the 60 mg ospemifene treatment group was not statistically significantly different versus the placebo group ($p = 0.0853$). This result is consistent with the original ITT analysis reported in the Clinical Study Report for Study 15-50821 included in the application ($p = 0.0803$ as shown in Table 13).

The Study 15-50821 reported results for vaginal dryness for the mITT population ($p = 0.0853$) is inconsistent, however, with the Study 15-50310 reported results for vaginal dryness in the mITT population ($p = 0.0136$). Further review was conducted to identify factors that may contribute to these inconsistent findings. Table 15 shows the reported change from Baseline to Week 12 in vaginal dryness for the mITT population at Week 12/LOCF in Study 15-50310. Table 15 shows the reported change in vaginal dryness for the mITT population at Week 12/LOCF in Study 15-50821.

Table 15: Change from Baseline to Week 12/LOCF in Vaginal Dryness in Study 15-50310; Modified ITT Population^a

	Ospemifene 30 mg N = 95	Ospemifene 60 mg N = 113	Placebo N = 100
<i>Change from Baseline to Week 12/LOCF</i>			
-3 (Severe to None)	11 (11.6%)	14 (12.4%)	5 (5.0%)
-2 (Severe to Mild or Moderate to None)	22 (23.2%)	36 (31.9%)	23 (23.0%)
-1 (Severe to Moderate or Moderate to Mild)	43 (44.2%)	36 (31.9%)	32 (32.0%)
0 (Severe to Severe or Moderate to Moderate)	20 (21.1%)	26 (23.0%)	36 (36.0%)
1 (Moderate to Severe)	0 (0.0%)	1 (0.9%)	4 (4.0%)
Mean (SD)	-1.3 (0.92)	-1.3 (0.99)	-0.9 (0.97)
P-value for Treatment Comparisons ^b	0.0407	0.0136	-

Source: Adapter from NDA 203505, Addendum to Study 15-50310 Clinical Study Report dated July 9, 2012, Table 14.9.4.1.2.

a Based on subjects who met all three baseline inclusion criteria: ≤ 5% superficial cells on a vaginal smear, a vaginal pH greater than 5.0, and a most bothersome moderate to severe vaginal symptom (vaginal dryness or dyspareunia).

b P-value was computed using Cochran-Mantel-Haenszel row mean score test controlling for uterus status (intact or not) and center.

Note: The dryness symptom severity was scored as: None = 0, Mild = 1, Moderate = 2, Severe = 3.

Definitions: LOCF = last observation carried forward, ITT = intent-to-treat, SD = standard deviation.

The reported results for Study 15-50310 in Table 15 show that the severity of vaginal dryness at Week 12/LOCF is reduced for a greater percent of subject in the 60 mg ospemifene group than the placebo group (combined 76.2% for the 60 mg ospemifene group versus 60.0% for the placebo group). In addition, Table 15 shows that the 60 mg ospemifene group had less subjects who reported no change in vaginal dryness at Week 12 (23% in the 60 mg ospemifene group versus 36% in the placebo group). These reported findings demonstrate a distinct ospemifene effect over placebo.

The change in vaginal dryness in Study 15-50821 is shown in Table 16.

Table 16: Change from Baseline to Week 12/LOCF in Vaginal Dryness in Study 15-50821; Modified ITT Population^a

	Ospemifene 60 mg N = 157	Placebo N = 150
<i>Change from Baseline to Week 12/LOCF</i>		
Week 12/LOCF		
-3 (Severe to None)	21 (13.4%)	13 (8.7%)
-2 (Severe to Mild or Moderate to None)	51 (32.5%)	38 (25.3%)
-1 (Severe to Moderate or Moderate to Mild)	39 (24.8%)	51 (34.0%)
0 (Severe to Severe or Moderate to Moderate)	43 (27.4%)	43 (28.7%)

1 (Moderate to Severe)	3 (1.9%)	5 (3.3%)
Mean (SD)	-1.3 (1.07)	-1.1 (1.01)
P-value for Treatment Comparisons ^a	0.0853	-

Source: Adapter from NDA 203505, Addendum to Study 15-50821 Clinical Study Report dated July 9, 2012, Table 14.9.4.3.2.

a Based on subjects who met all three baseline inclusion criteria: $\leq 5\%$ superficial cells on a vaginal smear, a vaginal pH greater than 5.0, and a most bothersome moderate to severe vaginal symptom (vaginal dryness or dyspareunia).

b P-value was computed using Cochran-Mantel-Haenszel row mean score test controlling for uterus status (intact or not) and center.

Definitions: LOCF = last observation carried forward, ITT = intent-to-treat, SD = standard deviation.

These reported results for Study 15-50821 in Table 16 show that there is no difference in the change in the severity of vaginal dryness at Week 12/LOCF between the two treatment groups (combined total of 70.7% of subjects in the 60 mg ospemifene group and 68.0% of subjects in the placebo group). Table 16 also shows that the same percent of subjects in both groups reported no change in severity at Week 12 (27.4% in the 60 mg ospemifene group and 28.7% in the placebo group). These reported findings demonstrate that the placebo group relieved vaginal dryness as effectively as the 60 mg ospemifene group, and highlights the differences in this study and Study 15-50310.

Across these two studies (Study 15-50310 and Study 15-50821) ospemifene 60 mg is not consistently effective in relieving the severity of moderate to severe vaginal dryness, a symptom of vulvar and vaginal atrophy, due to menopause ($P=0.0136$ in Study 15-50310 and $p=0.0853$ in Study 15-50821).

The primary efficacy results for the Dyspareunia Stratum reported in the Clinical Study Report for Study 15-50821, dated April 13, 2010, are shown in Table 17. These reported primary efficacy analyses are not based on subjects who met all three baseline inclusion criteria: $\leq 5\%$ superficial cells on a vaginal smear, a vaginal pH greater than 5, and a most bothersome moderate to severe symptom of vaginal dryness.

Table 17: Applicant-Reported Primary Efficacy Summary: Mean Change from Baseline to Week 12/LOCF (Dyspareunia Stratum) in Study 15-50821; ITT Population

	Ospemifene 60 mg N = 303	Placebo N = 302
% Superficial Cells		
- Baseline Mean (SD)	0.7 (1.40)	0.8 (1.79)
- Week 12/LOCF Mean (SD)	13.0 (14.64)	2.5 (7.03)
- Change from Baseline (SD)	12.3 (14.77)	1.7 (6.88)
- P-value for Treatment Comparison ^a	<0.0001	-
% Parabasal Cells		
- Baseline Mean (SD)	51.1 (38.21)	50.6 (39.87)
- Week 12/LOCF Mean (SD)	11.0 (21.87)	50.6 (38.81)
- Change from Baseline (SD)	-40.2 (38.80)	0.0 (30.00)
- Least Squares Mean (SE)	-40.3 (1.56)	-0.4 (1.57)

- P-value for Treatment Comparison ^b	<0.0001	-
Vaginal pH		
- Baseline Mean (SD)	6.31 (0.765)	6.31 (0.764)
- Week 12 Mean (SD)	5.37 (0.891)	6.25 (0.960)
- Change from Baseline (SD)	-0.94 (1.016)	-0.07 (0.814)
- Least Squares Mean (SE)	-0.94 (0.050)	-0.07 (0.050)
- P-value for Treatment Comparison ^b	<0.0001	-
Vaginal Dyspareunia		
- Baseline Mean (SD)	2.7 (0.47)	2.7 (0.49)
- Week 12 Mean/LOCF (SD)	1.1 (1.18)	1.5 (1.16)
- Change from Baseline (SD)	-1.5 (1.08)	-1.2 (1.12)
- P-value for Treatment Comparison ^c	0.0001	

Source: Adapted from NDA 203505, Study 15-50821 Clinical Study Report, Table 22 on page 73, Table 23 on page 74, Table 24 on page 75, Table 25 on page 76, Table 14.2.5.1.2, and Table 14.2.5.2.2.

- a P-value was computed using rank-based analysis of covariance (ANCOVA), stratifying by study center.
- b P-value was computed using ANCOVA where change from Baseline is response variable, Baseline assessment is the covariate, and treatment and center are fixed effects.
- c P-value was computed using Cochran-Mantel-Haenszel row mean score test controlling for center.
- Definitions: LOCF = last observation carried forward, ITT = intent-to-treat, SD = standard deviation, SE = standard error.

As noted previously, DRUP requested that the Applicant submit an addendum to the Clinical Study Report for Study 15-50821 with the recommended primary analyses (including only subjects who met all three recommended Baseline inclusion criteria; the modified ITT population) consistent with those presented in the “Summary of Clinical Efficacy” and the “Integrated Summary of Efficacy.” The addendum for Study 15-50821 was received on July 9, 2012.

The primary efficacy results for the Dyspareunia Stratum reported in the addendum to the Study 15-50821 Clinical Study Report, dated July 9, 2012, are shown in Tables 18. Per the Applicant, the addendum primary efficacy analyses are based on subjects who met all three baseline inclusion criteria: ≤ 5% superficial cells on a vaginal smear, a vaginal pH greater than 5, and moderate to severe vaginal dryness identified as most bothersome.

Table 18: Applicant-Revised Primary Efficacy Summary: Mean Change from Baseline to Week 12/LOCF (Dyspareunia Stratum) in Study 15-50821: Modified ITT Population^a

	Ospemifene 60 mg	Placebo
% Superficial Cells	n = 301	n = 297
- Baseline Mean (SD)	0.7 (1.32)	0.7 (1.31)
- Week 12/LOCF Mean (SD)	13.1 (14.66)	2.4 (6.99)
- Mean Change from Baseline (SD)	12.4 (14.76)	1.7 (6.93)
- Least Squares Mean (SE)	12.4 (0.68)	1.7 (0.68)
- P-value for Treatment Comparison ^b	<0.0001	-

% Parabasal Cells	n = 301	n = 297
- Baseline Mean (SD)	51.5 (38.11)	51.1 (39.76)
- Week 12/LOCF Mean (SD)	11.0 (21.91)	51.1 (38.70)
- Mean Change from Baseline (SD)	-40.4 (38.84)	0.0 (30.25)
- Least Squares Mean (SE)	-40.6 (1.57)	-0.5 (1.58)
- P-value for Treatment Comparison ^b	<0.0001	-
Vaginal pH	n = 301	n = 297
- Baseline Mean (SD)	6.32 (0.765)	6.32 (0.761)
- Week 12 Mean (SD)	5.37 (0.892)	6.24 (0.955)
- Mean Change from Baseline (SD)	-0.95 (1.014)	-0.07 (0.809)
- Least Squares Mean (SE)	-0.95 (0.050)	-0.08 (0.050)
- P-value for Treatment Comparison ^b	<0.0001	-
Vaginal Dyspareunia	n = 301	n = 297
- Baseline Mean (SD)	2.7 (0.47)	2.7 (0.47)
- Week 12 Mean (SD)	1.1 (1.09)	1.5 (1.15)
- Mean Change from Baseline (SD)	-1.5 (1.009)	-1.2 (1.13)
- P-value for Treatment Comparison ^c	<0.0001	-

Source: Adapted from NDA 203505, Addendum to Study 15-50821 Clinical Study Report dated July 9, 2012, Table 14.9.1.3.2, Table 14.9.2.3.2, Table 14.9.3.3.2, and Table 14.9.4.4.2.

- a Based on subjects who met all three baseline inclusion criteria: ≤ 5% superficial cells on a vaginal smear, a vaginal pH greater than 5.0, and a most bothersome moderate to severe vaginal symptom (vaginal dryness or dyspareunia).
- b P-value was computed using ANCOVA where change from Baseline is response variable, Baseline assessment is the covariate, and treatment and center are fixed effects.
- c P-value was computed using Cochran-Mantel-Haenszel row mean score test controlling for center.
- Definitions: LOCF = last observation carried forward, ITT = intent-to-treat, SD = standard deviation, SE = standard error.

Medical Officer's Comments:

Based on the reported findings in the addendum received for 12-week Study 15-50310 and Study 15-50821, ospemifene 60 mg is effective in relieving the severity of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause (p=.0012 in Study 15-50310 and p<0.0001 in Study 15-50821).

A re-analysis of the dyspareunia data in Studies 15-50310 and 15-50821, for the mITT population with LOCF, is presented in the Statistical Review for NDA 203505. Table 19 presents the data for the mean change in the severity of dyspareunia at Week 12.

Table 19: Dyspareunia Primary Efficacy Results: Mean Change from Baseline to Week 12 (mITT with Vaginal Pain Associated with Sexual Activity and LOCF)

Study	Co-primary Vaginal Endpoint	Ospemifene 60			Nominal P-value
		mg (N=110)	Placebo (N=113)	Difference (95% CI)	
15-50310	Pain with Sex [LS mean (SE)]	-1.39 (0.11)	-0.89 (0.11)	-0.51 (-0.81, -0.20) ^b	0.0012 ^a
	% Superficial Cells [(LS mean (SE)]	10.88 (1.27)	2.73 (1.27)	8.2 (4.7, 11.6)	<.0001 ^b
	% Parabasal Cells [(LS mean	-34.44 (2.44)	5.84 (2.44)	-40.3 (-46.9, -	<.0001 ^b

		Ospemifene 60 mg (N=301)	Placebo (N=297)	Difference (95% CI)	Nominal P-value
	(SE)]			33.7)	
	pH [(LS mean (SE)]	-0.97 (0.09)	-0.002 (0.09)	-0.97 (-1.22, -0.73)	<.0001 ^b
15-50821	Co-primary Vaginal Endpoint	Ospemifene 60 mg (N=301)	Placebo (N=297)	Difference (95% CI)	Nominal P-value
	Pain with Sex [LS mean (SE)]	-1.55 (0.06)	-1.29 (0.07)	-0.36 (-0.53, -0.18) ^b	<.0001 ^a
	% Superficial Cells [(LS mean (SE)]	12.35 (0.68)	1.69 (0.69)	10.7 (8.8, 12.5)	<.0001 ^b
	% Parabasal Cells [(LS mean (SE)]	-40.57 (1.57)	-0.56 (1.59)	-40.0 (-44.3, -35.7)	<.0001 ^b
	pH [(LS mean (SE)]	-0.95 (0.05)	-0.08 (0.05)	-0.9 (-1.0, -0.7)	<.0001 ^b

Source: Statistical reviewer's analysis based on ISE analysis datasets ADMBS310, ADMBS821, ADPH, ADPC, and ADSC

a: Test based on CMH stratified by pooled site (both studies), and uterus status (Study 15-50310 only)

b: Test based on ANCOVA model having fixed effect of treatment, uterus status (Study 15-50310 only), pooled site, and baseline

Medical Officer's Comments:

The results presented in Table 19, prepared by the Statistical reviewer, for the mean change in the severity of dyspareunia at Week 12/LOCF for the mITT population in 12-week Studies 15-50310 and 15-50821 support the results reported in the application. Ospemifene 60 mg oral tablets taken daily demonstrate a statistically significant improvement in the severity of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause (p=.0012 in Study 15-50310 and p<0.0001 in Study 15-50821).

Medical Officer's Overall Efficacy Comments:

The data presented in the 2 primary 12-week studies (Studies 15-50310 and 15-50821) for the mITT population support the approval of 60 mg ospemifene for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. Approval for the treatment of moderate to severe vaginal dryness is not supported by the data presented in the application for the mITT population.

6.1.5 Analysis of Secondary Endpoints(s)

Phase 3 Study 15-50310:

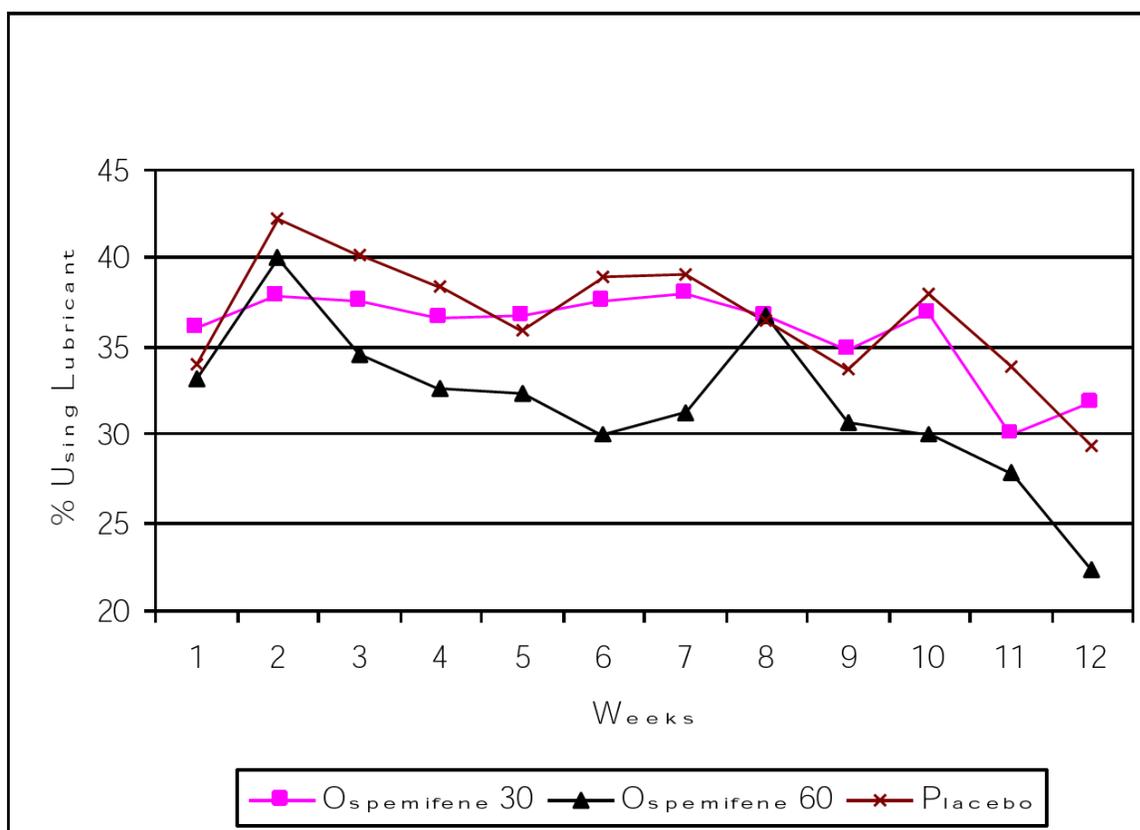
Only 1 of the numerous secondary endpoints for Study 15-50310, "frequency of lubricant application", will be discussed in this review.

In Study 15-50310, the percentage of all women (not just those women who met the three recommended inclusion criteria at Baseline) who reported any use of vaginal

lubricant (K-Y® Brand Jelly used either 1-2 times per week, or 3+ times per week) depending on the week, with all MBS combined, ranged from 2.9% to 33.9% in the 30 mg ospemifene treatment group, 2.1% to 36.6% in the 60 mg ospemifene treatment group, and 1.3% to 37.9% in the placebo treatment group.

As shown in Figure 1 provided in the application, the percent of women who reported vaginal lubricant use decreased slightly more in the 60 mg ospemifene group when compared to the 30 mg ospemifene group and the placebo group, after 3 weeks of treatment.

Figure 1: Percentage of Subjects Using Non-Hormonal Vaginal Lubricant in Study 14-40310, All Vaginal Symptoms Combined; ITT Population



Source: NDA203505 Clinical Study Report for Study 15-50310, Figure 11.4.1, page 75 and Table 14.2.5.12.

Medical Officer's Comments:

A non-hormonal lubricant was provided to all subjects with instruction to use it as needed. The Division initially recommended, however, that a daily vaginal lubricant (a

double-dummy study design) be used to demonstrate that the effect of oral ospemifene was above that achieved with the use of a vaginal lubricant alone (vaginal lubricant plus placebo tablet). The Applicant elected to not follow this recommendation.

Use of the vaginal lubricant was recorded in the medication diary by checking one of three boxes: 0 per week, 1-2 times per week, or 3+ times per week. As shown in Figure 1, lubricant use decreased the greatest in the 60 mg ospemifene group over the 12-week study duration. Figure 1, however, shows the reported results for all MBS combined for the ITT population in Study 15-50310. No information is available in the application for the individual symptoms of vaginal dryness or dyspareunia in either the original Study 15-50310 clinical study report or in the addendum submitted on July 9, 2012.

Phase 3 Study 15-50821:

Only 1 of the numerous secondary endpoints for Study 15-50821, “frequency of lubricant use and sexual activity”, will be discussed in this review.

In the Dryness Stratum of Study 15-50821, the percentage of subjects who reported any use of lubricant (K-Y® Brand Jelly used either 1-2 times per week or 3+ times per week) during each week of study participation (Weeks 1 through 12) ranged from 2.2% to 28.7% in the 60 mg ospemifene treatment group, and 2.8% to 29.5% in the placebo treatment group. Only subjects with data for all seven days of a given week are included in the summary. Per the Applicant, the frequency of lubricant use and sexual activity in the Dryness Stratum remained consistent across treatment weeks in both the 60 mg ospemifene and placebo treatment groups.

In the Dyspareunia Stratum of Study 15-50821, the percentage of subjects who reported any use of lubricant (K-Y® Brand Jelly) during each week of study participation (Weeks 1 through 12) ranged from 2.9% to 40.3% in the 60 mg ospemifene treatment group, and 4.8% to 42.2% in the placebo treatment group. Again, only subjects with data for all seven days of a given week are included in the summary. Per the Applicant, the frequency of lubricant use and sexual activity in the Dyspareunia Stratum remained consistent across treatment weeks in both the 60 mg ospemifene and placebo treatment groups.

The Statistical Reviewer for NDA 203505 analyzed dyspareunia and lubricant use for the mITT population/LOCF in 12-week Studies 15-50310 and 15-50821 to evaluate the effect of any lubricant use versus no lubricant use. See Table 20 for the any lubricant use subgroup in these 2 primary studies; see Table 21 for the no lubricant use subgroup.

Table 20: Dyspareunia Lubrication-User Subgroup Results: Mean Change from Baseline to Week 12 (mITT Subjects with Vaginal Pain Associated with Sexual Activity and LOCF)

Study	Co-Primary Vaginal Endpoint	Ospemifene 60 mg (N = 72)	Placebo (N = 89)	Difference (95% CI)	Nominal P-value
15-50310	Pain with Sex [LS mean (SE)]	-1.11 (0.14)	-0.62 (0.12)	-0.5 (-0.8, -0.2) ^b	0.0024 ^a
	pH [LS mean (SE)]	-1.16 (0.12)	-0.03 (0.11)	-1.1 (-1.4, -0.9)	<.0001 ^b
	% Parabasal Cells [LS mean (SE)]	-34.66 (3.22)	7.97 (2.90)	-42.6 (-50.3, -34.9)	<.0001 ^b
	% Superficial Cells [LS mean (SE)]	10.85 (1.84)	3.02 (1.65)	7.8 (3.5, 12.2)	0.0005 ^b
Study	Co-Primary Vaginal Endpoint	Ospemifene 60 mg (N = 230)	Placebo (N = 234)	Difference (95% CI)	Nominal P-value
15-50821	Pain with Sex [LS mean (SE)]	-1.48 (0.07)	-1.10 (0.07)	-0.4 (-0.6, -0.2)	0.0003 ^a
	pH [LS Mean (SE)]	-0.97 (0.06)	-0.05 (0.06)	-0.9 (-1.1, -0.8)	<.0001 ^b
	% Parabasal Cells [LS mean (SE)]	-39.54 (1.81)	-0.59 (1.78)	-39.0 (-43.8, -34.1)	<.0001 ^b
	% Superficial Cells [LS mean (SE)]	12.55 (0.78)	1.69 (0.77)	10.9 (8.8, 13.0)	0.0001 ^b

Source: Statistical reviewer's analysis based on ISE analysis datasets ADMBS310, ADMBS821, ADPH, ADPC, and ADSC.

a. Test based on CMH stratified by pooled sites (both studies), and uterus status (Study 15-50310 only).

b. Test based on AVCOVA model having fixed effect of treatment, uterus status (Study 15-50310 only), pooled sites, and baseline.

