CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203505Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader (CDTL) Review

Date	February 25, 2013
From	Shelley R. Slaughter, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	203505
Type of Submission	Original
Applicant	Shionogi, Inc.
Date of Submission	April 25, 2012
PDUFA Goal Date	February 25, 2012
Proprietary Name / Established (USAN) names	OSPHENA/ospemifene
Dosage forms / Strength	Oral tablet
Proposed Indication(s)	"OSPHENA 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)"
Recommended:	Approval is recommended for the indication of "treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause." Approval is not recommended for "treatment of moderate to severe vaginal dryness, a symptom of vulvar and vaginal atrophy, due to menopause."

1. Introduction and Executive Summary

With this 505(b)(1) original NDA submission, the Sponsor is seeking approval for OSPHENA (ospemifene), an estrogen receptor mixed agonist/antagonist for the indication of the treatment of moderate to severe dyspareunia and moderate to severe vaginal dryness, symptoms of vulvar and vaginal atrophy due to menopause. If approved, OSPHENA would be the first estrogen receptor mixed agonist/antagonist to receive approval for this indication or any other indication to treat symptoms due to the menopause.

Major issues emerging during the review and consideration of this application were:

1. Efficacy
   OSPHENA is a new molecular entity and as such two confirmatory randomized placebo-controlled Phase 3 clinical trials were recommended and conducted to support the efficacy of OSPHENA according to the recommendations on clinical trials for the indication of treatment of a moderate-to-severe symptom of vulvar and vaginal atrophy, as provided in the Agency's Draft 2003 Guidance for Industry, entitled, "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation", which will be referred to in this review as the 2003 Draft Clinical Trial Guidance.

   Confirmatory evidence for efficacy in both Study 15-50310 and Study 15-50821 was obtained only for the 60 mg dose of ospemifene for the indication of treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. Confirmatory evidence was not obtained for the efficacy of any dose of ospemifene for the indication of treatment of moderate to severe vaginal dryness.

   The Sponsor allowed the use of a vaginal lubricant in all arms of the study on an "as needed" basis in both clinical trials. The Agency's exploratory subgroup analyses by lubricant group showed no significant difference between treatment groups (60 mg ospemifene vs. placebo in lubricant users and non-users) for the dyspareunia co-primary endpoint.

2. Safety
   For review of products intended to influence the female reproductive system, the evaluation of endometrial safety is paramount. OSPHENA has estrogen agonistic effects on the endometrium. No cases of endometrial cancer were seen in the clinical trials for OSPHENA; however, the finding of endometrial cancer is rare in 1 to 2 year trials of estrogens. One case of endometrial hyperplasia was noted in a woman with approximately 9-months of OSPHENA 60 mg treatment. Assessment of endometrial histology with 60 mg ospemifene treatment exposure up to 52 weeks, revealed an incidence of any type of proliferative (weakly plus active plus disordered) endometrium of 86.1 per thousand women in OSPHENA vs. 13.3 per thousand women for placebo. Uterine polyps occurred at an incidence of 5.9 per thousand women vs. 1.8 per thousand women for placebo. Transvaginal ultrasound

evaluation of endometrial thickness revealed consistent evidence of estrogen agonistic (stimulatory) effect on the endometrium. Endometrial thickening equal to 5 mm or greater was seen in the OSPHENA treatment group at a rate of 60.1 per thousand women vs. 21.2 per thousand women for placebo.

The other major concern for treatment with estrogen (or a product with possible estrogen agonistic effects) is the cardiovascular and cerebrovascular thrombotic profile. The Women's Health Initiative (WHI) studies reported an increased risk of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) who received daily oral conjugated estrogens (CE) [0.625 mg]-alone therapy over 7.1 years as part of the (WHI). Ospemifene 60 mg had a cerebral thromboembolic incidence rate of 0.72 per thousand women (1 case in 1379 subjects treated with 60 mg ospemifene) vs. 1.04 per thousand women in placebo (1 case in 958 placebo-treated subjects). The incidence rate of hemorrhagic stroke in the 60 mg ospemifene group was 1.45 per thousand women (2 cases in 1379 subjects treated with 60 mg ospemifene) vs. 0 per thousand women, respectively in placebo. With respect to deep vein thrombosis, the incidence rate for ospemifene 60 mg was 1.45 per thousand women (2 cases in 1379 subjects treated with 60 mg ospemifene) vs. 1.04 per thousand in placebo (1 case in 958 placebo-treated subjects)