Table 21: Dyspareunia No-Lubrication-User Subgroup Results: Mean Change from Baseline to Week 12 (mITT Subjects with Vaginal Pain Associated with Sexual Activity and LOCF)

Study	Co-Primary Vaginal Endpoint	Ospemifene 60 mg (N = 72)	Placebo (N = 89)	Difference (95% CI)	Nominal P-value
15-50310	Pain with Sex [LS mean (SE)]	-1.58 (0.26)	-1.70 (0.35)	0.1 (-0.8, 1.0) ^b	0.8256 ^a
	pH [LS mean (SE)]	-0.93 (0.22)	-0.28 (0.30)	-1.2 (-2.0, -0.4)	0.0027 ^b
	% Parabasal Cells [LS mean (SE)]	-34.11 (5.69)	8.82 (7.55)	-42.9 (-62.6, -23.3)	<.0001 ^b
	% Superficial Cells [LS mean (SE)]	11.42 (2.86)	2.10 (3.93)	9.3 (-0.7, 19.3)	0.0676 ^b
Study	Co-Primary Vaginal Endpoint	Ospemifene 60 mg (N = 65)	Placebo (N = 56)	Difference (95% CI)	Nominal P-value
15-50821	Pain with Sex [LS mean	-1.84 (0.14)	-1.57 (0.16)	-0.3 (-0.7,	0.1926 ^a

	(SE)]			0.1) ^b	
	pH [LS mean) (SE)]	-1.00 (0.12)	-0.24 (0.13)	-0.8 (-1.1, -0.4)	<.0001 ^b
	% Parabasal Cells [LS mean) (SE)]	-46.19 (3.51)	-0.80 (3.87)	-45.4 (-55.5, -35.3)	<.0001 ^b
	Percent Superficial Cells [(LS Mean) (SD)]	12.56 (1.64)	1.72 (1.81)	10.8 (6.1, 15.6)	<.0001 ^b

Source: Statistical reviewer's analysis based on ISE analysis datasets ADMBS310, ADMBS821, ADPH, ADPC, and ADSC.

a. Test based on CMH stratified by pooled sites (both studies), and uterus status (Study 15-50310 only).

b. Test based on AVCOVA model having fixed effect of treatment, uterus status (Study 15-50310 only), pooled sites, and baseline.

Medical Officer's Comments:

The results presented in Tables 20 and 21 show that the use of any lubricant (1-2 times per week or 3 + times per week) did not greatly influence the effectiveness of 60 mg ospemifene oral tablets to relieve moderate to severe dyspareunia due to menopause.

The following statement appears in proposed labeling for 60 mg ospemifene (b) (4)

This reviewer recommends that the proposed statement not appear in labeling. The efficacy results reported in 12-week Studies 15-50310 and 15-50821 were not stratified on the basis of lubricant/non-lubricant users.

The Statistical reviewer for NDA 203505 also analyzed vaginal dryness and lubricant use for the mITT population/LOCF in 12-week Studies 15-50310 and 15-50821 to evaluate the effect of any lubricant use versus no lubricant use. See Table 22 for the any lubricant use subgroup in these 2 primary studies; see Table 23 for the no lubricant use subgroup.

Table 22: Change from Baseline to Week 12 – Lubrication User Subgroup Results (mITT Subjects with Moderate to Severe Vaginal Dryness/LOCF)

Study	Co-Primary Vaginal Endpoint	Ospemifene 60 mg (N = 77)	Placebo (N = 70)	Difference (95% CI)	P-value
15-50310	Percent Superficial Cells [(LS Mean) (SD)]	10.70 (1.26)	2.31 (1.30)	8.4 (4.9, 11.9)	<.0001 ^a
	Percent Parabasal Cells [(LS Mean) (SD)]	-30.63 (2.85)	-0.55 (2.96)	-30.1 (-38.1, -22.1)	<.0001 ^a
	pH [(LS Mean) (SD)]	-0.97 (0.11)	-0.16 (0.11)	-0.8 (-1.1, -0.5)	<.0001 ^a
	Vaginal Dryness [Mean (SD)]	-1.36 (1.06)	-0.83 (0.92)	-0.54	0.0290 ^b
		Ospemifene			

Study	Co-Primary Vaginal Endpoint	60 mg (N = 102)	Placebo (N = 96)	Difference (95% CI)	P-value
15-50821	Percent Superficial Cells [(LS Mean) (SD)]	11.85 (1.27)	3.67 (1.30)	8.2 (4.6, 11.8)	<.0001 ^a
	Percent Parabasal Cells [(LS Mean) (SD)]	-32.87 (2.55)	-3.74 (2.61)	-29.1 (-36.3, -21.9)	<.0001 ^a
	pH [(LS Mean) (SD)]	-0.94 (0.09)	-0.14 (0.09)	-0.8 (-1.0, -0.5)	<.0001 ^a
	Vaginal Dryness [Mean (SD)]	-1.34 (1.05)	-1.01 (1.06)	-0.33	0.0247 ^b

Source: Statistical reviewer's analysis based on ISE analysis datasets ADMBS310, ADMBS821, ADPH, ADPC, and ADSC.

a. Test based on AVCOVA model having fixed effect of treatment, pooled sites, and baseline value.

b. Test based on CMH stratified by pooled sites, randomization stratum

Table 23: Change from Baseline to Week 12 – No Lubrication User Subgroup Results (mITT Subjects with Moderate to Severe Vaginal Dryness/LOCF

Study	Co-Primary Vaginal Endpoint	Ospemifene 60 mg (N = 33)	Placebo (N = 27)	Difference (95% CI)	P-value
15-50310	Percent Superficial Cells [(LS Mean) (SD)]	10.08 (3.36)	-1.69 (3.77)	11.8 (2.2, 21.4)	0.0172 ^a
	Percent Parabasal Cells [(LS Mean) (SD)]	-16.99 (4.47)	1.71 (5.09)	-18.7 (-31.7, -5.7)	0.0054 ^a
	pH [(LS Mean) (SD)]	-0.79 (0.16)	-0.13 (0.19)	-0.7 (-1.1, -0.2)	0.0070 ^a
	Vaginal Dryness [Mean (SD)]	-1.30 (0.81)	-1.19 (1.04)	-0.12	0.7248 ^b
Study	Co-Primary Vaginal Endpoint	Ospemifene 60 mg (N = 53)	Placebo (N = 53)	Difference (95% CI)	P-value
15-50821	Percent Superficial Cells [(LS Mean) (SD)]	13.03 (2.20)	3.57 (2.13)	9.5 (3.6, 15.3)	0.0019 ^a
	Percent Parabasal Cells [(LS Mean) (SD)]	-31.59 (4.57)	-6.86 (4.39)	-24.7 (-36.9, -12.5)	0.0001 ^a
	pH [(LS Mean) (SD)]	-1.11 (0.13)	-0.43 (0.13)	-0.7 (-1.0, -0.3)	0.0003 ^a
	Vaginal Dryness [Mean (SD)]	-1.21 (1.10)	-1.21 (0.91)	-0.00	0.7248 ^b

Source: Statistical reviewer's analysis based on ISE analysis datasets ADMBS310, ADMBS821, ADPH, ADPC, and ADSC.

a. Test based on AVCOVA model having fixed effect of treatment, pooled sites, and baseline value.

b. Test based on CMH stratified by pooled sites, randomization stratum

Medical Officer's Comments:

The results presented in Tables 22 and 23 show that the use of any lubricant (1-2 times per week or 3 + times per week) appears to contributed to the effectiveness of the 60 mg ospemifene dose to relieve moderate to severe vaginal dryness due to menopause.

It was not the Agency intent, however, to have oral 60 mg ospemifene used in combination with a vaginal lubricant to reduce the severity of moderate to severe vaginal dryness. The intent of the Division's initial recommendation that a vaginal lubricant be used daily (a double-dummy study design) was to demonstrate the effect of oral ospemifene above that achieved with the use of a vaginal lubricant alone (vaginal lubricant plus placebo tablet). The Applicant, however, elected to not follow this recommendation. Overall, the reported findings in Tables 22 and 23 show that 60 mg ospemifene is not effective in the resolution of vaginal dryness when administered alone.

Medical Officer's Efficacy Summary Comments:

This reviewer recommends approval of 60 mg Osphena™ (ospemifene) tablets, taken orally daily, for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

The data presented in the application for 2 double-blind, placebo controlled 12-week clinical trials support the approval of ospemifene 60 mg, taken orally daily, for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause (mITT analysis: $p=0.0012$ in Study 15-50310 and $p<0.0001$ in Study 15-50821).

The data presented in the application does not consistently support the approval of ospemifene 60 mg, taken orally daily, for the treatment of moderate to severe vaginal dryness, a symptom of vulvar and vaginal atrophy, due to menopause (mITT analysis: $p=0.0136$ in Study 15-50310 and $p=0.0853$ in Study 15-50821). Therefore, approval of moderate to severe vaginal dryness, a symptom of vulvar and vaginal atrophy, due to menopause is not recommended.

6.1.6 Other Endpoints

No other endpoints for Study 15-50310 or Study 15-50821 will be discussed.

6.1.7 Subpopulations

Phase 3 Study 15-50310:

The study population in Study 15-50310 was stratified by uterine status, but not by MBS. Treatment group differences for demographic and baseline variables were examined.

The study population in Study 15-50821 was stratified by MBS into the Dryness Stratum and the Dyspareunia Stratum.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The reported differences in outcome analyses for the two ospemifene doses (30 mg and 60 mg) can be found in Subsection 6.1.4 Analysis of Primary Endpoint(s) of this review.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Phase 2 Study 15-50717 and Phase 3 Studies 15-50310 and 15-50821 are all 12-week clinical trials. The two long-term safety extension studies submitted in the application (40-week safety extension Study 14-50310X and 52-week safety extension Study 15-50312) did not collect efficacy data. Study 15-50718, a 52-week efficacy and safety study, collected efficacy data on only two of the three recommended co-primary endpoints during the first 12 week, but not thereafter.

6.1.10 Additional Efficacy Issues/Analyses

No additional primary efficacy analyses are presented in the application.

7 Review of Safety

7.1 Methods

The application contains 2 summary documents with investigations pertinent to safety: 1) Integrated Summary of Safety (ISS), and 2) Summary of Clinical Safety (SCS). While these two documents complement each other, the ISS is more inclusive of safety findings than the SCS. Per the Applicant, the focus of the ISS and SCS is to provide “an overall presentation of the number of subjects in the clinical development program, and to provide a complete summary of safety evaluations.” As described in the ISS and SCS, a total of 2471 subjects received ospemifene during the development program (single doses ranging from 10 to 800 mg; repeat doses up to 240 mg/day for 7 days, up to 200 mg/day for 12 weeks, and 60 mg/day up to 15 months of treatment).

The ISS and SCS include data for 637 subjects in Phase 1 studies (579 received ospemifene [10 to 800 mg] and 58 subjects received placebo). The clinical pharmacology studies comprised studies of the PK and PD of ospemifene derived from studies conducted in healthy subjects, subjects with hepatic impairment (Study 15-50820 and Study 15-50920), or subjects with renal impairment (Study 15-50921). The pooled Phase 1 data represents data from 21 single and multiple dose studies, double-blind and open-label studies, and parallel and crossover studies. The safety data from

all completed Phase 1 studies are combined into one database (Phase 1 Integrated Database).

The ISS and SCS also include data for 1583 subjects with VVA symptoms treated with ospemifene (5 mg to 90 mg) in Phase 2 and Phase 3 studies, and 309 subjects with “other post-menopausal symptoms” treated with ospemifene (for example, hot flushes and bone) (total of 1892 ospemifene-treated subjects). The safety data from all Phase 2 and 3 studies are combined into a separate database (Phase 2/3 Integrated Database).

The Phase 2/3 clinical studies comprised studies conducted in generally healthy postmenopausal women, with and without a uterus (65% of all ospemifene-treated subjects had a uterus, 1229 of 1892 subjects). The pooled Phase 2/3 data represents double-blind, placebo-controlled Phase 2/3 clinical studies and all Phase 2/3 studies including open-label and active-controlled clinical studies. In addition, the application included the individual final study reports for each Phase 2/3 study conducted.

All safety data is based on the safety population, defined as all enrolled subjects in any study group who received at least 1 dose of study medication.

In the ISS, data from the clinical trials are summarized separately for the following groupings: 1) double-blind, Phase 2/3, placebo-controlled studies, and 2) all Phase 2/3 studies. See Table 24.

Table 24: Study Groupings

Study Grouping	Studies Included in Grouping
Phase 2/3, double-blind, placebo-controlled	15-50615
	1506002
	15-50717
	15-50310
	15-50310X
	15-50718
	15-50821
All Phase 2/3	All Phase 2/3, double-blind, placebo-controlled
	1506001 (active-comparator)
	15-50312 (open-label)

Source: Adapted from NDA 203505, Integrated Summary of Safety, Table 23, Page 77.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Pooled Phase 1 Studies:

There were 21 clinical pharmacology studies performed and included in the Phase 1 database. A total of 637 subjects received at least 1 dose of study medication in the Phase 1 studies. Of these 637 subjects, 579 subjects received ospemifene (3 male

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subjects received 10 mg ospemifene/day, 11 female subjects received 25 mg ospemifene/day, 469 female subjects received 60 mg ospemifene/day, 11 female subjects received 100 mg ospemifene/day, 61 female subjects received 200 mg ospemifene/day, 3 male subjects received 400 mg ospemifene/day, and 10 male subjects received 800 mg ospemifene/day, and 58 received placebo. Eighty-one percent of subjects in the Phase 1 database (81%, 469 of 579 subjects) were treated with 60 mg ospemifene. The median (min, max) duration of exposure was 4 days (1, 85) in the combined ospemifene groups, 3 days (1, 12) in the 60 mg ospemifene group, and 7 days (7, 85) in the placebo group. Most subjects were Caucasian and accounted for 95% in both ospemifene and placebo groups.

No subjects died during the Phase 1 studies.

In the 21 Phase 1 studies, a total of 335 ospemifene-treated subjects (58%, 335 of 579 subjects) reported at least 1 treatment-emergent adverse event (TEAE) compared with 58 placebo subjects (100%, 58 of 58 placebo subjects). The most common TEAEs in Phase 1 studies were headache (22% in all ospemifene-treated subjects versus 7% in placebo-treated subjects), application site irritation due to ECG Holter electrodes in Study 15-50824 (18% in all ospemifene-treated subjects versus 86% in placebo-treated subjects), nausea (5% in all ospemifene-treated subjects versus 0% in placebo-treated subjects), and hot flushes (3.1% in all ospemifene-treated subjects versus 0% in placebo-treated subjects).

In the completed Phase 1 studies, no placebo-treated subject experienced a severe adverse event (SAE). Per the application, two (2) ospemifene-treated subjects (0.3%, 2 of 579 subjects) experienced a SAE:

- Pancreatitis in Subject 1506003-001-025 treated with 50 mg ospemifene/day, and
- Endometriosis in Subject 15-50823-001-201 treated with 60 mg ospemifene/day.

Discontinuations rarely occurred in the Phase 1 clinical studies (6 subjects [1%] in ospemifene-treated subjects and none [0%] in placebo). Discontinuations in the all ospemifene-treated groups included:

- Pancreatitis (50 mg ospemifene group; Subject 1506003-001-02),
- Blood in stool (60 mg ospemifene group; Subject 15-50716-001-009)
- Transient ischemia attack (60 mg ospemifene group [4 days after single dose]; Subject 15-50716-001-006),
- Urinary tract infection (60 mg ospemifene group; Subject 15-50719-001-006),
- Endometriosis, hematuria (60 mg ospemifene group; Subject 15-50823-001-201), and
- Asthenia, circadian rhythm sleep disorder, somnolence (60 mg ospemifene group; Subject 15-51031-01-0433)

Medical Officer's Comments:

The SAEs and TEAEs, at the reported incidence rates, in all Phase 1 studies do not raise safety concerns for 60 mg ospemifene. In the Phase 1 studies, no mean change in clinical laboratory evaluations observed were considered clinically significant. Shifts to high or low were observed for some clinical chemistry parameters including serum CK, ALT, AST, total bilirubin (more frequently in ospemifene-treated subjects compared with placebo-treated subjects). The mean changes at end-of-study for each hematology parameter were within the normal range for both the ospemifene and placebo groups. A slight mean change in body weight was observed (0.23 ± 1.663 kg) for the 60 mg ospemifene group in all Phase 1 studies.

See Subsection 7.4.4 Electrocardiogram (ECGs) of this review for a discussion of Phase 1 Study 15-50824 (Thorough QT_c study).

No further discussion of Phase 1 clinical pharmacology studies will be presented in this review. See the Clinical Pharmacology Review, dated January 12, 2013, for more discussion of Phase 1 studies.

Phase 2 and Phase 3 Clinical Studies:

A total of 9 Phase 2/3 studies are presented in the application. These 9 Phase 2/3 studies ranged from 6 weeks to 15 months in duration, and evaluate ospemifene doses ranging from 5 mg/day to 90 mg/day. See Table 25.

Table 25: Description of Clinical Phase 2/3 Safety Studies

Study ID - Number of Centers - Start Date - Completion Date - Number Enrolled	Study Design	Route and Regimen	Indication	Number of Subjects (Randomized/ Completed)	Treatment Duration Main Criteria for Inclusion
1506001 - 7 - 03May99 - 10Jan00 - 118	Randomized, multicenter, double-blind, parallel-group, active-controlled. Phase 2	Ospemifene Capsule 30 mg 60 mg 90 mg Raloxifene Capsules 60 mg	Bone turnover	<u>Randomized:</u> Ospemifene 30 mg = 29 60 mg = 30 90 mg = 30 Raloxifene = 30 <u>Completed:</u> 30 mg = 26	12 weeks Postmenopausal women 45 to 65 years of age with an intact uterus with 2-5 mild or 1-3 moderate hot flashes per day

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				60 mg = 25 90 mg = 28 Raloxifene = 28	
1506002 - 2 - 22Feb00 - 07Feb01 - 159	Randomized, multicenter, double-blind, parallel-group, placebo-controlled. Phase 2	Oral capsules 30 mg 60 mg 90 mg Placebo	Effects on bone, vascular endothelium, lipid metabolism and endometrium	<u>Randomized:</u> 30 mg = 40 60 mg = 40 90 mg = 40 Placebo = 40 <u>Completed:</u> 30 mg = 39 60 mg = 36 90 mg = 37 Placebo = 37	12 weeks Postmenopausal women 45 to 65 years of age with an intact uterus
15-50615 - 11 - 01Dec06 - 27Apr07 - 198	Randomized, multicenter, double-blind, parallel-group, placebo-controlled. Phase 2	Oral tablets 60 mg Placebo	Vasomotor symptoms	<u>Randomized:</u> 60 mg = 100 Placebo = 98 <u>Completed:</u> 60 mg = 93 Placebo = 92	6 weeks Postmenopausal women 40 to 70 years of age with ≥ 7 moderate, severe or very severe hot flashes per day or 50 per week
15-50717 - 9 - 09Aug07 - 11Feb 08 - 126	Randomized, multicenter, double-blind, parallel-group, placebo-controlled. Phase 2	Oral Tablets 5 mg 15 mg 30 mg Placebo	VVA	<u>Randomized:</u> 5 mg = 33 15 mg = 29 30 mg = 30 Placebo = 34 <u>Completed:</u> 5 mg = 29 15 mg = 28 30 mg = 27 Placebo = 33	12 weeks Postmenopausal women 40 to 80 years of age with vaginal pH >5.0 and $\leq 5\%$ superficial cells in vaginal smear
15-50310 - 83 ^a - 16Jan06 - 19Nov07 - 826	Randomized, multicenter, double-blind, parallel-group, placebo-controlled. Phase 3	Oral Tablet 30 mg 60 mg Placebo	VVA	<u>Randomized:</u> 30 mg = 282 60 mg = 276 Placebo = 268 <u>Completed:</u> 30 mg = 225 60 mg = 234 Placebo = 230	12 weeks Postmenopausal women 40 to 80 years of age with vaginal pH >5.0 , $\leq 5\%$ superficial cells in vaginal smear, and self-reported MBS of VVA

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15-50310X - 51 - 16May06 - 18Sep08 - 180	Randomized, multicenter, double-blind, parallel-group, placebo- controlled, long- term safety extension of Study 15-50310, women with an intact uterus Phase 3	Oral Tablet 30 mg 60 mg Placebo	VVA	<u>Randomized:</u> 30 mg = 62 60 mg = 60 Placebo = 49 <u>Completed:</u> 30 mg = 44 60 mg = 51 Placebo = 31	40 weeks Subjects with an intact uterus that completed Study 15-50310 without clinically significant abnormal findings
15-50312 - 59 - 08May06 - 22Dec08 - 301	Multicenter, open-label, long-term, safety follow-up, women without an intact uterus Phase 3	Ospemifene Tablet 60 mg	VVA	<u>Enrolled:</u> 60 mg = 301 <u>Completed:</u> 60 mg = 184	52 weeks Subjects without an intact uterus that completed Study 15-50310 without clinically significant abnormal findings
15-50821 - 119 ^p - 04Aug08 - 30Jul09 - 919	Randomized, multicenter, double-blind, parallel-group, placebo- controlled, stratified. Phase 3	Oral Tablet 60 mg Placebo	Moderate to severe vaginal dryness and pain associated with sexual activity, symptoms of VVA associated with menopause	<u>Randomized:</u> 60 mg = 463 Placebo = 456 <u>Completed:</u> 60 mg = 416 Placebo = 403	12 weeks Postmenopausal women 40 to 80 years of age with vaginal pH > 5, ≤ 5% superficial cells in vaginal smear, and self- reported MBS of VVA
15-50718 - 23 - 26Nov07 - 26Jun09 - 426	Randomized, multicenter, double-blind, parallel-group, placebo- controlled. Phase 3	Oral Tablet 60 mg Placebo	VVA	<u>Randomized:</u> 60 mg = 363 Placebo = 63 <u>Completed:</u> 60 mg = 294 Placebo = 55	52 weeks Postmenopausal women 40 to 80 years of age with an intact uterus with vaginal pH > 5 and ≤ 5% superficial cells in vaginal smear

Source: Adapted from NDA 203505 Integrated Summary of Safety, Table 25, page 79.

a Only 76 sites randomized at least 1 subject into the study.

b Only 112 sites randomized at least 1 subject into the study.

Definitions: VVA = vulvar and vaginal atrophy.

Medical Officer's Comments:

As shown in Table 25, the 2 initial 12-week studies conducted for ospemifene (Studies 1506001 and 1506002) focused on bone and/or vascular endothelium, lipid metabolism (Study 1506001 was active-controlled and Study 1506002 was placebo-controlled). Six (6) of the 7 remaining Phase 2/3 studies focused on VVA and were double-blinded and placebo-controlled. Study 15-50310X was a 40-week, double-blind extension of parent 12-week Study 15-50310 and included completers of parent Study 15-50310 with a uterus. Study 15-50312 was a 52-week open-label extension of 12-week parent Study 15-50310 and included completers of Study 15-50310 without an intact uterus. The 1 remaining placebo-controlled study (6-week Study 15-50615) focused on vasomotor symptoms.