3. Labeling

If approved, OSPHENA will be the first mixed estrogen receptor agonist approved for a gynecologic indication. The Division has taken the position, that unless it is proven to be not applicable, all estrogen and estrogen receptor modulating products with agonistic effects on the endometrium will receive estrogen class labeling with respect to their effects on the endometrium. A BOXED WARNING is recommended that states, "OSPHENA is an estrogen agonist/antagonist with tissue selective effects. In the endometrium, OSPHENA has estrogen agonistic effects. There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy reduces the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer."

In addition to the BOXED WARNING on the risk of endometrial cancer, a BOXED WARNING relative to the risk of cardiovascular and cerebrovascular thrombotic events is also proposed: "Estrogen-alone therapy has an increased risk of stroke and deep vein thrombosis (DVT). OSPHENA 60 mg had cerebral thromboembolic and hemorrhagic stroke incidence rates of 0.72 and 1.45 per thousand women, respectively vs. 1.04 and 0 per thousand women, respectively in placebo. For deep vein thrombosis, the incidence rate for OSPHENA 60 mg is 1.45 per thousand women vs. 1.04 per thousand women in placebo."

2. **Background and Regulatory History**

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

Per the Applicant, the purpose of this application is to obtain marketing authorization for OSPHENA in the treatment of moderate to severe vaginal dryness and moderate to severe dyspareunia, both symptoms of vulvar and vaginal atrophy, due to menopause. Ospemifene is a non-steroid estrogen agonist/antagonist. The Applicant states that ospemifene exerts an agonistic effect on estrogen receptors in the vagina. 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.

The following is a summary of the regulatory history of OSPHENA

- **April 07, 2003,** IND 067216 for ospemifene was received and opened for Hormos Medical Corporation (Finland). The initial submission to the IND was a protocol for a Phase 3, 12-week, double-blind, placebo-controlled study to assess the safety and efficacy of two ospemifene doses (60 mg and 90 mg) in 450 healthy postmenopausal women. The Sponsor had preliminary findings with ospemifene 5 mg, 15 mg and 30 mg and no safety issues were identified.

  The Division of Reproductive and Urologic Products [(DRUP) also referred to as "the Division" throughout this review] advised the Sponsor that two clinical trials would be required to demonstrate efficacy and that the lowest effect dose should be identified in the clinical development program

- **October 04, 2005**, an end-of-Phase 2 meeting was held with QUATRx. The Agency recommended:

  - Two confirmatory clinical trials should be conducted to support efficacy of the new molecular entity
  - The study should be powered adequately to demonstrate statistically significant differences vs. placebo in four co-primary endpoints
    - Mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as the most bothersome to her. For study inclusion, study participants would have self-identified at least one moderate to severe vulvar and vaginal atrophy symptom
    - Mean change from baseline to week 12 in vaginal pH. For study inclusion, study participants would have a vaginal pH > 5.0
    - Mean change from baseline to week 12 in the proportions of superficial and parabasal cells. For study inclusion, study participants would have no greater than 5% superficial cells on a vaginal smear
  - The clinical trials should compare to a placebo of a vaginal lubricant and should follow a double-blind, double-dummy design to demonstrate whether or not an oral drug 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

- The clinical trials should demonstrate the lowest effective dose
- The 2003 Draft Clinical Trial Guidance should be followed to assess for the risk of endometrial hyperplasia with this SERM drug product
- The Sponsor should take into consideration the number of women who enroll who will have a uterus and the drop-outs when considering the number of subjects to provide the needed long-term endometrial safety data
- A thorough QTc study should be conducted for this new molecular entity
- Effects of ospemifene on CYP2B6 and CYP2D6 substrates, and CYP2C9, CYP2C19 and CYP2B6 inhibitors should be addressed. 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