In the studies shown in Table 25, a total of 2654 subjects received at least 1 dose of study medication in all Phase 2/3 studies and 958 subjects received placebo. Except for 6-week Study 15-50615, other Phase 2/3 studies had study durations of at least 12 weeks. The median (min, max) duration of exposure in all Phase 2/3 studies was 85 (1, 395) days for all ospemifene dosage strengths, 86 (1, 395) days for 60 mg ospemifene/day dosage strength, and 84 (1,378) days for placebo.

7.1.2 Categorization of Adverse Events

A treatment-emergent adverse event (TEAE) was defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the study drug. Each TEAE was evaluated for duration, severity, association with the study drug or other cause, and seriousness and captured on the subjects' Case Report Form (CRF).

The severity of a TEAE was assessed according to the following scale:

- Mild = Awareness of sign or symptom, but was easily tolerated.
- Moderate = Discomfort enough to cause interference with usual activity.
- Severe = Incapacitating with inability to work or perform usual activity

The relationship of an AE to study drug was assessed according to the following definitions:

None (not related) = The existence of a clear alternative explanation (eg, mechanical bleeding at surgical site) or nonplausibility (eg, the subject was struck by an automobile or cancer developing a few days after drug administration).

Unlikely (remote) = A clinical event, including laboratory test abnormality (if applicable), with an improbable time sequence to drug administration and in

	which other drugs, chemicals, or underlying disease provided plausible explanations.
Possible =	A clinical event, including laboratory test abnormality (if applicable), with a reasonable time sequence to administration of the drug, which could also be explained by concurrent disease or other drugs or chemicals.
Probable =	A clinical event, including laboratory test abnormality (if applicable), with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which followed a clinically reasonable response on withdrawal.
Definite =	A clinical event, including laboratory test abnormality (if applicable), for which there was no uncertainty in the relationship to test product administration.

A treatment-emergent serious adverse event (TESAE; as defined by the Applicant) was any untoward medical occurrence that at any dose:

- Resulted in death
- Was life-threatening, (the term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Required inpatient hospitalization or prolongation of existing hospitalization
- Resulted in persistent or significant disability/incapacity
- Was a congenital anomaly or birth defect

Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA), either Version 10.0 or Version 12.0. Version 9.1 was used in Study 15-50312.

Any TESAE, whether deemed drug related or not, occurring in a subject following the signing of the informed consent, during treatment, or during the following 30 days post-treatment was reported to the Sponsor Medical Monitor within 24 hours of the Investigator becoming aware of its occurrence. A severe adverse event (SAE) form plus other supporting information as necessary was provided by the Investigator to the Applicant.

The Applicant was responsible for notifying the relevant regulatory authorities of any TESAE as outlined in the International Conference on Harmonization (ICH) Guidelines. The Applicant also notified all other participating Investigators as required by regulations. The Investigator was responsible for notifying his/her IRB directly.

When a TESAE or a TEAE that was believed to be at least possibly related to study drug persisted at the end of the study, the Investigator was to follow the subject until the subject and the Applicant agreed the event was satisfactorily resolved. Satisfactory resolution may have included referral to the subject's primary medical doctor.

Per the application, the ISS summarizes AEs that are considered treatment-emergent.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The reported results of pooled Phase 1 clinical pharmacology studies are discussed in Subsection 7.1.1 Studies/Clinical Trials Used to Evaluate Safety of this review.

The discussion of pooled safety data for double-blind, Phase 2/3, placebo-controlled studies and all Phase 2/3 studies follows.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure to Study Medication in Double-Blind, Phase 2/3, Placebo-Controlled Studies:

In the 7 double-blind, Phase 2/3, placebo-controlled studies, a total of 2654 subjects received at least 1 dose of study medication. Of the total 2654 subjects, 1696 subjects received ospemifene (62 subjects received ≤ 15 mg/day, 352 subjects received 30 mg/day, 1242 subjects received 60 mg/day, and 40 subjects received 90 mg/day) and 958 subjects received placebo. The median (min, max) duration of exposure was 85 (1,395) days in all ospemifene-treated groups, 86 (1,395) days in 60 mg ospemifene/day group, and 84 (1,378) days in placebo.

Four (4) of the 7 double-blind, placebo-controlled studies had study durations of 12 weeks (Studies 1506002, 15-50717, 15-50310, and 15-50821). For the subjects who received 30 mg ospemifene/day, 53 subjects had ≥ 24 weeks of exposure and 33 subjects had ≥ 52 weeks of exposure. For the subjects who received 60 mg ospemifene/day, 384 subjects had ≥ 24 weeks of exposure, 353 subjects had ≥ 48 weeks of exposure, and 191 subjects had ≥ 52 weeks of exposure. Only subjects who received placebo, 30 mg ospemifene/day, and 60 mg ospemifene/day had exposure to study medication greater than 12 weeks.

Two (2) of the 7 double-blind, placebo-controlled studies had study durations longer than 12-weeks. Study 15-50310X was a 40-week extension of 12-week parent Study

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15-50310. In Study 15-50310X, the mean duration of exposure (not including the 12-week exposure in parent study 15-50310) is as follows:

- 30 mg ospemifene group = 266.0 ± 98.01 days
- 60 mg ospemifene group = 253.6 ± 69.81 days
- Placebo group = 232.4 ± 92.99

Study 15-50718 was a 52-week long-term safety study. The mean duration of exposure in Study 15-50718 is as follows:

- 60 mg ospemifene group = 321.5 ± 97.06 days
- Placebo group = 339.3 ± 74.88 days

One additional 52-week long-term safety extension study (Study 15-50312) is included in the application. Study 15-50312 entitled, “Long term Safety of Ospemifene 60 mg Oral Daily Dose for the Treatment of Vulvar and Vaginal Atrophy (VVA) in Postmenopausal Women without a Uterus: A 52-Week Open-Label Follow-up to Protocol 15-50310” enrolled 301 subjects who did not have a uterus and who completed 12-week parent Study 15-50310 to receive a once-daily dose of 60 mg ospemifene. The mean duration of exposure (not including the 12-week exposure in parent Study 15-50310) in Study 15-50312 was 309.2 days.

Exposure to Ospemifene in All Phase 2/3 Studies:

A total of 1892 subjects received at least 1 dose of ospemifene in all Phase 2/3 studies (1696 subjects in all placebo-controlled Phase 2/3 studies plus 89 subjects in active-comparator Study 1506001 and 107 new ospemifene exposures in Study 15-50312). The median (min, max) duration of exposure to ospemifene was 89 (1, 629) days. Per the Applicant, one subject in 52-week extension Study 15-50312 was reported to have a dosing exposure of 629 days, however, the subject was only dispensed 400 tablets throughout the study. In order to account for this subject, and to assess the impact of incorrect exposure data, the Applicant set the subjects exposure date to 1 day (conservative case) and to 400 days (the number of tablets dispensed to the subject in Study 15-50312), and recalculated the ospemifene exposure data for all Phase 2/3 studies. It was determined that the impact of this one subject did not affect the overall exposure data. The mean (SD) duration of exposure in all Phase 2/3 studies was 181.8 (146.95) days.

The demographics of the safety population in the double-blind, Phase 2/3, placebo-controlled studies are presented in Table 26.

Table 26: Demographics: All Double-Blind, Phase 2/3, Placebo-Controlled Studies

Characteristics	All Ospemifene N = 1696	Placebo N = 958
Age (Years)		
Mean (SD)	59.3 (6.42)	59.1 (6.27)
Median (Min, Max)	59.0 (40, 80)	59.0 (41, 79)
Race (n [%])		
African-American	65 (3.8)	49 (5.1)
Asian	17 (1.0)	9 (0.9)
Caucasian	1583 (93.4)	871 (91.1)
Pacific Islander	4 (0.2)	0 (0.0)
Other	26 (1.5)	27 (2.8)
Body Mass Index (kg/m²)		
Mean (SD)	25.73 (4.073)	26.03 (4.191)
Median (Min, Max)	25.34 (14.7, 48.6)	25.45 (16.5, 40.8)
Weight (kg)		
Mean (SD)	67.96 (11.605)	68.69 (12.079)
Median (Min, Max)	66.65 (37.6, 113.0)	67.65 (39.6, 118.0)

Source: Adapted from NDA 302505, Integrated Summary of Safety, Table 31, page 91.

Definitions: SD = standard deviation; Min = minimum; Max = maximum; KG/m² = kilogram per meter squared.

The demographics of the ospemifene safety population in all Phase 2/3 clinical studies combined are presented in Table 27.

Table 27: Demographics, safety Population: All Phase 2/3 Studies

Characteristics	All Ospemifene N = 1892
Age (Years)	
Mean (SD)	59.2 (6.36)
Median (Min, Max)	59.0 (40, 80)
Race (n [%])	
African-American	69 (3.6)
Asian	18 (1.0)
Caucasian	1772 (93.7)
Pacific Islander	4 (0.2)
Other	28 (1.5)
Body Mass Index (kg/m²)	
Mean (SD)	25.73 (4.068)
Median (Min, Max)	25.31(14.7, 48.6)
Weight (kg)	
Mean (SD)	67.97 (11.611)
Median (Min, Max)	66.80 (37.6, 113.0)

Source: Adapted from NDA 302505, Integrated Summary of Safety, Table 34, page 94.

Definitions: SD = standard deviation; Min = minimum; Max = maximum; KG/m² = kilogram per meter squared.

7.2.2 Explorations for Dose Response

In Phase 1 studies, a total of 335 ospemifene-treated subjects (58%, 335 of 579 ospemifene-treated subjects) and 58 placebo-treated subjects (100%, 58 of 58 placebo-treated subjects) reported at least 1 TEAE in all Phase 1 studies. Phase 1 studies include an ospemifene dose range of 10 mg to 800 mg. See Table 28 which shows the occurrence of all TEAEs and treatment-related TEAEs in Phase 1 studies.

Table 28: Overview of Treatment-Emergent Events: All Phase 1 Studies

Adverse Event Category	Placebo	Number (%) of Subjects Ospemifene-Treated								
		10 mg N=58	25 mg N=3	50 mg N=11	60 mg N=469	100 mg N=11	200 mg N=61	400 mg N=3	800 mg N=10	All N=579
All TEAEs	59 (100)	0	8 (73)	7 (64)	254 (54)	7 (64)	58 (95)	0	1 (10)	335 (58)
Treatment-related AEs	5 (9)	0	1 (9)	6 (54)	116 (25)	4 (36)	10 (16)	0	0	137 (24)

Source: Adapted from NDA 203505, Integrated Summary of Safety, Table 6, page 35.

Definition: TEAE = treatment-emergent adverse event.

Medical Officer's Comments:

Per the application, "A TEAE was defined as an AE that had a date on or after the first dose date, up to 30 days following the last dose date; a treatment-related SAE that occurred at any time on or after the first dose date; and any AE with a missing start date, unless the end date of the AE was prior to the first dose of study drug. An SAE that was not related to treatment was reported only if it occurred up to 30 days following the last dose date."

As shown in Table 28, the number of study participants in Phase 1 studies, per ospemifene dose, with the exception of the 60 mg ospemifene dose, is too small, particularly above 100 mg ospemifene, to draw any conclusions regarding dose response. Nonetheless, Table 28 demonstrates that similar or more TEAEs were reported at ospemifene doses 60 mg to 200 mg with 95% of the subjects receiving 200 mg ospemifene reporting at least 1 TEAE.

In all double-blind, Phase 2/3, placebo-controlled studies, a total of 1118 ospemifene-treated subjects (66%, 1118 of 1696 ospemifene-treated subjects) and 518 placebo-treated subjects (54%, 518 of 958 placebo-treated subjects) reported at least 1 TEAE. These Phase 2/3 studies include an ospemifene dose range of ≤ 15 mg to 90 mg. See Table 29 which shows the occurrence of all TEAEs and treatment-related TEAEs in double-blind, Phase 2/3 studies.

Table 29: Overview of Treatment-Emergent Adverse Events: All Double-Blind, Phase 2/3, Placebo-Controlled Studies

Adverse Event Category	Placebo N=958	Number (%) of Subjects Ospemifene-Treated				
		≤ 15 mg N=62	30 mg n=352	60 mg N=1242	90 mg N=40	All N=1696
All TEAEs	518 (54.1)	28 (45.2)	235 (66.8)	840 (67.6)	15 (37.5)	1118 (65.9)
Treatment-related TEAEs	157 (16.4)	19 (30.6)	111 (31.5)	378 (30.4)	8 (20.0)	516 (30.4)

Source: Adapted from NDA 203505, Integrated Summary of Safety, Table 37, page 98.

Definition: TEAE = treatment-emergent adverse event.

Medical Officer's Comments:

The number of study participants in Phase 2/3 studies, at the 90 mg ospemifene dose, is too small to draw any conclusions regarding a dose response. Table 29 demonstrates that a similar percentage of TEAEs were reported at the 30 mg and 60 mg ospemifene doses (66.8% and 67.6%, respectively, for all TEAEs and 31.5% and 30.4%, respectively, for treatment-related TEAEs).

7.2.3 Special Animal and/or In Vitro Testing

See the Pharmacology/Toxicology Review for a full discussion of special animal and *in vitro* testing of ospemifene.

7.2.4 Routine Clinical Testing

The clinical evaluations conducted in the 7 placebo-controlled Phase 2/3 clinical studies met the recommended routine clinical standard for testing healthy postmenopausal women.

7.2.5 Metabolic, Clearance, and Interaction Workup

No outstanding biopharmaceutical issues have been identified.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Four (4) estrogen agonists/antagonists are currently approved:

1. Clomiphene citrate is approved for the treatment of ovulatory dysfunction in women desiring pregnancy.
2. Tamoxifen citrate is approved for the treatment of metastatic breast cancer in women (premenopausal and postmenopausal) and men.
3. Raloxifene hydrochloride is approved for: 1) Treatment and prevention of osteoporosis in postmenopausal women, and 2) Reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer.

4. Toremifene citrate is approved for the treatment of metastatic breast cancer in postmenopausal women with estrogen-receptor positive or unknown tumors.

Clomiphene citrate is only approved for use in premenopausal women. The most frequent adverse events included in the Adverse Reaction section of the 2012 approved CLOMID® (clomiphene citrate) labeling include: ovarian enlargement, hot flashes, abdominal-pelvic discomfort/distention/bloating, nausea and vomiting, breast discomfort, visual signs including blurred vision, headache, and abnormal uterine bleeding.

For tamoxifen citrate, the most frequent adverse reaction is hot flashes per the Adverse Reaction section of the NOLVADEX® (tamoxifen citrate) labeling approved in 2006, for use in patients treated for metastatic breast cancer. Other adverse reactions associated with tamoxifen citrate include: hypercalcemia, peripheral edema, distaste for food, pruritis vulvae, depression, dizziness, light-headedness, headache, hair-thinning and/or partial hair loss, and vaginal dryness. NOLVADEX® labeling includes a Boxed Warning as follows, but not limited to:

- “Serious and like-threatening events associated with NOLVADEX in the risk reduction setting (women at high risk for cancer and women with DCIS) include uterine malignancies, stroke and pulmonary embolism.”
- “Some of the strokes, pulmonary emboli, and uterine malignancies were fatal.”

The Warnings section of the 2006 approved NOLVADEX® labeling is summarized as follows:

- “Most uterine malignancies seen in association with NOLVADEX are classified as adenocarcinoma of the endometrium. However, rare uterine sarcomas, including malignant mixed mullerian tumors (MMMT), have also been reported.” “Some of the uterine malignancies (endometrial carcinoma or uterine sarcoma) have been fatal.”
- “An increased incidence of endometrial changes including hyperplasia and polyps have been reported.”
- “There have been a few reports of endometriosis and uterine fibroids in women receiving NOLVADEX.”
- “There is no evidence of an increased incidence of thromboembolic events, including deep vein thrombosis and pulmonary embolism, during NOLVADEX therapy.”
- “NOLVADEX has been associated with changes in liver enzyme levels, and on rare occasions, a spectrum of more severe liver abnormalities including fatty liver, cholestasis, hepatic and hepatic necrosis. A few of these cases included fatalities.”

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- “Ocular disturbances, including corneal changes, decrement in color vision perception, retinal vein thrombosis, and retinopathy have been reported in patients receiving NOLVADEX.”

NOLVADEX® labeling includes a Boxed Warning with the following information, but not limited to, the following:

“Uterine malignancies consist of both endometrial adenocarcinoma (incidence rate per 1,000 women-years of 2.20 for NOLVADEX vs 0.4 for placebo)*. For stroke, the incidence rate per 1,000 women-years was 1.43 for NOLVADEX vs 1.00 for placebo**. For pulmonary embolism, the incidence rate per 1,000 women-years was 0.75 for NOLVADEX versus 0.25 for placebo**.”

“Some of the strokes, pulmonary emboli, and uterine malignancies were fatal.”

For raloxifene hydrochloride, the reported common adverse reactions ($\geq 2\%$ and more common than placebo) in the 2007 approved labeling for Evista® (raloxifene hydrochloride) tablets are: hot flashes, leg cramps, peripheral edema, flu syndrome, arthralgia, and sweating. Adverse reactions reported since the market introduction of Evista® include “very rarely”: retinal vein occlusion, stroke, and death associated with venous thromboembolism (VTE). The Warnings and Precautions section of the 2007 approved Evista® labeling is summarized as follows:

- “In clinical trials, EVISTA-treated women had an increased risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism).”
- “In a clinical trial of postmenopausal women with documented coronary heart disease or at increased risk for coronary events, an increased risk of death due to stroke was observed after treatment with EVISTA.”

For toremifene citrate, the most common adverse reactions in the 2011 approved labeling for FARESTON® (toremifene citrate) are: hot flashes, sweating, nausea, and vaginal discharge. Serious adverse reactions occurring in clinical trials in at least 1% of patients receiving FARESTON®, by category, include Cardiac (cardiac failure, myocardial infarction, arrhythmia, angina pectoris), Ocular (cataracts, dry eye, abnormal visual fields, corneal keratopathy, glaucoma, abnormal vision), Thromboembolic (pulmonary embolism, thrombophlebitis, thrombosis, CVA/TIA), and Elevated Liver Tests (AST, alkaline phosphatase, bilirubin, and hypercalcemia). The following Boxed Warning appears in FARESTON® labeling:

“FARESTON has been shown to prolong the QT_c interval in a dose- and concentration-related manner [see *Clinical Pharmacology (12.2)*]. Prolongation of the QT interval can result in a type of ventricular tachycardia called Torsade de pointes, which may result in syncope, seizure, and/or death. Toremifene should not be prescribed to patients with congenital/acquired QT prolongation, uncorrected

hypokalemia or uncorrected hypomagnesemia. Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided [see *Warnings and Precautions (5.1)*].”

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during the ospemifene development program.

7.3.2 Nonfatal Serious Adverse Events

In the ISS, the majority of TEAEs reported in Phase 1 studies were classified with a maximum severity as mild or moderate. Per the application, 4 subjects (0.7%, 4 of 579 ospemifene-treated subjects) reporting TEAEs with an intensity of severe in Phase 1 studies:

- Pancreatitis (50 mg ospemifene group)
- Nausea (60 mg ospemifene group)
- Transient ischemic attack (60 mg ospemifene group)
- Hot flush (200 mg ospemifene group)

Medical Officer’s Comments:

The reported severe adverse reactions that occurred in all Phase 1 studies, noted above, do not raise safety concerns for the 60 mg ospemifene dose.

In all double-blind, Phase 2/3, placebo-controlled studies, a total of 39 ospemifene-treated subjects (2.3%, 39 of 1696 ospemifene-treated subjects) and 17 placebo-treated subjects (1.8%, 17 of 958 placebo-treated subjects) reported at least 1 serious adverse event (SAE). These double-blind, Phase 2/3, placebo-controlled studies include an ospemifene dose range of ≤ 15 mg to 90 mg. See Table 30 which shows the occurrence (number/%) of all SAEs and treatment-related SAEs in double-blind, Phase 2/3, placebo-controlled studies by dose.

Table 30: Overview of serious Adverse Events: All Double-Blind, Phase 2/3, Placebo-Controlled Studies

Adverse Event Category Number (%) of Subjects With SAEs	Placebo N=958	Number (%) of Subjects Ospemifene-Treated				
		≤ 15 mg N=62	30 mg n=352	60 mg N=1242	90 mg N=40	All N=1696
All SAEs	17 (1.8)	0	7 (2.0)	32 (2.6)	0	39 (2.3)

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Treatment-related SAEs	1 (0.1)	0	2 (0.6)	7 (0.6)	0	9 (0.5)
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Source: Adapted from NDA 203505, Integrated Summary of Safety, Table 37, page 98.

Definition: SAE = serious adverse event.

Medical Officer's Comments:

A similar percentage of SAEs occurred at the 30 mg and 60 mg ospemifene dosage strengths (2.0%, 7 of 352 subjects at the 30 mg ospemifene dose and 2.6%, 32 of 1242 subjects at the 60 mg dose).

Per the application, in all Phase 2/3 studies (including all double-blind, Phase 2/3, placebo-controlled studies, active comparator Study 1506001, and open-label Study 15-50312), a total of 52 SAEs (2.7%, 52 of 1892 subjects) occurred. Ten (10) subjects experienced treatment-related SAEs (0.5%, 10 of 1892 subjects in all Phase 2/3 studies).

Overall, the incidence of SAEs is low (2.7%) across all Phase 2/3 studies. This reported incidence of all SAEs does not raise safety concerns for 60 mg ospemifene.

Per the application, the most common treatment-emergent SAE in the ospemifene-treated subjects, occurring in more than 1 subject, in the double-blind, Phase 2/3, placebo-controlled studies were: osteoarthritis (3 subjects), appendicitis (2 subjects), cerebrovascular accident (CVA, 2 subjects in the 60 mg ospemifene group; 1 subject with a thalamic hemorrhage and 1 subject with the term CVA), diverticulitis (2 subjects), and deep vein thrombosis (DVT, 2 subjects). All other SAEs in ospemifene-treated subjects occurred in 1 subject only (incidence 0.1%). See Table 31.

Table 31: Overview of Serious Adverse Events: All Double-Blind, Phase 2/3, Placebo-Controlled Studies

System Organ Class Preferred Term	Placebo N=958	Number (%) of Subjects Ospemifene-Treated				
		≤ 15 mg N=62	30 mg n=352	60 mg N=1242	90 mg N=40	All N=1696
All Treatment-Emergent SAEs	17 (1.8)	0	7 (2.0)	32 (2.6)	0	39 (2.3)
Blood and Lymphatic System Disorder						
- Anemia	0	0	1 (0.3)	0	0	1 (0.1)
Endocrine Disorders						
- Autoimmune thyroiditis	0	0	0	1 (0.1)	0	1 (0.1)
- Hypoparathyroidism	0	0	0	1 (0.1)	0	1 (0.1)
Gastrointestinal Disorders						
- Duodenal stenosis	0	0	1 (0.3)	0	0	1 (0.1)
- Duodenitis	0	0	1 (0.3)	0	0	1 (0.1)
- Gastritis	1 (0.1)	0	0	1 (0.1)	0	1 (0.1)
- GI inflammation	0	0	0	1 (0.1)	0	1 (0.1)
- Hiatal hernia	0	0	0	1 (0.1)	0	1 (0.1)
- Nausea	1 (0.1)	0	0	1 (0.1)	0	1 (0.1)

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General Disorders and Admin. Site Conditions - Non-cardiac chest pain	1 (0.1)	0	0	1 (0.1)	0	1 (0.1)
Hepatobiliary Disorders - Cholelithiasis	0	0	0	1 (0.1)	0	1 (0.1)
Infections and Infestations - Appendicitis	0	0	0	2 (0.2)	0	2 (0.1)
- Diverticulitis	1 (0.1)	0	0	2 (0.2)	0	2 (0.1)
- Herpes encephalitis	0	0	0	1 (0.1)	0	1 (0.1)
- Candida meningitis	0	0	0	1 (0.1)	0	1 (0.1)
- URI	0	0	0	1 (0.1)	0	1 (0.1)
Injury, Poisoning, and Procedural Complications - Third degree burns	0	0	0	1 (0.1)	0	1 (0.1)
- Lower limb fracture	0	0	0	1 (0.1)	0	1 (0.1)
- Road traffic accident	0	0	0	1 (0.1)	0	1 (0.1)
Metabolism and Nutritional Disorders - Dehydration	0	0	0	1 (0.1)	0	1 (0.1)
Musculoskeletal and Connective Tissue Disorders - Osteoporosis	0	0	2 (0.6)	1 (0.1)	0	3 (0.2)
- Bone disorder	0	0	0	1 (0.1)	0	1 (0.1)
- Neck pain	0	0	1 (0.3)	0	0	1 (0.1)
- Spinal column stenosis	0	0	0	1 (0.1)	0	1 (0.1)
Neoplasms Benign, Malignant, Unspecified - Breast cancer metastatic	0	0	1 (0.3)	0	0	1 (0.1)
- Mesothelioma malignant	0	0	0	1 (0.1)	0	1 (0.1)
Nervous System Disorders - Cerebrovascular accidents	1 (0.1)	0	1 (0.3)	1 (0.1)	0	2 (0.1)
- Cerebral hemorrhage	0	0	0	1 (0.1)	0	1 (0.1)
- Global amnesia	0	0	0	1 (0.1)	0	1 (0.1)
- Headache	0	0	1 (0.3)	0	0	1 (0.1)
- Intracranial aneurysm	1 (0.1)	0	0	1 (0.1)	0	1 (0.1)
- Migraine	0	0	0	1 (0.1)	0	1 (0.1)
Reproductive System and Breast Disorders - Breast enlargement	0	0	0	1 (0.1)	0	1 (0.10)
- Hyperplasia ^a	0	0	0	1 (0.1)	0	1 (0.1)
- Ovarian cyst	0	0	0	1 (0.1)	0	1 (0.1)
Respiratory, Thoracic, and Mediastinal Disorders - COPD	0	0	0	1 (0.1)	0	1 (0.1)
Skin and Subcutaneous Tissue Disorders - Skin reaction	0	0	0	1 (0.1)	0	1 (0.1)
Surgical and Medical Procedures - Arthrodesis	0	0	0	1 (0.1)	0	1 (0.1)
- Blepharoplasty	0	0	0	1 (0.1)	0	1 (0.1)
- Breast prosthesis	0	0	0	1 (0.1)	0	1 (0.1)
- Cardiac ablation	0	0	0	1 (0.1)	0	1 (0.1)
- Carpal tunnel decompression	0	0	0	1 (0.1)	0	1 (0.1)
- Gastric bypass	0	0	1 (0.3)	0	0	1 (0.1)

- Mammoplasty	0	0	0	1 (0.1)	0	1 (0.1)
Vascular Disorders						
- Deep vein thrombosis	0	0	0	2 (0.2)	0	2 (0.1)

Source: Adapted from NDA 203505, Integrated Summary of Safety, Table 53, page 122.

Definition: SAE = serious adverse event, COPD = chronic obstructive pulmonary disease.

- a Simple hyperplasia without atypia was recorded for Subject 15-50718-0016-0111 in Study 15-50718. The histology finding was observed approximately 3 months after the last dose of study medication.

Medical Officer's Comments:

The following are brief narratives of the findings of interest (CVA, DVT, endometrial hyperplasia, and breast cancer) shown in Table 31:

- *Subject 15-50310-1016-3017 (30 mg ospemifene group) with baseline hypertension experienced a hypertensive cerebrovascular accident (study day 76) that resolved with sequelae; considered possibly related to study drug.*
- *Subject 15-50718-0016-0130 (60 mg ospemifene group) experienced a cerebrovascular accident of the right hemisphere with left hemiparesis (study day 347); reported recovered with sequelae; considered possibly related to study medication.*
- *Subject 15-50718-0011-0110 (60 mg ospemifene group) experienced a cerebral hemorrhage (study day 273) with right sided numbness; resolved; considered unlikely related to study drug.*
- *Subject 15-50821-0110-3010 (placebo group) experienced a cerebrovascular accident (left frontal/temporal insular infarction) 22 days after the last dose of study medication (completed the 12-week study); resolved with sequelae; considered unlikely related to study medication.*
- *Subject 15-50310-3849-0802 (30 mg ospemifene group) experienced metastatic breast cancer with unknown primary location (2 weeks of study medication) that was reported recovered with sequelae per the narrative; considered possibly related to study drug.*
- *Subject 15-50718-0016-0111 (60 mg ospemifene group); baseline TVU = 2 mm, baseline endometrial biopsy = atrophic endometrium; Week 26 TVU = 10.38 mm, endometrial biopsy = functional endometrial polyp; withdrawn from study; follow-up endometrial biopsy 88 days after last dose of study medication = simple hyperplasia without atypia; resolved following D&C; considered probably related to study drug.*
- *Subject 15-50718-0021-0132 (60 mg ospemifene group); history of thrombosis prophylaxis for approximately 1 year; experienced thrombophlebitis (day 234) and subsequent DVT (study day 249); withdrawn from study; clinically recovered; considered possibly related to study medication.*
- *Subject 15-50821-0236-1133 (60 mg ospemifene group); experienced DVT (study day 85) after 8 hour car trip; study medication discontinued; resolved; considered probable related to study medication.*

See Subsection 7.3.4 Significant Adverse Events in this review for additional information regarding the above noted subjects of interest.

Overall, the 39 SAEs reported in all double-blind, Phase 2/3, placebo-controlled clinical trials, with an incidence rate of 2.3% for all ospemifene-treated subjects, do not raise safety concerns for the 60 mg ospemifene dose.

No SAEs are reported in the 120-Day Safety Update received on August 24, 2012.

In the all Phase 2/3 studies, two additional SAEs of interest are noted:

- Subject 15-50312-4639-0678; 60 mg ospemifene; 60 years of age; acute myocardial infarction (non-ST elevation myocardial infarct following completion of 12-week parent Study 15-50310). This subject had a history of a prior stent placement. She experienced a “mild MI” following a laminectomy for a herniated disc; discontinued study medication; Investigator assessed herniated disc as definitely not related to study drug; the myocardial infarction was considered possible related to study drug.
- Subject 15-50312-4633-0993; 60 mg ospemifene; 59 years of age; hemorrhagic stroke/CVA following completion of 12-week parent study 15-50310; developed chest pain, nausea, vomiting, headache, right arm and right facial weakness; CT scan and MRI of the brain were suspicious for acute hemorrhagic infarction; 2 week follow-up CT scan showed “multiple subacute to old bilateral basal ganglia lacunar infarcts” and “no definite acute intracranial hemorrhage”; discontinued study medication; Investigator assessed hemorrhagic stroke/hemorrhagic CVA as unlikely related to study drug treatment.

Medical Officer’s Comments:

See Subsection 7.3.4 Significant Adverse Events in this review for additional information regarding the above noted subjects of interest.

7.3.3 Dropouts and/or Discontinuations

In the ISS, the Applicant presented subject disposition for the double-blind, Phase 2/3, placebo-controlled studies (Table 32) and for all Phase 2/3 studies (Table 33). Table 32 includes the reported findings from Study 15-50615, Study 1506002, Study 15-50717, Study 15-50310, Study 15-50310X, Study 15-50718, and Study 15-50821. Table 33 includes the reported findings from the same studies in Table 32 plus the following two studies: Study 1506001 (active-comparator) and Study 15-50312 (open-label).

Table 32: Subject Disposition: Double-Blind, Phase 2/3, Placebo-Controlled Studies

	Number of Subjects (%)					
	Ospemifene					
	Placebo N=958	≤15 mg N=62	30 mg N=352	60 mg N=1242	90 mg N=40	All Osp N=1696
Number of Subjects Completed	835 (87.2)	57 (91.9)	278 (79.0)	1061 (85.4)	37 (92.5)	1433 (84.5)
Number of Subjects Discontinued	123 (12.8)	5 (8.1)	74 (21.0)	181 (14.6)	3 (7.5)	263 (15.5)
AE	35 (3.7)	4 (6.5)	21 (6.0)	95 (7.6)	1 (2.5)	121 (7.1)
Lost to Follow-up	16 (1.7)	0	10 (2.8)	17 (1.4)	0	27 (1.6)
Protocol Violation	12 (1.3)	0	14 (4.0)	13 (1.0)	1 (2.5)	28 (1.7)
Other	60 (6.3)	1 (1.6)	29 (8.2)	56 (4.5)	1 (2.5)	87 (5.1)

Source: NDA 203505, Integrated Summary of Safety, Table 26, page 84.

Definitions: Osp = ospemifene, AE = adverse event.

Medical Officer's Comments:

As shown in Table 32, the percentage of subjects who discontinued in the all ospemifene group (15.5%) is similar to the placebo group (12.8%), and equally similar to the 60 mg ospemifene group (14.6%). The largest percentage of discontinuations occurred in the 30 mg ospemifene group (21.0%). The most common reason for discontinuation in the all ospemifene groups was AEs (7.1%), and the most common reason in the placebo group (6.3%) was Other (includes withdrew consent, lack of efficacy, non-compliance with study procedures, family obligations/emergencies, and moved).

Table 33: Subject Disposition: All Phase 2/3 Studies

	Number of Subjects (%)
	All Ospemifene
	N=1892
Number of Subjects Completed	1502 (79.4)
Number of Subjects Discontinued	390 (20.6)
AE	167 (8.8)
Lost to follow-up	44 (2.3)
Protocol violation	33 (1.7)
Other	146 (7.7)

Source: NDA 203505, Integrated Summary of Safety, Table 27, page 85.

Definition: AE = adverse event.

Medical Officer's Comments:

The all Phase 2/3 studies include all double-blind, Phase 2/3, placebo-controlled studies plus Study 1506001 (active-comparator) and Study 15-50312 (52-week open-label). The two additional studies increase the total number of subjects who discontinued (20.6%), due primarily to the number of reported AEs and Other (majority includes subject withdrew consent and subject non-compliant to treatment or study procedures).

Thirty-four (34) subjects discontinued 60 mg ospemifene in open-label Study 15-50312 (52-week extension of 12-week parent Study 15-50310; women without a uterus who completed 12-week Study 15-50310) due to a TEAE that was not ongoing from 12-week parent Study 15-50310.

Table 34 summarizes these 34 adverse events that occurred in Study 15-50312 that led to study discontinuation.

Table 34: Treatment-Emergent Adverse events that Led to Discontinuation in Study 15-50312: ITT Population

System Organ Class	Preferred Term	60 mg Ospemifene (N = 301)
Subjects with at least 1 AE that led to discontinuation		34 (11.3%) ¹
Gastrointestinal Disorders	Nausea	3 (1.0%)
Musculoskeletal and Connective Tissue Disorders	Muscle Spasms	2 (0.7%)
Nervous System Disorders	Headache	3 (1.0%)
Skin and Subcutaneous Tissue Disorders	Hyperhidrosis	2 (0.7%)
	Rash	2 (0.7%)
Vascular Disorders	Hot Flush	6 (2.0%)

Source: Adapted from NDA 203505, Final Study report for Study 15-50312, Table 12.4, page 35 of 56.

¹ This count does not include 3 subjects with ongoing AEs from parent Study 15-50310.

As shown in Table 34, the most common reason for discontinuations in long-term Study 15-50312 was hot flushes. The reported TEAEs causing discontinuation from long-term safety extension Study 15-50312 do not raise safety concerns for 60 mg ospemifene.

7.3.4 Significant Adverse Events

Uterine/Endometrial Safety:

Uterine safety was monitored in Phase 2/3 studies by TVU at baseline and during treatment to evaluate endometrial thickness, by endometrial biopsies at baseline and end-of-study to evaluate endometrial histology, and by endometrial biopsies during treatment as needed for subjects with findings of endometrial thickness ≥ 4 mm or for symptoms of vaginal bleeding as clinically indicated. Per the application, whenever possible, “histopathology of all endometrial polyps was determined per regulatory guidance, and central expert review of polyp histopathology was performed.”

Medical Officer’s Comments:

As previously noted in this review, the Applicant’s procedure for the histologic assessment of endometrial biopsy specimens was not in accordance with the recommendations in the Agency’s 2003 draft Clinical Evaluation Guidance for Industry.

The Clinical Evaluation Guidance for Industry recommends that three independent expert pathologists from different institutions, blinded to treatment group and to each other's readings, be used to determine the diagnosis of endometrial biopsy slides. The concurrence of two of the three pathologists would be accepted as the final diagnosis. When there is no agreement among the three pathologists, the most severe diagnosis would be used as the final diagnosis.

Per the application, endometrial biopsy specimen slides were initially read by two pathologists, and only sent to the third pathologist if there was disagreement between the first two pathologists. This step-wise procedure might lead to an introduction of bias in the evaluation conducted by the third pathologists, thus affecting the final diagnosis.

Also previously stated in this review, this reviewer is not in agreement the Applicant's process for sending "diagnostic-quality digital slides of any treatment-emergent endometrial biopsy sample suggestive of an endometrial polyp" to a selected "expert gynecological pathologist" to determine the diagnosis. The use of an "expert gynecological pathologist" to determine an "endometrial polyp" diagnosis is not in compliance with the Applicant's stated process for determining a final diagnosis in Phase 2/3 studies, "The concurrence of two of the three independent pathologists was used as the final diagnosis. However, if there was no agreement among the three pathologists, then the most severe histopathologic diagnosis was used as the final diagnosis."

Endometrial Thickness:

Per the application, "In the double-blind, Phase 2/3, placebo-controlled studies, there was a slight increase in mean endometrial thickness (double-wall TVU recorded as mm thickness) over time in the ospemifene groups." The following information is available in the application:

Mean Endometrial thickness: Baseline:	All Ospemifene groups: 2.107 ± 0.8179	Placebo group: 2.214 ± 0.8312
Mean Change in Endometrial Thickness:		
12 Weeks:	0.474 ± 1.4292	0.040 ± 0.6281
6 Months:	0.568 ± 1.6434	0.045 ± 1.2625
12 Months:	0.800 ± 1.6893	0.069 ± 1.2290

Medical Officer's Comments:

Over the exposure time as noted above, there is a steady increase in the mean endometrial thickness in the all ospemifene groups as compared with little or no increase in endometrial thickness in the placebo group. This increase in endometrial

thickness with ospemifene use demonstrates its agonistic (stimulatory) effect in endometrial tissue.

More important to this reviewer, however, is the individual subject change in endometrial thickness as determined by a double-wall TVU.

In the double-blind, Phase 2/3, placebo-controlled studies, an endometrial thickness of ≥ 4 mm (endometrial thickness of ≤ 4 mm was an inclusion criterion in clinical trials) at last observation in clinical trials was reported in 10.3% of subjects in the ospemifene-treated groups (117 of 1136 ospemifene-treated subjects) versus 3.5% in the placebo-treated groups (20 of 567 placebo-treated subjects). In these subjects, 1.1% of the ospemifene groups (12 of 1136 ospemifene-treated subjects) had a double-wall thickness ≥ 8 mm versus 0.2% in the placebo group (1 of 567 placebo-treated subjects). The following table shows a summary of endometrial thickness at any time post-baseline and at last observation in the double-blind, Phase 2/3, placebo-controlled studies.

Table 35: Summary of Endometrial Thickness: Double-Blind, Phase 2/3, Placebo-Controlled Studies

	Placebo N=570	Number (%) of Subjects Ospemifene-Treated				
		≤ 15 mg N=53	30 mg N=196	60 mg N=851	90 mg N=40	All N=1140
N with post-baseline endometrial thickness assessments	n=567	n=53	n=195	n=848	n=40	n=1136
Any Time Post-Baseline n (%)						
≥ 4 mm	29 (5.1)	1 (1.9)	23 (11.8)	141 (16.6)	2 (5.0)	167 (14.7)
≥ 5 mm	14 (2.5)	0	15 (7.7)	71 (8.4)	0	86 (7.6)
≥ 8 mm	2 (0.4)	0	3 (1.5)	12 (1.4)	0	15 (1.3)
At Last Observation ^a n (%)						
≥ 4 mm	20 (3.5)	1 (1.9)	16 (8.2)	98 (11.6)	2 (5.0)	117 (10.3)
≥ 5 mm	12 (2.1)	0	11 (5.6)	51 (6.0)	0	62 (5.5)
≥ 8 mm	1 (0.2)	0	3 (1.5)	9 (1.1)	0	12 (1.1)

Source: Adapted from NDA 303505, Integrated Summary of Safety, Table 80, page 193.

a. Prior to or within 14 days of last dose of study drug.

Medical Officer's Comments:

Table 35 demonstrates a clear relationship of ospemifene exposure to endometrial thickness. A 2-fold or greater increase in endometrial thickness is observed in the ospemifene-treated subjects in clinical studies, particularly at the 30 mg ospemifene and 60 mg ospemifene dosage strengths. In addition, endometrial thickness ≥ 4 mm is greatest in the 60 mg ospemifene group.

A similar finding is reported in all Phase 2/3 studies, which includes all double-blind, Phase 2/3, placebo controlled studies, 12-week active comparator Study 1506001, and 52-week open-label Study 15-50312 in women without a uterus. See Table 36.

Table 36: Summary of Endometrial Thickness: All Phase 2/3 Studies

	Ospemifene-Treated Subjects
	N = 1229 ^a
Number with Post-Baseline Endometrial Thickness Assessments	n = 1225
Endometrial thickness at any time-point post-baseline, n (%)	
≥ 4 mm	179 (14.6)
≥ 5 mm	91 (7.4)
≥ 8 mm	15 (1.2)
Endometrial Thickness at last observation, n (%)	
≥ 4 mm	129 (10.5)
≥ 5 mm	67 (5.5)
≥ 8 mm	12 (1.0)

Source: Adapted from NDA 303505, Integrated Summary of Safety, Table 82, page 196.

a. Prior to or within 14 days of last dose of study drug.

Medical Officer's Comments:

The reported increase in endometrial thickness in the ospemifene-treated subjects is an observed estrogenic effect of ospemifene on the endometrium. The calculated incidence rate of endometrial thickness ≥ 5 mm for all ospemifene-treated subjects in all Phase 2/3 studies (as shown in Table 36) is 54.7 per 1000 women (67 of 1225 ospemifene-treated women with a uterus with a post-baseline endometrial thickness assessment) versus 21.2 per 1000 women for placebo (12 of 567 placebo-treated women with a uterus with a post-baseline endometrial thickness assessment as shown in Table 35). The calculated incidence rate of endometrial thickness ≥ 5 mm for subjects treated only with 60 mg ospemifene in the double-blind, Phase 2/3, placebo-controlled clinical trials is 60.1 per 1000 women (51 of 848 women with a uterus treated with 60 mg ospemifene with a post-baseline endometrial thickness assessment as shown in table 35). This reviewer recommends that these incidence rates for endometrial thickness ≥ 5 mm for ospemifene-treated subjects, either one or both calculated incidence rates, and placebo-treated subject in Phase 2/3 studies be included in ospemifene labeling under Section 5 Warnings and Precautions, Subsection 5.2 Malignant Neoplasms. The intent is to inform healthcare providers of the rate of endometrial hypertrophy obtained in clinical trials with ospemifene use.

Endometrial Histology:

In the ospemifene development program, endometrial histology was reported at baseline, 12 weeks, and 12 months. Biopsy findings were determined using Blaustein's criteria for classification:

- No tissue
- Tissue insufficient for diagnosis
- Atrophic
- Inactive
- Proliferative
 - weakly proliferative
 - active proliferative
 - disordered proliferative
- Secretory pattern
 - cyclic type
 - progestational type (including stromal decidualization)
- Menstrual type
- Simple hyperplasia without atypia
- Simple hyperplasia with atypia
- Complex hyperplasia without atypia
- Complex hyperplasia with atypia
- Carcinoma, specify type
- Other, specify in comments

Additional histologic characteristics for polyps, stromal tissue, metaplasia, and cervical tissue are included and are appropriate.

Per the application, in the double-blind, Phase 2/3, placebo-controlled studies, there were no occurrences of endometrial hyperplasia or carcinoma at 12 months in any subject who received ospemifene or placebo. One subject (Subject 15-50718-0016-0111), however, had an endometrial biopsy result of simple hyperplasia without atypia that was documented approximately 3 months after the last dose of study medication (60 mg ospemifene).

- Subject 15-50718-0016-0111, 54 years of age, with a baseline TVU = 1 mm and baseline endometrial biopsy result of atrophic endometrium, took her first dose of 60 mg ospemifene on February 25, 2008. On August 15, 2008, she experience 2 days of vaginal spotting (mild in severity) which spontaneously resolved without treatment (no evaluation performed). Her Week 26 TVU examination (performed on study day 182, (b) (6)) showed a double-wall thickness of 10.38 mm and the possible presence of a polyp. She had an endometrial biopsy on (b) (6) which reported a uterine polyp (functional endometrial type). The Investigator reported the AE of endometrial hypertrophy as probably related to study drug. Because of the polyp finding, this subject was withdrawn from the study. Her last dose of study medication was on November 24, 2008 (total of 273 days of study medication). A repeat TVU and endometrial biopsy performed on (b) (6) showed a TVU = 11.12 mm and active proliferation, respectively. A scheduled follow-up biopsy, performed on (b) (6) (88 days after last dose of study medication) showed simple hyperplasia without

atypia. She was treated with a progestin and underwent dilatation and curettage (D&C) on [REDACTED] (b) (6). D&C showed a primary polyp (functional endometrial type), an inactive endometrium, and no evidence of hyperplasia. Expert review of the reported polyp, per protocol, indicated “This sample has weakly proliferative epithelium without any pattern that would even suggest a polyp.”

Per the application, “However, as the endometrial biopsy was obtained more than 2 weeks after the last dose of study drug, the results are not included in Table 85” in the application. Table 85 entitled, “Summary of Endometrial Biopsy Findings at 12 Weeks and 12 Months: All Phase 2/3 Studies” indicated zero (0) cases of simple hyperplasia without atypia in the ospemifene development program.

Medical Officer’s Comments:

This reviewer understands that, per protocol, this 1 case of simple hyperplasia without atypia was diagnosed outside the 30 day post-treatment window. However, this subject experienced vaginal bleeding, showed an increased degree of endometrial thickness between Baseline, Week 26, and Early Termination (> 10 mm), and received a diagnosis of active proliferative endometrium on the Early Termination endometrial biopsy. This pattern strongly suggests progressive endometrial stimulation. Therefore, this reviewer disagrees with the Applicant that no cases of hyperplasia occurred in double-blind, Phase 2/3, placebo-controlled clinical trials. For completeness, Subject 15-50718-0016-0111 should be counted as 1 case of simple hyperplasia without atypia at the 60 mg ospemifene dose. Further, no cases of complex hyperplasia (with or without atypia) or carcinoma occurred in the ospemifene development program.

The occurrence of 1 case of simple hyperplasia without atypia in all Phase 2/3 clinical trials (0.1%) does not raise safety concerns for the 60 mg ospemifene tablet, however.

An overall summary of endometrial biopsy findings is presented in Table 37 for the double-blind, Phase 2/3, placebo-controlled studies. This grouping is selected for presentation because the active-comparator Study 1506001 was a 12-week study, and long-term Study 15-50312 was conducted in women without a uterus.