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

- **January 9, 2007**, Advice/Information Request letter to QUATRx Pharmaceuticals with DRUP's recommendations
  - Subjects should be enrolled who meet each of the following inclusion criteria:
    - a vaginal pH greater than 5.0
    - no greater than 5% superficial cells on a vaginal smear
    - at least one moderate to severe symptom of vulvar and vaginal atrophy that the subject has self-identified as most bothersome to her
  - Each moderate to severe symptom self-identified as most bothersome by the subject should be analyzed separately (the Sponsor initially proposed to submit a composite analysis of all symptoms)

- **April 29 2008,** Type C Guidance meeting with QUATRx Pharmaceuticals to discuss plans for 2nd clinical trial
  - DRUP continued to recommend a dose ranging study with 30, 45 and 60 mg of ospemifene
  - DRUP indicated that the Sponsor's proposed method of analyzing the two independent populations is acceptable for one dose. For multiple doses, you may need to adjust the overall study alpha level for each population depending on how the doses will be tested. We request additional information on your rationale for designing this study with two independent populations instead of conducting two independent studies. We also note that your proposal to test the four co-primary efficacy endpoints in a step-

down manner is not necessary as all four co-primary endpoints need to demonstrate a statistically significant difference for efficacy to be claimed

- The Sponsor informed the Division that they had added lubricant in the first study (on an "as needed" basis) and did not intend to provide lubricant in the second study. The use of lubricant was minimal and declined with effective therapy at 60 mg [redacted (b) (4)]"
- The Division was not in concurrence and reminded the Sponsor of its recommendation that ospemifene be compared to vaginal lubricant in a double-blind, double-dummy design approach, the intent being to demonstrate whether or not oral drug product treatment demonstrated statistically significant improvement in relief of vaginal symptoms beyond that of placebo vaginal lubricant. The Division continued to make for 2nd clinical trial, the same recommendation for placebo vaginal lubricant use that it had proposed for the previous study
- The Sponsor indicated their reluctance to "force" use of vaginal lubricant on women and held that information can be extracted to address whether or not oral drug product treatment in combination with placebo vaginal lubricant demonstrates significant improvement beyond that of either oral placebo drug product or vaginal lubricant in both studies where vaginal lubricant had been allowed on an "as needed" basis
- The Division agreed in concept but asked for final protocols for review and comment
- 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

- **September 29, 2009** pre NDA with QUATRx Pharmaceuticals
  - DRUP advised:
    - 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

- **April 12, 2011**, Type C Guidance meeting with Shionogi USA, Inc.
  - DRUP advised:
    - This new molecular entity (NME) should be supported by two adequate and well-controlled Phase 3 studies for safety and efficacy
    - Efficacy will be based on the results of each pivotal Phase 3 study (15-50310 and 15-50821), analyzed separately and not on overall efficacy findings combined across the two Phase 3 studies
    - Our preliminary review of Studies 15-50310 and 15-50821 suggests statistically significant differences, in favor of your product vs. placebo, in the change from baseline to Week 12 (ITT population) for vaginal pain associated with sexual activity (dyspareunia) in both studies. However, only one of your two studies, 15-50310, reported a statistically significant finding compared to placebo for vaginal dryness
    - The primary efficacy analyses should be based on subjects meeting all three of the baseline inclusion criteria: vaginal pH greater than 5, less than 5% superficial cells on vaginal smear, and a most bothersome moderate to severe vaginal symptom
    - Perform a secondary analysis for the co-primary most bothersome moderate to severe symptom endpoints of vaginal dryness and pain associated with sexual activity using the ANCOVA model, as used for the primary efficacy analysis, that includes an indicator for vaginal lubricant use (Y/N) at Week 12
    - Safety data should be presented in the ISS and for each individual study.
    - There appears to be sufficient subjects enrolled in study 15-50718 to satisfy our long term requirements for an NME
    - We note that there were two subjects who experienced deep vein thrombosis, two subjects with cerebrovascular accident, and one subject with an acute myocardial infarction; these potential safety signals will be review issues
    - The results of a thorough QTc study should be submitted with the NDA
    - If, upon complete review, the data support approval, the clinical indication should read: "Treatment of moderate to severe X (where X= dyspareunia and/or vaginal dryness), a symptom of vulvar and vaginal atrophy, due to menopause"
    - The Penn 5 formulation used in Study 15-50310 and the (b) (4) (b) (4) formulation used in Study 15-50821 both

need to show bioequivalence with the [redacted] commercial formulation in order to adequately bridge the formulations