Table 37: Summary of Endometrial Biopsy Findings in the Double-Blind, Phase 2/3, Placebo-Controlled Studies

Time Point - Category	Placebo N=469	Number (%) of Subjects Ospemifene-Treated				
		≤ 15 mg N=0	30 mg N=169	60 mg N=773	90 mg N=40	All N=982
Baseline (Randomization)	n=467	n=0	n=169	n=773	n=40	n=978
- No tissue	0	-	0	1 (0.10)	1 (2.5)	2 (0.2)
- Tissue insufficient	196 (42.1)	-	61 (36.3)	261 (33.9)	2 (5.0)	324 (33.1)
- Atrophic	245 (52.6)	-	91 (54.2)	484 (62.9)	32 (80.0)	607 (62.1)
- Inactive	6 (1.3)	-	1 (0.6)	9 (1.2)	0	10 (1.0)

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- Weakly proliferative	15 (3.2)	-	10 (6.0)	9 (1.2)	3 (7.5)	22 (2.2)
- Active proliferative	0	-	3 (1.8)	2 (0.3)	2 (5.0)	7 (0.7)
- Proliferative, disordered	1 (0.2)	-	0	0	0	0
- Secretory, cyclic	0	-	0	0	0	0
- Secretory, proliferative	1 (0.2)	-	0	0	0	0
- Menstrual type	0	-	1 (0.6)	0	0	1 (0.1)
- Simple hyperplasia without atypia	0	-	0	0	0	0
- Simple hyperplasia with atypia	0	-	0	0	0	0
- Complex hyperplasia without atypia	0	-	0	0	0	0
- Complex hyperplasia With atypia	0	-	0	0	0	0
- Carcinoma	0	-	0	0	0	0
- Other ^a	2 (0.4)	-	1 (0.6)	4 (0.5)	0	5 (0.5)
12 Weeks	N=339	n=0	n=133	N=357	n=35	n=525
- No tissue	0	-	0	1 (0.3)	0	1 (0.2)
- Tissue insufficient	173 (51.0)	-	50 (37.6)	112 (31.4)	0	162 (30.9)
- Atrophic	152 (44.8)	-	44 (33.1)	149 (41.7)	10 (28.6)	203 (38.7)
- Inactive	0	-	10 (7.5)	43 (12.0)	0	53 (10.1)
- Weakly proliferative	12 (3.5)	-	17 (12.8)	41 (11.5)	17 (48.6)	75 (14.3)
- Active proliferative	2 (0.6)	-	11 (8.3)	9 (2.5)	8 (22.9)	28 (5.3)
- Proliferative, disordered	0	-	0	2 (0.6)	0	2 (0.4)
- Secretory, cyclic	0	-	0	0	0	0
- Secretory, proliferative	0	-	0	0	0	0
- Menstrual type	0	-	0	0	0	0
- Simple hyperplasia without atypia	0	-	0	0	0	0
- Simple hyperplasia with atypia	0	-	0	0	0	0
- Complex hyperplasia without atypia	0	-	0	0	0	0
- Complex hyperplasia With atypia	0	-	0	0	0	0
- Carcinoma	0	-	0	0	0	0
- Other ^a	0	-	1 (0.8)	0	0	1 (0.2)
12 Months	n=83	n=0	n=46	n=342	n=0	n=388
- No tissue	31 (37.3)	-	0	0	-	0
- Tissue insufficient	51 (61.4)	-	14 (30.4)	49 (14.3)	-	63 (16.2)
- Atrophic	1 (1.2)	-	23 (50.0)	273 (79.8)	-	296 (76.3)
- Inactive	0	-	5 (10.9)	8 (2.3)	-	13 (3.4)
- Weakly proliferative	0	-	3 (6.5)	7 (2.0)	-	10 (2.6)
- Active proliferative	0	-	0	1 (0.3)	-	1 (0.3)
- Proliferative, disordered	0	-	0	1 (0.3)	-	1 (0.3)
- Secretory, cyclic	0	-	0	0	-	0
- Secretory, proliferative	0	-	0	0	-	0
- Menstrual type	0	-	0	0	-	0
- Simple hyperplasia without atypia	0	-	0	0	-	0
- Simple hyperplasia with Atypia	0	-	0	0	-	0
- Complex hyperplasia without atypia	0	-	0	0	-	0
- Complex hyperplasia With atypia	0	-	0	0	-	0
- Carcinoma	0	-	0	0	-	0
- Other ^a	0	-	1 (2.2)	3 (0.9)	-	4 (1.0)

Source: Adapted from NDA 202505, Integrated Summary of Safety, Table 84, page 199.

- a. Findings categorized as other at baseline included polyp, atrophic type (Subject 15-50310-4633-0033, subject 15-50718-35-114, and Subject 15-50821-152-3696), endometrium, non-secretory pattern with breakdown bleeding (Subject 15-50310-3126-0076), atypical epithelial proliferation (Subject 15-50718-32-120 and Subject 15-50718-34-101), and chronic endometritis (Subject 15-50718-42-107). Findings at 12 weeks included atypical epithelial proliferation (Subject 15-50310-4652-0152). Findings at 12 months included atypical epithelial proliferation (Subject 15-50310-4652-0252), polyp, atrophic type (Subject 15-50718-14-111), polyp, functional endometrial type (Subject 15-50718-24-109), and polyp, otherwise specified (Subject-15-50718-37-106).

Medical Officer's Comments:

As shown in Table 37, expected histological findings in a postmenopausal population were present at Baseline: tissue insufficient for diagnosis or tissue atrophic, inactive, or weakly proliferative.

At Week 12 and 12 months, the majority of subjects in the placebo group had endometrial findings classified as tissue insufficient for diagnosis or atrophic, which was similar to Baseline. In the all ospemifene group at Week 12, however, there was a decrease in the percentage of subjects with endometrial biopsy findings classified as atrophic (62.1% at Baseline versus 38.7% at Week 12) with a shift in the percentage of subjects from atrophic to inactive (10.1%), weekly proliferative (14.3%), and to active proliferation (5.3%). These findings support the estrogenic stimulatory effect of ospemifene on the endometrium. These findings were not sustained at 12 months, however, with the majority of the all ospemifene-treated subjects (76.3%) showing an atrophic endometrium.

Uterine Polyps:

Per the application, in the double-blind, Phase 2/3, placebo controlled studies, 9 subjects with endometrial biopsy samples available for expert review were reported to have possible uterine polyps (7 subjects received ospemifene and 2 subjects received placebo):

1. Subject 15-50310X-3849-0249: 60 mg ospemifene; 67 years of age:
 - Baseline TVU = 3.5 mm and no polyps present
 - TVU at Week 12 = 4.4 mm and no polyps present, endometrial biopsy reported as "unsatisfactory for diagnosis: limited surface endometrium present"
 - TVU on Study Day 176 (study day counted from study day 1 in parent study 15-50310) = 7.3 mm and "uncertain" polyps, endometrial biopsy = "inactive to weak proliferation, early atrophy/weak stimulation"
 - Week 52 TVU (Study Day 369) = 8.0 mm and "uncertain" polyps present, endometrial biopsy showed atrophic endometrium
 - Last dose of study medication = (b) (6) (Study Day 369)

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- Dedicated TVU and saline-infused sonogram (SIS, [REDACTED]) = uterine polyp
 - Hysteroscopy on [REDACTED] (b) (6) = small solitary endometrial polyp
 - Curettage and polypectomy performed, [REDACTED] (b) (4) [REDACTED] (b) (4) diagnosed benign endometrial polyp. [REDACTED] (b) (4) expert review reports “cystic atrophy or cystic change in adenomyosis with fibrous stroma and one fragment might be a small atrophic polyp
2. Subject 15-50718-0014-0111: 60 mg ospemifene; 63 years of age:
 - Baseline TVU = local read, 3.2 mm, central read, 1.81 mm; endometrial biopsy = atrophic endometrium
 - Week 12 TVU = central read, 2.67 mm, “probably” polyp
 - Week 26 TVU = central read, 3.21 mm, no endometrial polyp
 - Week 52 TVU = central read, 5.97 mm, no endometrial polyp present; endometrial biopsy = “polyp, atrophic type”; no Investigator causality presented
 - Expert review = “The medium power view above shows several findings that are not expected in a polyp: 1) lack of a central larger vessel and 2) a lack of change in stromal density from the center (denser) to the periphery. There findings do not entirely exclude a polyp, but they do suggest there is a reasonable chance that this is not truly a polyp.” “This sample has atrophic endometrium with one intact fragment that by its shape and stroma suggests a polyp.”
 3. Subject 15-50718-0016-0111; 60 mg ospemifene; see the information for this subject presented on page 118 of this review; expert review of the slides from both “polyps” indicated that the tissue most likely did not represent true endometrial polyps.
 4. Subject 15-50718-0022-0108; 60 mg ospemifene; 54 year of age:
 - Baseline TVU = 3.54 mm; baseline endometrial biopsy = atrophic endometrium
 - Week 26 TVU = 4.33 mm, endometrial biopsy (Study Day 228) = polyp, atrophic type
 - Discontinued per protocol (Study Day 257)
 - End-of-Study TVU = 3.75 (Study Day 288); uterine polyp “resolved”; Investigator assessed the endometrial thickness and uterine polyp as possibly related to study drug
 - Expert review assessed the “tissue as showing benign pseudo-cribiform glands in a dense stroma, with the apparent polyp shape of one of the fragments likely being an artifact created by the biopsy catheter rather than a true polyp”
 5. Subject 15-50718-0024-0109; 60 mg ospemifene; 70 years of age:
 - Baseline TVU = 1.83 mm, endometrial biopsy = atrophic endometrium
 - Week 12 TVU = 3.08 mm, no endometrial polyp present
 - Week 26 TVU = 2.72 mm, no endometrial polyp present
 - Week 52 TVU = 3.85 mm, endometrial biopsy = atrophic endometrium evaluated by 3 independent pathologist; the concurrence of 2 of the 3 independent pathologist was used as final diagnosis
 - Expert review = “inadequate biopsy rather than a polyp”
 6. Subject 15-50718-0034-0117; 60 mg ospemifene; 58 years of age:
 - Baseline TVU = 1.59 mm, endometrial biopsy = atrophic endometrium

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- Week 12 TVU = 2.4 mm and “abnormal”
 - Week 26 TVU = 2.59 mm and “abnormal”
 - Week 52 TVU = 4.34 mm and also an endometrial polyp, endometrial biopsy = atrophic endometrium (post-menopausal)
 - Repeat endometrial biopsy = polyp (functional endometrial type); Investigator assessed polyp as possibly related to study medication
 - Expert review of digital slides = polyp shaped tissue of inactive to weakly proliferative endometrium; “artifact of the biopsy catheter, rather than true polyp”
7. Subject 15-50718-0036-0106; 60 mg ospemifene; 66 years of age:
- Baseline TVU = 2.75 mm, endometrial biopsy = atrophic endometrium
 - Week 12 TVU (Study Day 89) = 5.84 mm, endometrial biopsy = polyp, atrophic type
 - Discontinued from study per protocol on Study Day 120; uterine polyp “ongoing”; Investigator assessed as unlikely related to study medication
 - Expert review = “mound of cystic atrophy mimicking a polyp rather than a true polyp”
8. Subject 15-50718-0015-0107; placebo; 50 years of age:
- Baseline TVU = 3.47 mm, endometrial biopsy = atrophic endometrium
 - Week 12 TVU = 2.98 mm, endometrial biopsy = polyp, atrophic type
 - Discontinued per protocol on December 5, 2008; End-of Study TVU = 2.55 mm: Investigator assessed AE as possibly related to study medication
 - Subsequent hysteroscopy = “tiny endometrial polyp” resected = benign; mistakenly reported as endocervical polyp
 - Expert review of slides = “atrophic endometrium that mimicked a polyp in shape as an artifact of the sampling”
9. Subject 15-50821-0199-3379; placebo; 64 years of age:
- Baseline TVU = 3.8 mm, endometrial biopsy = “tissue volume too scant for diagnosis – no endometrium present”
 - Week 12 TVU (Study Day 86) = “normal” local read; “uncertain” central read; endometrial biopsy = “unsatisfactory for diagnosis: limited surface endometrium present”
 - Repeat TVU on Study Day 170 = 3.1 mm and an endometrial fluid measurement of 8.0 mm; possible polyp
 - SIS performed Study Day 170 = endometrial polyp; Investigator assessed as possibly related to study medication
 - Hysteroscopy and polypectomy performed post-study completion approximately 4 months later = “solitary polyp”; (b) (4) diagnosis = benign endometrial polyp
 - Expert review = benign endometrial polyp, atrophic type

In the application however, other polyps, with and without samples for expert review, were reported as follows:

Subject 15-50718-0016-0135: 60 mg ospemifene; 60 years of age:

- Baseline TVU = 2.53 mm; endometrial biopsy = atrophic endometrium

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- Week 26 TVU (Study Day 190) = 3.48 mm; suspect uterine polyp on local read but not the central read; endometrial biopsy = atrophic endometrium
- Discontinuation per protocol on February 11, 2009
- End-of Study TVU = 4.41 mm, no polyp detected; endometrial biopsy = atrophic endometrium, no polyp; Investigator indicated polyp “resolved”.

Subject 15-50718-0021-0111: 60 mg ospemifene; 74 years of age:

- Baseline TVU = 3.22 mm; endometrial biopsy = atrophic endometrium
- Week 12 TVU (Study Day 84) = 5.5 mm by local read (central read = 1.46 mm)
- Hysteroscopy by local gynecologist (Study Day 133) = 1 cm pedunculated uterine polyp excised = uterine polyp without atypia or malignancy
- Discontinued on Study Day 156; Investigator reported endometrial hypertrophy and uterine polyp as possibly related to study drug
- Local hospital could not provide slides for pathologists review

Subject 15-50821-0127-3574; 60 mg ospemifene; 48 years of age:

- Baseline TVU = 3.3 mm, endometrial biopsy = atrophic endometrium
- Week 12 TVU (Study Day 87) = 5.4 mm, endometrial biopsy = inactive endometrium
- Central read of Week 12 TVU = “could not rule out a possible endometrial polyp”
- Local Investigator = “did not feel that there was an actual polyp present”

Subject 15-50718-0034-0108; 60 mg ospemifene; 61 years of age:

- Baseline TVU = 3.22 mm; endometrial biopsy = atrophic endometrium
- Week 26 TVU (Study Day 176) = 2.94 mm; suspect polyp
- Repeat TVU = 4.21 mm; endometrial biopsy = “inactive to weak proliferation”
- Discontinued per protocol on October 22, 2008
- Hysteroscopy on [REDACTED] = no polyp detected (coded as “ultrasound uterus abnormal”); Investigator considered polyp possibly related to study medication when originally reported

Medical Officer’s Comments:

A total of 13 cases that report “uterine polyp” (preferred term) occurred in the ospemifene development program (11 in ospemifene-treated subjects and 2 in placebo-treated subjects). The full narratives for these subjects are presented in Appendix 2 of the ISS. This total number includes, however, all cases that report uterine polyps even those polyps that were felt to be an artifact of endometrial sampling by the expert reviewer and those polyps with and without samples for review by study pathologists. This total number also includes Subject 15-50718-0016-0111 with a final diagnosis of simple hyperplasia without atypia.

Nonetheless, the overall number of polyps reported in all Phase 2/3 studies (excluding Subject 15-50718-0016-0111), even including all other reported cases of polyps, is

small: 10 ospemifene-treated subjects in all Phase 2/3 studies (0.8%, 10 of 1229 ospemifene-treated subjects with an intact uterus) versus 2 placebo-treated subjects (0.35%, 2 of 570 placebo-treated subjects with an intact uterus).

All of the polyps reported in the ospemifene-treated groups in the Phase 2/3 studies occurred, however, at the 60 mg ospemifene dosage strength (1.1%, 10 of 881 subjects treated with 60 mg ospemifene in the ospemifene development program with an intact uterus). Overall, the incidence of uterine polyps in the ospemifene development program is low and does not raise concerns for the 60 mg ospemifene tablet. The occurrence of polyps supports, however, the estrogenic agonistic effect of 60 mg ospemifene on the uterus.

Cardiovascular Safety:

In the ospemifene development program, stroke cases were identified by higher level terms of central nervous system hemorrhages and cerebrovascular accidents, cerebrovascular and spinal necrosis and vascular insufficiency, nervous system hemorrhagic disorders, cerebrovascular embolism and thrombosis, and cerebrovascular and spinal vascular disorders; and a preferred term of post procedural stroke. Myocardial infarction cases were identified by preferred terms of acute myocardial infarction, myocardial infarction, papillary muscle infarction, post procedural myocardial infarction, and silent myocardial infarction. Venous thromboembolism events were identified by preferred terms of pulmonary embolism, deep vein thrombosis, deep vein thrombosis postoperative, pelvic venous thrombosis, retinal vein thrombosis, venous thrombosis limb, and embolism venous.

Cardiovascular/Cerebrovascular/Thrombotic Events:

One (1) cardiovascular/cerebrovascular/thrombotic (CV) event occurred in Phase 1 studies:

Subject 15-50716-001-0006; 60 mg ospemifene (1 dose); 75 years of age; TIA

- Baseline = History of brain infarction 5 years previously
- Single dose received on May 7, 2007; developed symptoms of paresis with paresthesia on May 15, 2007 with weakness and motor disability of the left upper limb; resolved same day
- ECG normal on May 17, 2007
- Neurologist visit = transient cerebral ischemic attack (TIA); MRI = old infarction
- Discontinued study; investigator assessed event as possibly related to study medication

Six (6) subjects experienced cardiovascular/cerebrovascular/thrombotic-related events in the double-blind, Phase 2/3, placebo-controlled studies (5 ospemifene-treated subjects and 1 placebo-treated subject). See Table 38. Of the 5 ospemifene-treated

subjects, 4 (0.2%) discontinued the study due to the cardiovascular event (2 subjects due to cerebrovascular accidents and 2 subjects due to deep vein thrombosis).

Table 38: Cardiovascular/Cerebrovascular/Thrombotic-Related Events: Double-Blind, Phase 2/3, Placebo-Controlled Studies

Preferred Term	Placebo N=958	Number (%) of Subjects Ospemifene-Treated				
		≤ 15 mg N=62	30 mg N=352	60 mg N=1242	90 mg N=40	All N=1696
Any CV-Related TEAE	1 (0.1)	0	1 (0.3)	4 (0.3)	0	54(0.3)
- Cerebrovascular Accident	1 (0.1)	0	1 (0.3)	1 (0.1)	0	2 (0.1)
- Deep Vein Thrombosis	0	0	0	2 (0.2)	0	2 (0.1)
- Cerebral Hemorrhage	0	0	0	1 (0.1)	0	1 (0.1)

Source: Adapted from NDA 203505, Integrated Summary of Safety, Table 113, page 231.
Definitions: CV = cardiovascular/cerebrovascular/thrombotic, TEAE = treatment-emergent adverse event.

Two (2) additional cardiovascular/cerebrovascular/thrombotic events were reported in all Phase 2/3 studies (1 subject with an acute myocardial infarction and 1 subject with a hemorrhagic stroke). See Table 39. Both of these subjects discontinued due to their adverse event.

Table 39: Cardiovascular/Cerebrovascular/Thrombotic-Related Events: All Phase 2/3 Studies

Preferred Term	Number (%) of Subjects Ospemifene-Treated N=1892
Any CV-Related TEAE	7 (0.4)
- Cerebrovascular Accident	2 (0.1)
- Deep Vein Thrombosis	2 (0.1)
- Acute Myocardial Infarction	1 (0.1)
- Cerebral Hemorrhage	1 (0.1)
- Hemorrhagic Stroke	1 (0.1)

Source: Adapted from NDA 203505, Integrated Summary of Safety, Table 114, page 231.
Definitions: CV = cardiovascular/cerebrovascular/thrombotic, TEAE = treatment-emergent adverse event.

Medical Officer's Comments:

Overall, the reported incidence of cardiovascular/cerebrovascular/thrombotic events is low in the ospemifene development program: one CV-related event in Phase 1 studies, and a total of 7 (0.4%, 7 of 1892 ospemifene-treated subjects) CV-related events in all Phase 2/3 studies (Table 39). Of these 7 CV-related events, 1 occurred in the 30 mg ospemifene treatment group (0.3%, 1 of 381 subjects treated with 30 mg of ospemifene in all Phase 2/3 studies), 1 occurred in the placebo treatment group (0.1%, 1 in 958 placebo-treated subjects in all Phase 2/3 studies), and 5 occurred in the 60 mg

ospemifene treatment group (0.4%, 5 of 1379 subjects treated with 60 mg ospemifene in all Phase 2/3 studies).

A brief discussion of each subject with a cardiovascular/cerebrovascular/thrombotic event in all Phase 2/3 studies follows:

Ischemic Cerebrovascular Accidents (CVA):

Subject 15-50310-1016-3017; 30 mg ospemifene; 57 years of age; ischemic CVA:

- *Baseline medical history included hypertension, hypercholesterolemia, diabetes, depression, and peripheral neuropathy*
- *Study Day 76 = left sided facial drooping, weakness of left lower extremity, slurred speech, and an unsteady gait*
- *Hospitalized with left lower facial palsy, hypoglossal nerve palsy with left tongue deviation; CT scan without contrast = no acute infarcts, edema, or hemorrhage; old ischemic lacunar infarction to the right anterior basal ganglia (stated to be > 3 months old)*
- *Hospitalized and treated with aspirin and IV enoxaparin sodium; MRI revealed focal (1 cm) area of acute infarct in the right corona radiate with no hemorrhage; blood pressure stabilized with lisinopril*
- *Discharged on medication; discharge summary reports that the stroke was probably related to her hypertension; recovered with sequelae; Investigator assessed event as possibly related to study medication*

Subject 15-50718-0016-0130; 60 mg ospemifene; 58 years of age; ischemic CVA:

- *Baseline medical history included hypercholesterolemia*
- *Study Day 348 = CVA of right hemisphere with left hemiparesis; CT scan = ischemic lesion, right fronto-temporo-parietal region; cerebral scintigraphy confirms*
- *Hospitalized; intravenous and intra-arterial thrombolysis procedures unsuccessful; cerebral hemorrhage and edema following operation*
- *Discontinued from study; referred to neurological rehabilitation unit; recovered with sequelae; Investigator assessed event as possibly related to study drug*

Subject 15-50821-0110-3010; placebo; 56 years of age; ischemic CVA post-embolization of carotid ophthalmic artery; subsequent deep vein thrombosis:

- *Completed study; 22 days after last dose of study medication [REDACTED] (b) (6) subject was hospitalized due to cerebral brain aneurysm (intracranial aneurysm); cerebral CT angiogram = left carotid ophthalmic aneurysm and subarachnoid hemorrhage; successful balloon assisted coil embolization; developed moderate to severe vasospasm; subject subsequently developed cerebral infarct secondary to vasospasm [REDACTED] (b) (6)*

- Head CT scan = evolving infarct in left middle cerebral artery; multiple treatments/procedures provided; subsequently developed left-sided proximal femoral, posterior tibial, and peroneal DVT (b) (6)
- Transferred to rehabilitation facility; discharged with sequelae; Investigator assessed cerebral brain aneurysm and cerebrovascular accident as unlikely related to study drug; no assessment of the DVT was provided

This reviewer agrees with the Investigator assessments for these 3 cases of ischemic stroke.

Hemorrhagic Cerebrovascular Accident:

Subject 15-50718-0011-0110; 60 mg ospemifene; 62 years of age; cerebral hemorrhage:

- Baseline history of hypertension under treatment
- Study Day 273 = numbness of right leg, right arm, and right side of face
- Hospitalized with diagnosis of cerebral hemorrhage with 1.7 cm hematoma of the left thalamus; symptoms resolved within 1 day (only facial numbness remained); laboratory tests showed increased prothrombin time and hypercholesterolemia; CT scan = intra-cerebral hematoma; no deviation of the medulla
- Discharged from hospital; discharge summary = right-sided numbness caused by bleeding in the left thalamus; considered resolved; completed Study 15-50718; Investigator considered event as unlikely related to study drug

Subject 15-50310-4633-0993; 60 mg ospemifene; 59 years of age; hemorrhagic CVA

- Completed preceding parent Study 15-50310, received 30 mg ospemifene; entered open-label Study 15-50312 (July 10, 2007), received 60 mg ospemifene
- Developed chest pain, nausea, vomiting, headache, right arm and right facial weakness on (b) (6)
- Neurologic assessment = right hemiparesis and intracranial bleed; CT scan = acute hematoma, acute left basal ganglion hemorrhage; intravenous dexamethasone provided
- Hospitalized; MRI = suspicious of acute hemorrhagic infarction; multiple medications provided
- Discharged to home with medication; follow-up CT scan (b) (6) = "multiple subacute to old bilateral basal ganglia lacunar infarcts, chronic small vessel ischemic changes, no definite acute intracranial hemorrhage"; Investigator assessed hemorrhagic stroke/hemorrhagic CVA as unlikely related to study drug treatment; outcome recovered

This reviewer does not agree with the Investigator assessments that these 2 cases of hemorrhagic stroke were "unlikely related" to study medication. This reviewer considers that 2 cases of hemorrhagic stroke occurred at the 60 mg ospemifene dose during the

ospemifene development program (1 case in Study 15-50718 and 1 case in extension Study 15-50312 receiving 60 mg ospemifene).

Middle Cerebral Artery Aneurism:

One additional subject (Subject 15-50821-0152-3826; 60 mg ospemifene in 12-week Study 15-50821) was hospitalized 67 days after the start of study medication with mild left-sided weakness, migraine, shortness of breath, nausea, photophobia, blurry vision and diplopia. Her past history included a left middle cerebral artery aneurism (MCA) with clipping. A CT angiogram of the brain confirmed clipping of left MCA, no hemorrhage was seen. Study medication was interrupted then restarted. This subject completed Study 15-50821. The Investigator assessed the right MCA as definitely not related to study drug.

This reviewer agrees with the Investigator assessment of this 1 case of middle cerebral artery aneurism. The decision to enroll this subject in Study 15-50821 is questionable.

Acute Myocardial Infarction:

Subject 15-50310-4639-0678: 60 mg ospemifene; 60 years of age: acute myocardial infarction:

- *Completed preceding parent Study 15-50310; entered open-label Study 15-50312*
- *Past history of heart catheterization and stent placement*
- *Back surgery performed (laminectomy with fusion) during Study 15-50312; discharged with medication including nitroglycerin sublingual*
- *Developed chest pain; in emergency room ECG showed no evidence of acute ischemia, no ST elevations*
- *Hospitalized; left heart catheterization revealed patent stent; discharged on medications; Investigator assessed non-ST elevation myocardial infarction as possibly related to study drug treatment*

This reviewer agrees with the Investigator assessment of this 1 case of acute myocardial infarction as “possibly related to drug treatment”.

In addition, one case of global amnesia is reported in the 60 mg ospemifene treatment group:

Subject 13-50718-; 60 mg ospemifene; 69 years of age:

- *Baseline history including coronary artery disease, ventricular extrasystoles, hypertension and hypercholesterolemia*
- *Study Day 143 = experienced amnesia and difficulty speaking*
- *Hospitalized = suspected TIA; unremarkable neurological examination; MRI = normal; discharged recovered; final diagnosis = transient global amnesia*

- *Discontinued study; Investigator assessed event as possibly related to study drug*

This reviewer agrees with the Investigator assessment of this 1 case of global amnesia as “possibly related to study drug”.

Deep Vein Thrombosis (DVT):

Subject 15-50718-0021-0132; 60 mg ospemifene; 65 years of age; DVT:

- *Baseline history including thrombosis prophylaxis (acetylsalicylic acid and magnesium hydroxide)*
- *Study Day 234 = thrombophlebitis of right foot with swelling and pain*
- *Hospitalized Study Day 249 = “deep venous thrombosis on the right side”; thrombosis prophylaxis stopped; treated with warfarin and dalteparin sodium and compression bandage*
- *Discharged; clinically resolved*
- *Discontinued from study; Investigator assessed DVT as possibly related to study drug*

Subject 15-50821-0236-1133; 60 mg ospemifene; 67 years of age; DVT:

- *Baseline history of knee replacement, arthritis, migraines, hypertension*
- *End-of-Study (Study Day 85) = DVT of the right leg with red streaking in the right calf; denied acute injury; pain began during 8-hour car trip*
- *Treatment in ER; chest CT negative for pulmonary embolism; discharged home with warfarin and enoxaparin, right leg elevation, and intermittent heat; Investigator assessed acute DVT as probably related to study drug; Applicant assessed DVT = “study drug may have contributed”, “the relative immobilization from the 8-hour car ride during which her symptoms developed likely played a significant role in the pathogenesis of the event.”*

This reviewer agrees with the Investigator assessment of causality for these two cases of DVT reported for 60 mg ospemifene (“possibly related to study drug” for Subject 15-50718-0021-0132, and “probably related to study drug” for Subject 15-50821-0236-1133). The concern expressed by the Applicant that the 8-hour car ride with immobilization contributed to the occurrence of a DVT in Subject 15-50821-0236-1133 is appreciated.

One subject in the placebo treatment group of Study 15-50821 (Subject 15-50821-0110-3010) developed a DVT following hospitalization for an ischemic CVA post-embolization of the carotid ophthalmic artery. The narrative for this subject can be viewed on page 127 of this review.

Per the application, the “incidence of VTEs was low and was similar between the active (2 subjects, incidence rate of 2.12/1000 person years [0.26, 7.67]) and placebo 1 subject, incidence rate of 3.66/100 person years (0.09, 20.41)) arms.”

As previously noted in this review, subjects in Phase 2/3 clinical studies were screened for Factor V Leiden (FVL) at baseline and excluded if positive. Also previously noted in this review, 2 heterozygous positive subjects in Study 15-50310 were randomized and completed the 12-week study without an adverse event. A third heterozygous positive subject participated in Study 15-50718 but discontinued early due to an unrelated adverse event.

Per the Office of Clinical Pharmacology (OCP), Genomics Group Review of NDA 203505, FVL is a “genetic characteristics marked by poor anticoagulant responses to activated protein C (APC) resulting from a glutamine to arginine substitution at the Arg506 APC cleavage site in the Factor V gene. This single amino acid substitution leads to Factor V resistance to APC and subsequent increased thrombin generation. The FVL polymorphism is common in the U.S. population. The prevalence of carrying at least one allele in whites is 5.3%; the prevalence is lower in other ethnicities (Hispanic Americans: 2.2%, Native Americans 1.3%, African Americans 1.2%, Asian Americans: 0.5 %;). In the US population, homozygosity for FVL polymorphisms is uncommon at a frequency of 0.02%. The absolute risk for developing VTE in the general population is low (<1/1000 patient years) but increased if other risk factors are present. The absolute risk associated with FVL for developing a VTE is comparable to the absolute risk associated with other known risk factors (i.e., oral contraceptive (OC) use + increased age). VTE risk is exaggerated in the presence of more than one risk factor.”

The OCP Genomic Group reviewer assessed whether: “1) the risk estimation for venous thrombotic event (VTE) was biased due to exclusion of FVL carriers in Phase 2 and Phase 3 trials and 2) whether screening for FVL is indicated for patients who are eligible for ospemifene therapy.”

The OCP Genomics Group Review, included in the January 12, 2013 Clinical Pharmacology Review, concludes the following:

“Known risk factors for developing a VTE include increased age, OC/HRT/SERM therapy, smoking and inherited factors (e.g., FVL, prothrombin polymorphisms). VTE risk is ~2-3 fold higher in FVL carriers compared to non-carriers, and further increased if other known risk factors are present.

The sponsor excluded FVL carriers from Phase 2 and Phase 3 clinical trials. We do not expect that additional VTE cases would have been observed if FVL carriers were included in Phase 2/3 trials based on estimates of the incidence of VTE and prevalence of FVL. Therefore, the risk estimation for VTE is reasonable.

Routine screening for FVL in patients receiving ospemifene is not recommended given estimates that more than 1000 patients would need to be screened in order to prevent a single VTE. However, FVL carriers receiving ospemifene may still be at greater risk for VTE (compared to FVL non-carriers) given the experience with other SERMs. Screening may be considered in patients with multiple risk factors known to be associated with VTEs (e.g. increased age, smoking, prior VTE)."

Medical Officer's Comments:

This reviewer agrees with the OCP Genomics Group reviewer conclusion that, "Based on the estimated prevalence of FVL and considering the increased risk associated with FVL, few/no additional VTE cases would have been observed if FVL carriers were included in Phase 2/3 trials. Therefore, current risk estimates are reasonable. Additionally, screening for FVL in patients being considered for ospemifene is not recommended given the estimates that more than 1000 patients would need to be screened in order to prevent a single VTE."

Three cases of superficial thrombophlebitis are reported in the application:

Subject 15-50310-1004-3010; 60 mg ospemifene; 60 years of age; thrombophlebitis:

- Baseline history of irritable bowel disease, acid reflux, and diverticulitis
- Completed preceding parent Study 15-50310; entered open-label Study 15-50312
- Hospitalized for exacerbation of diverticulitis; developed leg pain and erythematous area; CT scan = basilica vein thrombosis; treated with heparin overnight; resolved and discharged
- Re-hospitalized and underwent sigmoidectomy and cholecystectomy; resolved and discharged; Investigator assessed events of diverticulitis and basilica vein thrombosis as definitely not related to study drug

Subject 15-50718-0041-0101; 60 mg ospemifene; 68 years of age; thrombophlebitis:

- Baseline history of hypertension and gastritis
- Study Day 59 = experienced thrombophlebitis of left thigh; treated with mucopolysaccharide polysulfuric acid topically; resolved
- Antithrombin III, protein C, and protein S did not show evidence of deficiency
- Completed Study 15-50718; Investigator assessed thrombophlebitis event as not related to study drug
- Per Applicant, it is "notable that the event was treated only with topical mucopolysaccharide polysulfate, resolved without being treated with a parenteral heparin or heprinoid or with Coumadin, and was not regarded as being a serious adverse event. In the opinion of the sponsor, based on the totality of the available case information, this was most likely a case of superficial thrombophlebitis rather than deep vein thrombosis."

Subject 15-50718-0041-0104; 60 mg ospemifene; 71 years of age; thrombophlebitis:

- Baseline history of arthralgia, hypotonic bladder, hyperlipidemia, depression and hypothyroidism
- Study Day 51 = experience thrombophlebitis of right thigh; treated with mucopolysaccharide polysulfuric acid topically; resolved
- Antithrombin III, protein C, and protein S were “consistently normal”
- Completed Study 15-50718; Investigator assessed thrombophlebitis event as unlikely related to study drug
- Per Applicant, it is “notable that the event was treated only with topical mucopolysaccharide polysulfate, resolved without being treated with a parenteral heparin or heprinoid or with Coumadin, and was not regarded as being a serious adverse event. In the opinion of the sponsor, based on the totality of the available case information, this was most likely a case of superficial thrombophlebitis rather than deep vein thrombosis.”

Medical Officer’s Comments:

This reviewer agrees with the assessed causality of these 3 reported cases of superficial thrombophlebitis.

Medical Officer’s Safety Summary Comments:

In the application, four ospemifene-treated subjects were diagnosed with either thrombotic or hemorrhagic stroke (1 case was reported in the 30 mg ospemifene treatment group and 3 cases were reported in the 60 mg ospemifene treatment group; one of these 3 cases was initially randomized to 30 mg ospemifene in parent Study 15-50310 and was changed to 60 mg ospemifene in extension Study 15-50312)). One (1) case of thrombotic stroke was reported in the placebo group that occurred post-embolization of the carotid ophthalmic artery.

The incidence rate for thrombotic stroke per 1000 ospemifene-treated subjects is 1.06 (2 thrombotic strokes in 1892 ospemifene-treated subjects in all Phase 2/3 studies) versus 1.04 per 1000 women in the placebo treatment group (1 thrombotic stroke in 958 placebo-treated subjects). The incidence rate for hemorrhagic stroke per 1000 ospemifene-treated subjects is also 1.06 (2 hemorrhagic strokes in 1892 ospemifene-treated subjects in all Phase 2/3 studies. However, these 2 hemorrhagic strokes occurred in subjects being treated with 60 mg ospemifene (incidence rate of 1.45 per 1000 women, 2 in 1379 subjects treated with 60 mg ospemifene). No hemorrhagic strokes occurred in the placebo treatment group. Per the NDA application, the “incidence rate of each event was 2.12/1000 person years [0.26, 7.67]).” “For the placebo subject, the incidence rate for the CVA was 3.66/1000 person years [0.09, 20.41]).” No deaths occurred due to stroke in the ospemifene development program.

Two 60 mg ospemifene-treated subjects were diagnosed with deep vein thrombosis (DVT). One of the 2 subjects was on DVT prophylaxis at the time of study entry. The incidence rate for DVT per 1000 ospemifene-treated subjects in all Phase 2/3 studies is 1.06 (2 DVTs in 1892 ospemifene-treated subjects in all Phase 2/3 studies). Both DVT occurred in the 60 mg ospemifene treatment group, however (incidence rate of 1.45 per 1000 women, 2 in 1379 subjects treated with 60 mg ospemifene). One (1) DVT occurred in the placebo treatment group (incidence rate of 1.04 per 1000 women, 1 in 958 placebo-treated subjects).

The occurrence of these reported cardiovascular/cerebrovascular/thrombotic events, at the incidence rates calculated, do not raise any overall safety concerns for the 60 mg ospemifene dose. This reviewer recommends that the incidence rates for these reported cardiovascular/cerebrovascular/thrombotic events, either the rate for all ospemifene treated subjects in all Phase 2/3 studies or the incidence rate only for the 60 mg ospemifene dose or both incidence rates, be included in a Boxed Warning in the ospemifene labeling and under Section 5 Warnings and Precautions, Subsection 5.1 Cardiovascular Disorders. The intent is to advise healthcare providers of the increased risk of DVT with estrogen containing drug products, and to inform them of the rates obtained in the clinical trials with ospemifene, an estrogen agonist/antagonist.

7.3.5 Submission Specific Primary Safety Concerns

Pelvic Organ Prolapse:

TEAEs related to pelvic organ prolapse included reported occurrence of enterocele, rectocele, bladder prolapse, colpocele, cystocele, genital prolapse, hysterocele, pelvic prolapse, rectocele, urogenital prolapse, uterine prolapse, uterovaginal prolapse, vaginal prolapse, and colporrhapy. In all Phase 2/3 studies, 3 ospemifene-treated subjects and 1 placebo-treated subject experienced a pelvic organ prolapse:

Subject 15-50310-3144-1014; 60 mg ospemifene; 64 years of age without a uterus:

- Baseline = medical history included hysterectomy and oophorectomy in 1996; no uterine or vaginal prolapse; completed preceding parent Study 15-50310
- Cystocele reported on Study Day 274 of Study 15-5012; assessed as “mild severity, nonserious, and unlikely related to study drug”; no action take
- Completed Study 15-50312

Subject 15-50718-0016-0102; 60 mg ospemifene; 63 years of age with a uterus:

- Baseline = no uterine or vaginal prolapse
- Fluconazole intravaginally for vaginal infection during study; cystitis, vulvovaginal candidiasis, and vulvovaginal mycotic infection also reported
- Bladder prolapse reported on Study Day 245; assessed as being “moderate severity and not related to study drug”; no action taken

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- Completed Study 15-50718; gynecological examination at End-of-Study assessed as “normal”

Subject 15-50718-0034-0110; 60 mg ospemifene; 63 year of age with a uterus:

- Baseline = Grade 1 uterine prolapse; “Grade 1 – Some bulging during Valsalva, no symptoms”
- Cystocele diagnosed on Study Day 136; no action taken; Investigator considered prolapse to be “moderate severity and possibly related to study drug”; no action taken
- Completed Study 15-50718; gynecological examination at End-of-Study described as “abnormal, not clinically significant”

Subject 15-50821-0179-1183; Placebo; 53 years of age without a uterus:

- Baseline = hysterectomy for uterine prolapse
- Study Day 47 = hospitalized for “severe worsening bladder prolapse”; Grade 2 cystocele without urinary incontinence and Grade 0-1 rectocele with no cuff prolapse; vaginal vault suspension performed; event resolved; interruption of study drug for 1 day; Investigator assessed worsening of bladder prolapse as definitely not related to study drug
- Completed Study 15-50821

Medical Officer’s Comments:

In the published literature, estrogen agonist/antagonist products (also referred to as SERMs), approved and under investigation, have been reported to increase the risk of pelvic organ prolapse. However, the published literature is not consistent regarding these products and pelvic organ prolapse.

Furthermore, labeling for the currently approved estrogen agonist/antagonist products, previously discussed in this review, does not include pelvic organ prolapse as side effects of these approved products. These reported cases of pelvic organ prolapse do not raise safety concerns for 60 mg ospemifene.

Breast Safety:

In the double-blind, Phase 2/3, placebo-controlled studies, a total of 63 subjects (0.3%, 63 of 2297 subjects) reported a breast-related TEAE (42 ospemifene-treated subjects and 21 placebo-treated subjects). Two (2) of the 42 ospemifene-treated subjects discontinued, and 1 placebo-treated subject discontinued:

Subject 15-50310-3849-0802: 30 mg ospemifene; 59 years of age:

- Baseline mammogram = heterogeneously dense breast parenchyma; no masses or calcifications

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- Study Day 16 = enlarged lymph node left groin; primary gynecologist recommends follow-up in 2 months
- Study Day 52 = left groin enlarged lymph node; excision = metastatic carcinoma, poorly differentiated
- MRI of breast = no primary for the metastatic carcinoma
- Oncologist examination = “metastatic breast cancer, unknown primary location based on ER/PR positivity, CK7 positivity, CK 20 negativity and GCFAP positivity”; subject received exemestane and zoledronic acid treatment; reported recovered with sequelae
- Discontinued from study; Investigator assessed event as possibly related to study drug

Subject 15-50310-1019-0628; 30 mg ospemifene; breast tenderness; discontinued

Subject 15-50310-4016-0009; placebo; 56 years of age:

- Baseline mammogram = heterogeneously dense breast parenchyma
- Study Visit 3 = lump in right breast; breast ultrasound = 10 mm nodule; unilateral mammogram and biopsy = infiltrating lobular carcinoma, Grade 1, with associated lobular carcinoma *in situ*
- Discontinued from study; lost to follow-up; Investigator assessed event as unlikely related to study drug

One additional case of *in situ* breast cancer in a placebo-treated subject is reported:

Subject 15-50310X-2007-005: placebo; 63 years of age:

- Baseline mammogram = no evidence of malignancy
- End-of-Study Visit = scattered fibroglandular densities, no masses, 2 foci of calcifications in left breast
- Left diagnostic mammogram and biopsy = ductal carcinoma *in situ*, ER/PR positive; left breast simple mastectomy with reconstruction; no evidence of residual carcinoma
- Investigator assessed event as possibly related to study drug treatment

No additional breast cancers were reported in all Phase 2/3 studies.

Medical Officer's Comments:

No breast cancers were reported in the 60 mg ospemifene treatment group. The single reported case of metastatic breast cancer of unknown primary location (MRI of breast showed no primary cancer) in the 30 mg ospemifene group does not raise safety concerns. Further, there were 2 cases of breast cancer in placebo-treated subjects.

Vaginal Bleeding and Spotting:

Per the application, subjects with the following preferred terms were included: coital bleeding, postmenopausal hemorrhage, genital hemorrhage, vaginal hemorrhage, uterine hemorrhage, metrorrhagia, dysfunctional uterine bleeding, bleeding anovulatory menorrhagia, and polymenorrhagia. Post-endometrial biopsy bleeding/spotting cases (with a preferred term of post-procedural hemorrhage) were not included.

In the double-blind, Phase 2/3, placebo-controlled studies, a total of 22 subjects with an intact uterus reported vaginal bleeding and/or spotting (17 ospemifene-treated subjects [1.5%] and 5 placebo-treated subjects [0.9%]). Ten (10) of the 17 ospemifene-treated subjects were treated with 60 mg ospemifene (1.2%, 10 of 851 subjects with an intact uterus). None of the vaginal bleeding and/or spotting TEAEs led to discontinuations.

Four (4) subjects (0.7%) without an intact uterus reported vaginal bleeding and/or spotting (3 subjects treated with 30 mg ospemifene, and 1 subject treated with 60 mg ospemifene), none discontinued. See Table 40.

Table 40: Vaginal Bleeding- and/or Spotting-Related Adverse events: Double-Blind, Phase 2/3, Placebo-Controlled Studies

Preferred Term	Placebo	Number (%) of Subjects Ospemifene-Treated				
		≤ 15 mg	30 mg	60 mg	90 mg	All
Subjects With an Intact Uterus	N=570	N=53	N=196	N=851	N=40	N=1140
Any Vaginal Bleeding and/or Spotting	5 (0.9)	1 (1.9)	6 (3.1)	10 (1.2)	0	17 (1.5)
- Vaginal hemorrhage	5 (0.9)	1 (1.9)	3 (1.5)	7 (0.8)	0	
- Postmenopausal	0	0	3 (1.5)	0	0	
- Coital bleeding	0	0	0	1 (0.1)	0	
- Irregular menstruation	0	0	0	1 (0.1)	0	
- Menorrhagia	0	0	0	1 (0.1)	0	
Subject Without an Intact Uterus	n=387	N=9	N=156	N=391	N=0	N=556
Any Vaginal Bleeding and/or Spotting	0	0	3 (1.9)	1 (0.3)	-	4 (0.7)
- Vaginal hemorrhage	0	0	3 (1.9)	1 (0.3)	-	4 (0.7)

Source: Adapted from NDA 203505, Integrated Summary of Safety, Table 90, page 208.

Medical Officer's Comments:

The application only includes narratives for women with a uterus who reported vaginal bleeding/spotting. Therefore, limited information is available for women without an intact uterus who reported vaginal bleeding/spotting. No safety concerns result for the information presented, however, regarding vaginal bleeding and/or spotting for 60 mg ospemifene.

Uterine Leiomyomas ("Fibroids"):

In all Phase 2/3 studies, a total of 14 subjects with an intact uterus reported a uterine neoplasm-related TEAE (11 ospemifene-treated subjects [0.9%, 11 of 1229 ospemifene-treated subjects with a uterus; 9 at 60 mg ospemifene and 2 at 30 mg ospemifene] and 3 placebo-treated subjects [0.5%, 3 of 570 placebo-treated subjects with a uterus]). One (1) of the ospemifene-treated subjects discontinued due to the uterine fibroid. None of the placebo-treated subjects discontinued.

Medical Officer's Comments:

There reported cases of uterine fibroids do not raise safety concerns for 60 mg ospemifene.

Urinary Symptoms and Infections:

In the application, TEAEs related to urinary tract infections (UTIs) were identified. In the double-blind, Phase 2/3, placebo-controlled studies, a total of 221 subjects reported a UTI-related TEAE (161 ospemifene-treated subjects [9.5%] and 60 placebo-treated subjects [6.3%]). The most common UTI-related TEAE (greater than 1%) in both the ospemifene and placebo groups were urinary tract infection (6.4% versus 4.8%, respectively), cystitis (1.5% versus 0.6%, respectively), and bacterial UTI (1.0% versus 0.6%, respectively). In the all Phase 2/3 studies, 23 additional subjects reported UTIs and 1 additional subject reported cystitis. Overall, only 1 subject discontinued with a UTI-related TEAE in all Phase 2/3 studies.

Ocular Events:

In the double-blind, Phase 2/3, placebo-controlled studies, a total of 34 subjects reported an ocular-related TEAE (includes ocular events having an SOC of eye disorder, or a higher level groups term of eye therapeutic procedures). Twenty-four (24) of these 34 reported ocular events occurred in ospemifene-treated subjects (1.4%, 24 of 1696 ospemifene-treated subjects), and 10 occurred in placebo-treated subjects (1.0%, 10 of 958 placebo-treated subjects).

Per the application, ocular events in ospemifene-treated subjects only occurred at the 30 mg and 60 mg ospemifene dosage strengths. The following ocular events occurred either at the 30 or the 60 mg dosage strength, presented in order of decreasing frequency: conjunctivitis, cataract, blepharoplasty, cataract operation, eye pain, retinal tear, blurred vision, allergic conjunctivitis, dry eye, eye edema, eye operation increased lacrimation, pterygium, ulcerative keratitis, and visual impairment. Four (4) subject treated with 60 mg ospemifene developed cataracts (0.3%, 4 of 1242 subjects treated) versus 2 placebo-treated subjects (0.2%, 2 of 958 placebo-treated subjects). Two (2) ospemifene-treated subjects had cataract operations (0.2%, 2 of 1241 subject treated with 60 mg ospemifene) and 1 placebo-treated subject had a cataract operation (0.1%,

1 of 958 placebo-treated subjects). In the all Phase 2/3 studies, 1 additional subject treated with 60 mg ospemifene reported a cataract (total of 5 cataracts, 0.3%, 5 of 1892 ospemifene-treated subjects).

Two (2) subjects discontinued treatment in the ospemifene treatment group due to an ocular event. No placebo subject discontinued due to ocular-related TEAEs.

Medical Officer's Comments:

The reported ocular events in the ospemifene development program do not raise safety concerns for 60 mg ospemifene.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A treatment-emergent adverse event (TEAE) was defined as an adverse event that had an onset date on or after the first dose of study medication, up to 30 days following the last dose of study medication.

Double-Blind, Phase 2/3, Placebo-Controlled Studies:

In the 7 double-blind, Phase 2/3, placebo-controlled clinical trials conducted during the ospemifene development program, a total of 1118 ospemifene-treated subjects experienced at least 1 TEAE (65.9%, 1118 of 1696 ospemifene-treated subjects) compared with 54.1% of placebo subjects (518 of 958 placebo-treated subjects).

A summary of TEAEs occurring in $\geq 1\%$ of subjects by preferred term sorted by decreasing frequency is presented in Table 41.

Table 41: Summary of Number (%) of treatment-Emergent Adverse Events on $\geq 1\%$ of Subjects by Preferred Term, by Decreasing Frequency in All Double-Blind, Phase 2/3, Placebo-Controlled Studies

Preferred Term	Placebo N=958	Number (%) of Subjects Ospemifene-Treated				
		≤ 15 mg N=62	30 mg n=352	60 mg N=1242	90 mg N=40	All N=1696
Any TEAE	518 (54.1)	28 (45.2)	236 (66.8)	840 (67.6)	15 (37.5)	1118 (65.9)
- Hot flush	32 (3.3)	6 (9.7)	32 (9.1)	106 (8.5)	1 (2.5)	145 (8.5)
- Headache	57 (5.9)	6 (9.7)	31 (8.8)	67 (5.4)	5 (10.0)	108 (6.4)
- Urinary tract infection	46 (4.8)	1 (1.6)	26 (7.4)	81 (6.5)	0	108 (6.4)
- Nasopharyngitis	30 (3.1)	2 (3.2)	5 (1.4)	67 (5.4)	0	74 (4.4)
- Vaginal discharge	4 (0.4)	2 (3.2)	15 (4.3)	55 (4.4)	0	72 (4.2)

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- Muscle spasms	13 (1.4)	0	11 (3.2)	55 (4.4)	1 (2.5)	67 (4.0)
- Vulvovaginal Candidiasis	5 (0.5)	1 (1.6)	9 (2.6)	53 (4.3)	0	63 (3.7)
- Sinusitis	36 (3.8)	0	11 (3.1)	37 (3.0)	0	48 (2.8)
- Back pain	23 (2.4)	2 (3.2)	6 (1.7)	37 (3.0)	0	45 (2.7)
- Vulvovaginal Mycosis	5 (0.5)	0	5 (1.4)	38 (3.1)	0	43 (2.5)
- Diarrhea	16 (1.7)	0	7 (2.0)	30 (2.4)	0	37 (2.2)
- Arthralgia	24 (2.5)	1 (1.6)	8 (2.3)	27 (2.2)	0	36 (2.1)
- Insomnia	11 (1.1)	1 (1.6)	6 (1.7)	27 (2.2)	2 (5.0)	36 (2.1)
- Nausea	11 (1.1)	1 (1.6)	10 (2.8)	23 (1.9)	1 (2.5)	35 (2.1)
- URT infection	34 (3.5)	0	8 (2.3)	26 (2.1)	1 (2.5)	35 (2.1)
- Genital discharge	2 (0.2)	2 (3.2)	9 (2.6)	18 (1.4)	2 (5.0)	31 (1.8)
- Hyperhidrosis	9 (0.9)	0	5 (1.4)	24 (1.9)	2 (5.0)	31 (1.8)
- Bronchitis	13 (1.4)	0	4 (1.1)	25 (2.0)	1 (2.5)	30 (1.8)
- Pain in extremity	11 (1.1)	1 (1.6)	6 (1.7)	22 (1.8)	0	29 (1.7)
- Cystitis	6 (0.6)	0	1 (0.3)	23 (1.9)	1 (2.5)	25 (1.5)
- Dizziness	11 (1.1)	0	7 (2.0)	15 (1.2)	2 (5.0)	24 (1.4)
- Hypertension	6 (0.6)	1 (1.6)	8 (2.3)	15 (1.2)	0	24 (1.4)
- Influenza like illness	10 (1.0)	0	0	23 (1.9)	0	23 (1.4)
- Vulvovaginal pruritis	7 (0.7)	0	5 (1.4)	18 (1.4)	0	23 (1.4)
- Constipation	13 (1.4)	1 (1.6)	5 (1.4)	15 (1.2)	0	21 (1.2)
- Depression	10 (1.0)	0	4 (1.1)	17 (1.4)	0	21 (1.2)
- Weight increased	7 (0.7)	0	7 (2.0)	14 (1.1)	0	21 (1.2)
- Abdominal pain	13 (1.4)	0	4 (1.1)	14 (1.1)	1 (2.5)	19 (1.1)
- Rash	8 (0.8)	1 (1.6)	4 (1.1)	14 (1.4)	0	19 (1.1)
- Hypercholesterolemia	11 (1.1)	0	3 (0.9)	15 (1.2)	0	18 (1.1)
- Vaginal infection	6 (0.6)	0	3 (0.9)	13 (1.0)	2 (5.0)	18 (1.1)
- Abdominal pain lower	5 (0.5)	0	3 (0.9)	14 (1.1)	0	17 (1.0)
- Osteoporosis	1 (0.1)	0	3 (0.9)	14 (1.1)	0	17 (1.0)
- UTI bacterial	6 (0.6)	0	0	17 (1.4)	0	17 (1.0)
- Vulvovaginal dryness	1 (0.1)	0	4 (1.1)	13 (1.0)	0	17 (1.0)

Source: Adapted from NDA 203505, Integrated Summary of Safety, Table 39, page 101.

Definitions: TEAE = treatment-emergent adverse event, URT – upper respiratory tract, UTI = urinary tract infection.

Medical Officer's Comments:

As shown in Table 41, the most common TEAEs in subjects receiving ospemifene are hot flush (8.5% for all ospemifene groups versus 3.3% for placebo), headache (6.4% for all ospemifene groups versus 5.9% for placebo), and UTI (6.4% for all ospemifene groups versus 4.8% for placebo). There does not appear to be a clear dose-relationship for these TEAEs, however. Very few TEAEs were reported at the 90 mg ospemifene dose. However, the number of subjects at this dose level is very small.

In the application, the Applicant also provided the number and percentage of AEs related to study medication. An event was considered related to treatment if it was possible related, probably related, definitely related, or if this information was missing or unknown. The reported treatment-related AEs are hot flush (7.5% for all ospemifene groups and 2.6% for placebo), vaginal discharge (3.7% for all ospemifene groups and 0.3% for placebo), and headache (3.12% for ospemifene and 2.45 for placebo). See Table 42.

Table 42: Summary of Number (%) of Treatment-Emergent Adverse Events in $\geq 1\%$ in All Double-Blind, Phase 2/3, Placebo-Controlled Studies

Preferred Term	Placebo N=958	Number (%) of Subjects Ospemifene-Treated				
		≤ 15 mg N=62	30 mg n=352	60 mg N=1242	90 mg N=40	All N=1696
Any Treatment-Related AE	157 (16.4)	19 (30.6)	111 (31.5)	378 (30.4)	8 (20.0)	516 (30.4)
Investigations						
- Weight increased	5 (0.5)	0	7 (2.0)	11 (0.9)	0	18 (1.1)
Musculoskeletal and Connective Tissue Disorders						
- Muscle spasms	9 (0.9)	0	7 (2.0)	40 (3.2)	0	47 (2.8)
Nervous System Disorders						
- Headache	23 (2.4)	4 (6.5)	15 (4.3)	30 (2.4)	4 (10.0)	53 (3.1)
Reproductive System and Breast Disorders						
- Vaginal discharge	3 (0.3)	2 (3.2)	13 (3.7)	47 (3.8)	0	62 (3.7)
- Genital discharge	1 (0.1)	2 (3.2)	9 (2.6)	16 (1.3)	2 (5.0)	29 (1.7)
Skin and Subcutaneous Tissue Disorders						
- Hyperhidrosis	6 (0.6)	0	4 (1.1)	20 (1.6)	2 (5.0)	26 (1.5)
Vascular Disorders						
- Hot flush	25 (2.6)	6 (9.7)	28 (8.0)	93 (7.5)	1 (2.5)	128 (7.5)

Source: Adapted from NDA 203505, Integrated Summary of Safety, Table 40, page 103

Definition: AE = adverse event.

Medical Officer's Comments:

The following Table 43 shows these reported treatment-related TEAEs sorted by decreasing frequency.

Table 43: Summary of Number (%) of Subjects with Treatment-Related Adverse Events in $\geq 1\%$ by Preferred Term, by Decreasing Frequency in All Double-Blind, Phase 2/3, Placebo-Controlled Studies

Preferred Term	Placebo N=958	Number (%) of Subjects Ospemifene-Treated				
		≤ 15 mg N=62	30 mg n=352	60 mg N=1242	90 mg N=40	All N=1696
Any Treatment-Related AE	157 (16.4)	19 (30.6)	111 (31.5)	378 (30.4)	8 (20.0)	516 (30.4)
- Hot flush	25 (2.6)	6 (9.7)	28 (8.0)	93 (7.5)	1 (2.5)	128 (7.5)
- Vaginal discharge	3 (0.3)	2 (3.2)	13 (3.7)	47 (3.8)	0	62 (3.7)
- Headache	23 (2.4)	4 (6.5)	15 (4.3)	30 (2.4)	4 (10.0)	53 (3.1)
- Muscle spasms	9 (0.9)	0	7 (2.0)	40 (3.2)	0	47 (2.8)
- Genital discharge	1 (0.1)	2 (3.2)	9 (2.6)	16 (1.3)	2 (5.0)	29 (1.7)
- Hyperhidrosis	6 (0.6)	0	4 (1.1)	20 (1.6)	2 (5.0)	26 (1.5)
- Weight increased	5 (0.5)	0	7 (2.0)	11 (0.9)	0	18 (1.1)

Source: Adapted from NDA 203505, Integrated Summary of Safety, Table 41, page 104.

Definition: AE = adverse event.

In Table 43, there is a clear relationship between the occurrence of hot flush in all ospemifene-treated subjects versus placebo-treated subjects (7.5% of subjects [128 of 1696 ospemifene-treated subjects] compared to 2.6% in the placebo group [25 of 958 placebo-treated subjects]). Hot flashes are known to be one of the most commonly reported adverse events with the currently available SERMs, and suggest estrogen antagonistic effect on the hypothalamus.

Likewise, there is a clear relationship between the occurrence of vaginal discharge, genital discharge, and hyperhidrosis (excessive sweating) in all ospemifene-treated subjects versus placebo-treated subjects. Vaginal and genital discharge is also commonly associated with estrogen drug products.

There is no clear dose relationship, however, between any of these reported treatment-related adverse events (hot flush, vaginal discharge, genital discharge, and hyperhidrosis) and the 30 mg and 60 mg ospemifene treatment groups. The 30 mg ospemifene group demonstrated a higher occurrence of headache and weight increase compared with placebo than the 60 mg ospemifene group.

The incidence of muscle spasms, also a commonly reported adverse events with currently available estrogen agonist/antagonist, was higher in the all ospemifene groups with 2.8 % of subjects (47 of 1696 ospemifene-treated subjects) compared to 0.9% in the placebo group (9 of 958 placebo-treated subjects). Almost all of the AEs under the preferred term muscle spasms were leg cramps, a common adverse event of currently approved estrogen agonists/antagonists.

In general, the reproductive-system related AEs are expected in postmenopausal women with VVA; and the AEs such as vaginal and genital discharge are expected based on the mechanism of action of ospemifene on vaginal epithelium.

These reported treatment-related AEs do not raise safety concerns for 60 mg ospemifene tablets.

In the all Phase 2/3 studies review of the safety data, the most commonly reported treatment-related AEs for all ospemifene-treated subjects are hot flush (8.8%, 166 of 1892 ospemifene-treated subjects), vaginal discharge (3.5%, 67 of 1892 ospemifene-treated subjects), and headache (3.3%, 63 of 1892 ospemifene-treated subjects). The reported incidence of these specific AEs are similar to the incidence reported in the double-blind, Phase 2/3, placebo-controlled studies.

7.4.2 Laboratory Findings

Coagulation Parameters:

A summary of select coagulation parameters, including activated partial thromboplastin time (aPTT), fibrinogen, antithrombin antigen (antithrombin III), protein C antigen (Ag), and protein S Ag free, for baseline, 12 weeks, 6 months, and 12 months are presented in the application for double-blind, Phase 2/3, placebo-controlled studies and all Phase 2/3 studies.

For aPTT, in the double-blind, Phase 2/3, placebo-controlled studies, minimal changes in mean values were observed for the ospemifene groups and the placebo group. For fibrinogen, a slight mean decrease was observed at all time points that were slightly higher than the mean decrease in the placebo group. Similar findings were observed for antithrombin antigen.

For protein C Ag, a slight mean decrease was observed for the ospemifene group from baseline to all time points. Changes for protein C Ag were also observed for the placebo group, however, a decrease was only observed for the change from baseline to 12 weeks, with an increase observed for 6 and 12 months.

For protein S Ag free, a slight mean increase from baseline to all time points was observed in both the ospemifene group and the placebo group.

In the all Phase 2/3 studies, the overall findings for coagulation parameters were similar to the findings in the double-blind, Phase 2/3, placebo-controlled studies.

Medical Officer's Comments:

Overall, changes observed at the noted time points for coagulation parameters in ospemifene-treated subjects were minor and not notably different from changes observed for placebo-treated subjects.

For the coagulation parameter of protein S Ag free, reported results show a greater increase from baseline for the 60 mg ospemifene dose compared with the 30 mg ospemifene dose (5.8 ± 15.62 versus 3.6 ± 11.46 at 12 weeks, 6.8 ± 12.82 versus 4.6 ± 13.44 at 6 months, and 11.5 ± 13.70 versus 7.1 ± 16.77 at 12 months). These results suggest a dose-related trend for protein S Ag free for 60 mg ospemifene. However, no data is available for the lowest ospemifene dose (≤ 15 mg ospemifene) or the highest ospemifene dose (90 mg ospemifene) utilized in the double-blind, Phase 2/3, placebo-controlled studies. No conclusion can be drawn from this data.

Lipids:

In the double-blind, Phase 2/3, placebo-controlled studies, a total of 49 subjects developed lipid-related TEAEs. Twenty-seven (27) were ospemifene-treated subjects (1.6%, 27 of 1696 ospemifene-treated subjects: 6 subjects received 30 mg ospemifene per day and 21 subjects received 60 mg per day), and 22 were placebo-treated subjects

(2.3%, 22 of 958 placebo-treated subjects). The most common lipid-related TEAE in the ospemifene-treated subjects were hypercholesterolemia (18 subjects [1.1%]), and hyperlipidemia (7 subjects [0.4%]). Two (2) of the 27 ospemifene-treated subjects (Subject 15-50310X-4629-0421 and Subject 15-50310-3932-1190) and 1 of the placebo-treated subjects discontinued (Subject 15-50310-4599-0754) due to hyperlipidemia.

In the all Phase 2/3 studies grouping, 6 additional subjects had hypercholesterolemia (total of 24 subjects [1.3%]) and 3 additional subjects had hyperlipidemia (total of 10 subjects [0.5%]). One (1) additional subject discontinued due to blood cholesterol increased (Subject 15-50312-4631-0610). These lipid-related and other lipid-related events are displayed in Table 44 and Table 45.

Table 44: Lipid-Related adverse Events: Double-Blind, Phase 2/3, Placebo-Controlled Studies

Preferred Term	Placebo N=958	Number (%) of Subjects Ospemifene-Treated				
		≤ 15 mg N=62	30 mg n=352	60 mg N=1242	90 mg N=40	All N=1696
Any Lipid-Related TEAE	22 (2.3)	0	6 (1.7)	21 (1.7)	0	27 (1.6)
- Hypercholesterolemia	11 (1.1)	0	3 (0.9)	15 (1.2)	0	18 (1.1)
- Hyperlipidemia	2 (0.2)	0	3 (0.9)	4 (0.3)	0	7 (0.4)
- Triglycerides Increased	4 (0.4)	0	0	1 (0.1)	0	1 (0.1)
- Hypertriglyceridemia	1 (0.1)	0	0	1 (0.1)	0	1 (0.1)
- Cholesterol Increased	5 (0.5)	0	0	0	0	0
- Dyslipidemia	1 (0.1)	0	0	0	0	0

Source: Adapted from NDA 203505, Integrated Summary of Safety, Table 117, page 242.

Definition: TEAE = treatment-emergent adverse event.

Table 45: Lipid-Related adverse events: All Phase 2/3 Studies

Preferred Term	Number (%) of Subjects	
	All Ospemifene	
	N = 1892	
Any Lipid-Related TEAE	47 (2.5)	
- Hypercholesterolemia	24 (1.3)	
- Hyperlipidemia	10 (0.5)	
- Triglycerides Increased	5 (0.3)	
- Hypertriglyceridemia	4 (0.2)	
- Cholesterol Increased	4 (0.2)	
- Dyslipidemia	1(0.1)	

Source: Adapted from NDA 203505, Integrated Summary of Safety, Table 118, page 242.

Definition: TEAE = treatment-emergent adverse event.

Medical Officer's Comments:

In the double-blind, Phase 2/3, placebo-controlled studies, the overall percentages of subjects experiencing lipid-related TEAEs were similar between ospemifene and

placebo subjects. In the all Phase 2/3 studies, the percentage of subjects with lipid-related TEAEs was similar to that observed in the double-blind, Phase 2.3, placebo-controlled studies.

Of interest, in this postmenopausal normolipidemic population, low-density lipoproteins (LDL) decreased from baseline to end-of-study in a dose-dependent manner, with the decrease for 60 mg ospemifene at 12 months being $-6.96 \pm 18.08\%$, compared to $-2.13 \pm 18.42\%$ for placebo. Likewise of interest, mean high-density lipoprotein (HDL) increased by $2.28 \pm 14.95\%$ in the 60 mg ospemifene group compared with $-1.91 \pm 12.68\%$.

7.4.3 Vital Signs

In all clinical studies, vital signs were assessed for each study group. Baseline, end-of-study (termination), and change from baseline to end-of-study (termination) were summarized for systolic and diastolic blood pressure, pulse, weight, and BMI.

In the double-blind, Phase 2/3, placebo-controlled studies, a small mean decrease in systolic blood pressure was observed in both the ospemifene treatment group (-0.3 ± 14.30 mm Hg) and the placebo group (-0.5 ± 13.03 mm Hg). Findings for diastolic blood pressure were similar (-0.2 ± 8.99 mm Hg and -0.2 ± 8.73 mm Hg, respectively). There was no consistent trend for change in mean pulse rate across all doses of ospemifene in double-blind, Phase 2/3, placebo-controlled studies.

In the all Phase 2/3 studies, similar results are reported for systolic and diastolic blood pressure and pulse.

A minor increase in weight, between baseline and end-of-study (termination), in both the ospemifene and placebo treatment groups is reported in the double-blind, Phase 2/3, placebo-controlled studies. The mean change in weight (kg) for the all ospemifene-treated subjects at end-of-study (termination) was 0.29 ± 2.650 kg versus 0.27 ± 2.530 kg for placebo-treated subjects. In the all Phase 2/3 studies, a mean increase of 0.35 ± 3.100 kg was observed at 12 months, and 0.49 ± 4.143 kg was observed at 15 months for all ospemifene-treated subjects.

Medical Officer's Comments:

No notable changes from baseline to end-of-study (termination) were observed for systolic and diastolic blood pressure in subjects treated with ospemifene versus those treated with placebo.

Minimal increases in weight were observed in ospemifene-treated and placebo-treated subjects. At 12 months in the double-blind, Phase 2/3, placebo-controlled studies, the mean increase in weight was higher in the placebo group (0.64 ± 2.998 kg) compared

with the ospemifene group (0.31 ± 3.003) kg. Findings were similar for ospemifene and placebo for changes in BMI.

7.4.4 Electrocardiograms (ECGs)

ECG parameters were summarized both quantitatively and categorically for all study groups. Descriptive statistics were provided for all ECG parameters (HR, RR, PR interval, QRS, QT_c interval, QT_cF (QT interval, Fridericia correction formula), and QT_cB (QT interval, Bazett correction formula). For 12-week Studies 15-50310 and 15-50821, ECG parameters were determined by the central ECG laboratory, while for 12-week Phase 2 Study 15-50717 and 52-week Study 15-50718 local assessments of ECG parameters were performed. The long-term safety extension studies (Study 15-50310X and 15-50312) and Study 1506001 did not conduct ECG evaluations.

Medical Officer's Comments:

A review of the descriptive summary of ECG parameters read by the central laboratory, and the descriptive summary of ECG parameters read by the local ECG laboratories shows that few subjects had notably abnormal values for the ECG parameters listed above.

Phase 3 Study 15-50824:

Phase 1 Study 15-50824 was a double-blind, randomized, parallel-group trial to assess the effects of a therapeutic and suprathreshold dose of ospemifene compared with placebo and moxifloxacin (positive control) on time-matched changes from baseline in QT_c based on an individually determined QT interval correction (QT_cI) in healthy men and women 18 and 45 years of age. The total treatment duration was 7 days, and subjects were randomized to receive placebo daily (50 subjects), 60 mg ospemifene/day (50 subjects), 240 mg ospemifene/day (50 subjects), or moxifloxacin (50 subjects). A centralized ECG reading lab was used to read the ECGs with interpretation by a high-resolution manual on-screen caliper method with annotations to minimize inter-reader variability. The central ECG laboratory was blinded to subjects and their treatment. Endpoint ECG results were evaluated based on data extracted from continuous 12-lead digital ECG recordings obtained on Days -1 and 7.

Per the application, the results of this ECG trial showed no signal of any ospemifene effect on heart rate (HR), atrioventricular (AV) conduction, or cardiac depolarization as measured by the PR and QRS interval durations. There were no new (defined as "not present on any baseline ECG but present on at least 1 on-treatment ECG") clear clinically relevant morphological changes. The effect of ospemifene on cardiac repolarization using the QT_cI interval and the PK-PD relationships showed no safety signal. A four-fold increase in dose from 60 mg/day to 249 mg ospemifene/day was demonstrated following 7 days of drug administration.

On December 12, 2012, DRUP requested that the Division of Cardiovascular and Renal Products, QT Interdisciplinary Team, review the final study report for Study 15-50824 included in the application. Per the consultation response, received on January 15, 2013:

“No significant QT_c prolongation effect of ospemifene was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between ospemifene and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for $\Delta\Delta$ QT_cI for moxifloxacin was not greater than 5 ms, but the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that assay sensitivity was established.”

Per the consultation response, based on the overall summary of findings in Study 15-50812:

“The suprathereapeutic dose produced a C_{max} value that is 2.9-fold the C_{max} following the therapeutic dose. These concentrations are above the predicted worse case scenario (concomitant administration of a strong CYP3A and CYP2C9 inhibitor, such as fluconazole to hepatic impaired patients (70% increase in C_{max})) and show that at these concentrations there are no detectable prolongations of the QT-interval.”

Medical Officer's Comments:

This reviewer concurs with the QT Interdisciplinary Team response that no significant QT_c prolongation was detected in Study 15-50824.

7.4.5 Special Safety Studies/Clinical Trials

See Subsection 7.3.4 Significant Adverse Events of this review.

7.4.6 Immunogenicity

No human immunogenicity studies, data, or published literature regarding same were submitted in the NDA application.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See Subsection 7.4.1 Common Adverse Events of this review. There is no clear dose-related increase in TEAEs, with similar percentages of subjects reporting TEAEs for ≤ 15 mg ospemifene/day, 30 mg ospemifene/day, and 60 mg ospemifene/day. Very few TEAEs occurred in the double-blind, Phase 2/3, placebo-controlled studies at the 90 mg ospemifene/day dosage strength. However, the study population was very small at this dosage strength.

7.5.2 Time Dependency for Adverse Events

TEAEs, by time of exposure, in the double-blind, Phase 2/3, placebo-controlled studies are summarized in Table 46.

Table 46: Summary of Number (%) of Subjects with Treatment-Emergent Adverse Events by Duration of Exposure: Double-Blind, phase 2/3, Placebo-controlled Studies

Preferred Term	Duration of exposure								
	1-3 days	4-7 days	8-14 days	15 days-<4 weeks	4 weeks-<12 weeks	12 weeks-<26 weeks	26 weeks-<39 weeks	39 weeks-<52 weeks	≥52 weeks
Placebo n (%)	n=958	n=948	n=941	n=937	n=925	n=568	n=96	n=90	n=53
Any TEAE n (%)	93 (9.7)	57 (6.0)	84 (8.9)	133 (14.2)	291 (31.5)	119 (21.0)	27 (28.1)	25 (27.8)	3 (5.7)
Hot flush	4 (0.4)	4 (0.4)	5 (0.5)	6 (0.6)	11 (1.2)	4 (0.7)	0	1 (1.1)	0
UTI	5 (0.5)	0	4 (0.4)	6 (0.6)	19 (2.1)	11 (1.9)	5 (5.2)	2 (2.2)	0
Headache	15 (1.6)	5 (0.5)	7 (0.7)	14 (1.5)	14 (1.5)	6 (1.1)	2 (2.1)	1 (1.1)	0
Nasopharyngitis	2 (0.2)	0	6 (0.6)	5 (0.5)	13 (1.4)	4 (0.7)	1 (1.0)	2 (2.2)	0
Vaginal discharge	0	1(0.1)	0	0	3 (0.3)	0	0	0	0
All Osphemifene n (%)	n=1696	n=1676	n=1672	n=1654	n=1618	n=1153	n=434	n=412	n=224
Any TEAE n (%)	192 (11.3)	149 (8.9)	181 (10.8)	262 (15.8)	552 (33.5)	334 (29.0)	2161 (50.0)	133 (32.3)	37 (16.5)
Hot flush	26 (1.5)	17 (1.0)	31 (1.9)	19 (1.1)	34 (2.1)	13 (1.1)	4 (0.9)	4 (1.0)	2 (0.9)
UTI	14 (0.8)	6 (0.4)	6 (0.4)	11(0.7)	48 (3.0)	25 (2.2)	6 (1.4)	2 (0.5)	1 (0.4)
Headache	27 (1.6)	9 (0.5)	10 (0.6)	21 (1.3)	30 (1.9)	13 (1.1)	8 (1.8)	7 (1.7)	2 (0.9)
Nasopharyngitis	2 (0.1)	2 (0.1)	3 (0.2)	11 (0.7)	25 (1.5)	12 (3.5)	15 (3.5)	15 (3.6)	0
Vaginal discharge	7 (0.4)	13(0.8)	22 (1.3)	10 (0.6)	13 (0.8)	2 (0.2)	5 (1.2)	2 (0.5)	0

Source: NDA 292505, Integrated Summary of Safety, Table 43, page 108.

Definitions: TEAE = treatment-emergent adverse event, UTI = urinary tract infection

Note: Percentages for the exposure interval were based on the number of subjects who were exposed as of the first day of the interval. If a subject had more than 1 TEAE that coded with the same preferred term within the interval, the subject was counted only once for that preferred term.

Medical Officer's Comments:

As noted in Table 46, hot flush was numerically higher in the ospemifene group than the placebo group at most intervals of exposure.

7.5.3 Drug-Demographic Interactions

In the application, the Applicant presented TEAEs, SAE, and discontinuation due to AEs summarized by demographic subgroups including age (<65 years of age versus ≥ 65 years of age), race, intact uterus (yes, no), prior history of vaginal birth (yes, no), and previous hormone therapy (yes, no) for the double-blind, Phase 2/3, placebo-controlled studies. The findings for the age subgroups are presented below.

A summary of subjects reporting TEAEs by SOC and preferred term occurring in ≥ 2% of subjects in all ospemifene treatment groups in either age group is presented in Table 47.

Table 47: Summary of Number (%) of TEAEs in ≥ 2% of Subjects by Age: Double-Blind, Phase 2/3, Placebo-Controlled Studies

System Organ Class	Number (%) of Subjects			
	< 65 Years of Age		≥ 65 Years of Age	
- Preferred Term	Placebo N=783	All Osp N=1357	Placebo N=175	All Osp N=339
Any TEAE	430 (54.9)	870 (64.1)	88 (50.3)	248 (73.2)
Gastrointestinal Disorders	77 (9.8)	153 (11.2)	22 (12.6)	50 (14.7)
- Diarrhea	12 (1.5)	25 (1.8)	4 (2.3)	12 (3.5)
- Nausea	8 (1.0)	23 (1.7)	3 (1.7)	12 (3.5)
- Lower abdominal pain	4 (0.5)	9 (0.7)	1 (0.6)	8 (2.4)
Infections and Infestations	194 (24.8)	388 (28.6)	35 (20.0)	119 (35.1)
- Urinary tract infection	34 (4.3)	82 (6.0)	12 (6.9)	26 (7.7)
- Nasopharyngitis	27 (3.4)	56 (4.1)	3 (1.7)	18 (5.3)
- Vulvovaginal Candidiasis	4 (0.5)	45 (3.3)	1 (0.6)	18 (5.3)
- Sinusitis	33 (4.2)	39 (2.9)	3 (1.7)	9 (2.7)
- Vulvovaginal mycotic infection	5 (0.6)	38 (2.8)	0	5 (1.5)
- Upper respiratory infection	28 (3.6)	29 (2.1)	6 (3.4)	6 (1.8)
- Cystitis	5 (0.6)	16 (1.2)	1 (0.6)	9 (2.7)
- Bronchitis	10 (1.3)	23 (1.7)	3 (1.7)	7 (2.1)
Musculoskeletal and Connective Tissue Disorders	81 (10.3)	185 (13.6)	22 (12.6)	69 (20.4)
- Muscle spasm	10 (1.3)	49 (3.6)	3 (1.7)	18 (5.3)
- Back pain	19 (2.4)	32 (2.4)	4 (2.3)	13 (3.8)
- Arthralgia	22 (2.8)	25 (1.8)	2 (1.1)	11 (3.2)
- Pain in extremity	9 (1.1)	20 (1.5)	2 (1.1)	9 (2.7)
- Osteoarthritis	1 (0.1)	10 (0.7)	0	7 (2.1)
Nervous System Disorders	65 (8.3)	142 (10.5)	22 (12.6)	37 (10.9)
- Headache	46 (5.9)	90 (6.6)	11 (6.3)	18 (5.3)
- Dizziness	6 (0.8)	16 (1.2)	5 (2.9)	8 (2.4)
Psychiatric Disorders	35 (4.5)	63 (4.6)	3 (1.7)	21 (6.2)
- Insomnia	9 (1.1)	25 (1.8)	2 (1.1)	11 (3.2)
- Depression	10 (1.3)	14 (1.0)	0	7 (2.1)

Reproductive System and Breast Disorders	58 (7.4)	179 (13.2)	6 (3.4)	53 (15.6)
- Vaginal discharge	4 (0.5)	53 (3.9)	0	19 (5.6)
- Genital discharge	2 (0.3)	23 (1.7)	0	8 (2.4)
Respiratory, Thoracic, and Mediastinal Disorders	20 (2.6)	50 (3.7)	4 (2.3)	24 (7.1)
- Cough	4 (0.5)	9 (0.7)	1 (0.6)	7 (2.1)
Skin and Subcutaneous Tissue Disorders	41 (5.4)	101 (7.4)	7 (4.0)	39 (11.5)
- Hyperhidrosis	6 (0.8)	19 (1.4)	3 (1.7)	12 (3.5)
Vascular Disorders	32 (4.1)	126 (9.3)	10 (5.7)	49 (14.5)
- Hot flush	25 (3.2)	111 (8.2)	7 (4.0)	34 (10.0)
- Hypertension	4 (0.5)	15 (1.1)	1 (1.1)	9 (2.7)

Source: Adapted from NDA 203505, Integrated Summary of Safety, Table 139, page 292.

Medical Officer's Comments:

Overall, the percentage of subjects reporting TEAEs was higher in the ospemifene-treated subjects who were ≥ 65 years of age than in the ospemifene-treated subjects < 65 years of age, while for placebo the percentages were similar for both age groups. This finding is not unexpected. Even in a healthy population of postmenopausal women, one could anticipate a higher percentage of TEAEs in women at the older age of the spectrum studied.

Of interest, the incidence of hot flush was higher in both ospemifene age groups (8.2 % and 10.0%, respectively) than in placebo (3.2% and 4.0%, respectively). Similarly, the incidence of vaginal discharge was higher in both ospemifene age groups (3.9% and 5.6%, respectively) than in placebo (0.5% and 0.0%, respectively). In addition, the incidence of muscle spasm was also higher in both ospemifene age groups (3.6% and 5.3%, respectively) than placebo (1.3% and 1.7%, respectively).

Overall, the TEAE profile of ospemifene was similar, however, between subjects < 65 years of age or ≥ 65 years of age.

In the double-blind, Phase 2/3, placebo-controlled studies, SAEs occurred in 2.2% of subjects in the ospemifene-treated group (30 of 1357 ospemifene-treated subjects) who were < 65 years of age and in 2.7% of subjects in the ospemifene-treated group who were ≥ 65 years of age. There were no notable differences between age groups for the incidence of SAEs for any given preferred term as few SAEs occurred in more than 1 subject.

Discontinuations due to TEAEs by age group indicates that subjects ≥ 65 years of age had a higher discontinuation rate (9.1%, 31 of 339 ospemifene-treated subjects ≥ 65 years of age) than subjects who were < 65 years of age (6.5%, 88 of 1357 ospemifene-treated subjects who were < 65 years of age). The incidence of diarrhea as a reason for discontinuations was higher in subjects ≥ 65 years of age (0.9%) than in subjects

< 65 years of age (0.1%).

Medical Officer's Comments:

The higher discontinuation rate in subjects \geq 65 years of age does not raise safety concerns for 60 mg ospemifene. As previously mentioned, even in a healthy postmenopausal population, one could anticipate a higher percentage of women discontinuing in this age group.

7.5.4 Drug-Disease Interactions

No drug-disease interactions were studied in the ospemifene development program.

7.5.5 Drug-Drug Interactions

Five (5) drug-drug interaction studies were conducted to characterize the potential of CYP enzyme-mediated drug interactions:

1. Study 15-50614 (open-label, balanced, 2-period crossover study with a single dose of warfarin) evaluated the effect of ospemifene on the CYP2C9 activity using warfarin, a sensitive CYP2C9 substrate. Per the reported results of Study 15-50614, "there is no PK interaction between ospemifene and warfarin".
2. Study 15-50719 (open-label, balanced, 2-period crossover study with single doses of omeprazole) evaluated the possible effect of ospemifene on the CYP2C19 and CYP3A activity using omeprazole, a sensitive CYP2C19 and CYP3A substrate. Per the reported results of Study 15-50719, "treatment with ospemifene 60 mg once daily did not affect CYP2C19 and CYP3A4 activities when evaluated using omeprazole as a probe substrate".
3. Study 15-50825 (open-label, balanced, 2-period crossover study with single doses of bupropion for 7 days) evaluated the effect of ospemifene on the CYP2B6 activity using bupropion, a sensitive CYP2B6 substrate. Per the reported results of Study 15-50825, "treatment with ospemifene 60 mg did not inhibit CYP2B6 activity when evaluated using bupropion as a probe substrate".
4. Study 15-50823 (open-label, randomized, 3-period crossover with single doses of ospemifene given with and without fluconazole or omeprazole) evaluated the possible effects of fluconazole (a potent CYP3A/CYP2C9/CYP2C19 inhibitor) and omeprazole (a potent CYP2C19 inhibitor) on the pharmacokinetics of ospemifene. Per the reported results of Study 15-50823, "Fluconazole moderately increased the concentrations of ospemifene in serum, most likely by inhibiting the CYP2C9 (and CYP3A4) mediated metabolism of ospemifene. Omeprazole (a CYP2C19 inhibitor) had only a negligible effect on concentrations of ospemifene and its metabolites".
5. Study 15-50716 (open-label, balanced, randomized, 3-period crossover with single doses of ospemifene given with and without rifampicin or ketoconazole) evaluated the effects of rifampicin (a potent CYP3A/CYP2C9 inducer) and ketoconazole (a

potent CYP3A inhibitor) on ospemifene pharmacokinetics. Per the reported results of Study 15-50716, “Rifampicin moderately decreased and ketoconazole weakly increased the exposure to ospemifene and 4- hydroxyospemifene in serum by inducing and inhibiting mainly the CYP3A4-mediated metabolism of the parent and metabolite”.

Medical Officer’s Comments:

See the Clinical Pharmacology Review, dated January 12, 2013, for a full discussion of the drug-drug interaction studies and the Agency’s interpretation of the findings.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

All preclinical studies were submitted in the NDA application. See the Pharmacology/Toxicology review for a complete discussion of this information.

7.6.2 Human Reproduction and Pregnancy Data

No pregnancies were reported during the ospemifene development program.

7.6.3 Pediatrics and Assessment of Effects on Growth

The ospemifene development program addressed indications applicable only in postmenopausal women.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Per the application, “No withdrawal effects are expected with this class of compounds, other than gradual reversion of the therapeutic effect back to the baseline state. No TEAEs with the preferred terms of ‘withdrawal syndrome’ or ‘drug withdrawal syndrome’ occurred in any ospemifene-treated subject in all Phase 2/3 studies.”

7.7 Additional Submissions / Safety Issues

See Subsection 7.3.4 Significant Adverse Events and Subsection 6.3.5 Submission Specific Primary Safety Concerns of this review.

8 Postmarket Experience

There is no postmarketing data for NDA 203505. Ospemifene is not currently approved in the United States or internationally.

9 Appendices

9.1 Literature Review/References

The application includes the scientific literature relating to selective estrogen receptor modulators (SERMs). No additional review of the published literature was conducted by this reviewer.

9.2 Labeling Recommendations

This reviewer recommends approval of 60 mg ospemifene for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause provided that an agreement is reached between DRUP and the Applicant regarding labeling.

Medical Officer's Comments:

As of the date of this review, final agreed upon labeling for 60 mg ospemifene for the above indication remains under negotiation between DRUP and the Applicant. An addendum to this review will be prepared when agreement is reached with the Applicant regarding final labeling.

9.3 Advisory Committee Meeting

No advisory committee was conducted for NDA 203505.

9.4 Tables of Currently Available Treatment for a VVA Indication

Estrogen-Alone Products Approved for the Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause

Oral Estrogen-Alone Products	Available Dosage Strengths
Cenestin® (synthetic conjugated estrogens, A)	0.3 mg once daily
Enjuvia® (synthetic conjugated estrogens, B)	0.3 mg once daily
Estrace® (estradiol)	0.5 mg, 1.0 mg, or 2.0 mg once daily
Menest® (esterified estrogens)*	0.3 mg, 0.625 mg, 1.25 mg, or 2.5 mg once daily
Ogen (estropipate)	0.625 mg, 1.25 mg, or 2.5 mg once daily
Premarin® (conjugated estrogens) Tablets	0.3 mg, 0.45 mg, 0.625 mg, 0.9 m, or 1.25 mg once daily
Transdermal Products	Available Dosage Strengths
Alora® (estradiol transdermal system)	0.025 mg/day, 0.05 mg/day, 0.075 mg/day, or 0.1 mg/day; patch applied twice weekly
Climara® (estradiol transdermal system)	0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, or 0.1 mg/day; patch applied once weekly
Esclim® (estradiol transdermal system)	0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, or 0.1 mg/day; patch applied twice weekly
Estraderm® (estradiol transdermal system)	0.05 mg/day or 0.1 mg/day; patch applied twice weekly
VivelleDot® (estradiol transdermal system)	0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, or 0.1 mg/day; patch applied twice weekly
Various Generics (estradiol transdermal system)	0.05 mg/day or 0.1 mg/day; patch applied once or twice weekly
Topical Products	Available Dosage Strengths
EstroGel® 0.06% (estradiol gel)	0.075 mg/day; 1.25 gram applied once daily
Vaginal Cream	Available Dosage Strengths
Estrace (estradiol) Vaginal Cream	2 to 4 grams (0.1 mg per gram) inserted intravaginal daily for 1 to 2 weeks, then 1 gram inserted intravaginal daily thereafter
Premarin® (conjugated estrogens) Vaginal Cream	0.5 to 2 grams (0.625 mg per gram) inserted intravaginal daily
Vaginal Rings	Available Dosage Strengths
Estring® (estradiol)	Release of 7.5 mcg estradiol/day; ring worn for 90 days
Femring® (estradiol acetate)	Release of 0.05 mg estradiol/day or 0.10 mg estradiol/day; ring worn for 90 days
Vaginal Tablet	Available Dosage Strengths
Vagifem® (estradiol hemihydrate)	10 mcg/day or 25 mcg/day; vaginal tablet inserted twice weekly

Estrogen Plus Progestin Products Approved for the Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause

Oral Estrogen Plus Progestin Products	Available Dosage Strengths
Angeliq® (estradiol [E2] plus drospirenone)	1 mg E2/day plus 0.5 mg drospirenone/day taken daily
Prefest® (estradiol [E2] plus norgestimate)	1 mg E2/day taken daily for 3 days, then 1 mg E2 plus 0.09 mg norgestimate/day taken daily for 3 days, repeated continuously
Premphase® (conjugated estrogens [CE] plus	0.625 mg CE/day taken daily for 14 days, then

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 Osphena™ (ospemifene) tablets, for oral use

medroxyprogesterone acetate [MPA]	0.625 mg CE plus 5.0 mg MPA/day taken daily on days 15-18
Prempro® (conjugated estrogens [CE] plus medroxyprogesterone acetate [MPA])	0.3 mg or 0.45 mg CE/day plus 1.5 mg MPA/day taken daily or 0.625 mg CE/day plus 2.5 mg or 5.0 mg MPA/day taken daily
Transdermal Estrogen Plus Progestin Products	Available Dosage Strengths
CombiPatch (estradiol [E2] plus norethindrone Acetate [NETA])	0.05 mg E2/day plus 0.14 mg NETA/day; patch applied twice weekly 0.05 mg E2/day plus 0.25 mg NETA/day; patch applied twice weekly

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/s/

THERESA H VAN DER VLUGT
02/06/2013

SHELLEY R SLAUGHTER
02/08/2013

I concur with the recommendation of Dr. van der Vlugt that the application receive approval for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	<p>moderate to severe symptoms of dyspareunia and/or vaginal dryness and physiological changes (parabasal cells, superficial cells and pH).</p> <p>Pivotal Study #2 12-week Study 15-50821 Indication: Treatment of vulvar and vaginal atrophy due to menopause, including moderate to severe symptoms of dyspareunia and/or vaginal dryness and physiological changes (parabasal cells, superficial cells and pH).</p>				The 40-week safety extension of Study 15-50310 (Study 15-50310X and Study 15-50312) are included in the application.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			The full study report for QT _c Study 15-50821 is included in the application.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?		X		Ospemifene is not approved and marketed outside the U.S.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ²) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the sponsor submitted the coding dictionary ³ used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the sponsor adequately evaluated the safety issues that	X			

² For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

³ The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	are known to occur with the drugs in the class to which the new drug belongs?				
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	X			<p>The primary efficacy analyses reported in the individual final study reports for 12-week Study 15-50310 and 12-week Study 15-50821 are not based on subjects who met all three baseline inclusion criteria: vaginal pH greater than 5, less than 5% superficial cells on a vaginal smear, and a most bothersome moderate to severe vaginal symptom. The analyses reported in the application in the "Summary of Clinical Efficacy" document and the "Integrated Summary of Efficacy" document, however, appear to be based on subjects meeting all three of the recommended baseline inclusion criteria. A teleconference was held with the Applicant on June 27, 2012 to discuss the discrepancy of these reported primary analyses. The Applicant confirmed that the reported analyses in the "Summary of Clinical Efficacy" document and the "Integrated Summary of Efficacy" document are the correct analyses. The Applicant committed to the submission of an addendum to each</p>

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
					of the individual study reports with the correct primary analyses.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The pediatric waiver request is included in the NDA application. A pediatric waiver should be granted.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			
CONCLUSION					
40.	From a clinical perspective, is this application fileable? If not, please state why.	X			

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The primary efficacy analyses reported in the individual final study reports for 12-week Study 15-50310 and 12-week Study 15-50821 are not based on subjects who met all three baseline inclusion criteria: vaginal pH greater than 5, less than 5% superficial cells on a vaginal smear, and a most bothersome moderate to severe vaginal symptom. We will make our determination of efficacy based on demonstration of statistically significant improvement versus placebo in the recommended co-primary endpoints [most bothersome moderate to severe symptom (e.g., vaginal dryness and dyspareunia), vaginal pH and superficial and parabasal vaginal cells] for those subjects who met the three baseline criteria for a clinical trial of treatment of the symptoms of vulvar and vaginal atrophy. The analyses reported in the application in the “Summary of Clinical Efficacy” document and the “Integrated Summary of Efficacy” document, however, appear to be based on subjects meeting all three of the recommended baseline inclusion criteria. The analyses presented in all documents should be consistent and, as stated, should be based on those subjects meeting all three of the recommended baseline inclusion criteria [a most bothersome moderate to severe vaginal symptom (consistent with the symptom to be analyzed), vaginal pH greater than 5 and less than 5% superficial cells on a vaginal smear].

Submit an addendum to the final study reports for Study 15-50310 and Study 15-50821 with the correct primary analyses.

Theresa H. van der Vlugt, M.D., M.P.H.

Reviewing Medical Officer

Date

Shelley R. Slaughter, M.D., Ph.D.

Clinical Team Leader

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THERESA H VAN DER VLUGT
07/09/2012

SHELLEY R SLAUGHTER
07/11/2012
I concur.