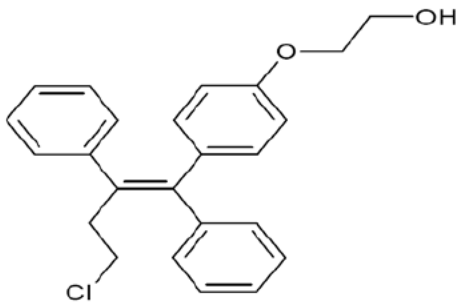
- It is acceptable to submit additional stability data by the 12-Day Safety Update
- It is a review issue as to whether your stability package will support a 2-year expiry
- Additional information on drug product batches manufactured with different [redacted] content needs to be provided to help determine whether a specification should be set.

3. CMC/Biopharmaceutics/Device

The Chemistry and Biopharmaceutics information in the application were reviewed by Hitesh Shroff, Ph.D., Office of New Drug Quality Assessment (ONDQA), Division of New Drug Quality Assessment II, Branch IV and Kareen Riviere, Ph.D., ONDQA, Division of Biopharmaceutics.

OSPHENA tablets contain 60 mg of the active ingredient, ospemifene. Ospemifene is a white to off-white powder with the chemical structure, molecular formula and molecular weight as shown in Figure 1.

Figure 1 Chemical Structure, Molecular Formula and Molecular Weight of Ospemifene



Molecular Formula: C24H23ClO2
Molecular Weight: 378.9

Ospemifene is manufactured at [redacted]. The detailed CMC related information for ospemifene is provided in DMF [redacted]. The manufacturer provided a letter of authorization to reference DMF [redacted] in connection with NDA 203-505. The DMF [redacted] was reviewed on 12-12-2012 and found to be adequate.

OSPHENA tablets are white to off-white, oval, film-coated, biconvex tablets, with one side engraved "60". OSPHENA tablets are supplied in bottles and blisters to protect it from light and moisture. In addition to 60 mg of ospemifene, OSPHENA tablets contain, the following inactive ingredients, pregelatinized starch, mannitol, povidone, sodium starch glycolate, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate The tablets are coated with [redacted] white coloring [redacted]

(b) (4) See Table 1 for composition and function of each component. There were no novel excipients used in OSPHENA tablets. All ingredients are compendial.

Table 1 Composition of OSPHENA Tablets

Component	Function	Quantity per Tablet (mg)	Quantity Standard
Ospemifene	Active	60.0	In-house
Pregelatinized starch (b) (4)	(b) (4)	(b) (4)	NF
Mannitol			USP
Povidone (b) (4)			USP
Sodium starch glycolate			NF
Microcrystalline cellulose (b) (4)			NF
Colloidal silicon dioxide (b) (4)			NF
Magnesium stearate			NF
(b) (4)			In-house
(b) (4)			USP
(b) (4)			

Source: Chemistry Review

The manufacturing of OSPHENA tablets is performed using conventional manufacturing methods such as (b) (4)
Three primary stability batches containing approximately (b) (4) tablets were manufactured at Penn Pharmaceutical Services Ltd. in UK.

The proposed release specification of the finished product includes appearance, identification, assay of the active ingredient, content uniformity, impurities, and microbial limits. The proposed specifications are deemed adequate to assure the identity, strength, purity, and quality of the drug product.

The to-be marketed Ospemifene tablets are supplied in bottles and blisters. Each bottle contains 100 Ospemifene tablets. The (b) (4) bottles are composed of high density polyethylene and blisters are made of clear laminate (b) (4) and push through aluminum. The container closure systems are adequate to protect the drug product from light, moisture and air. The container closure systems are in compliance with USP <661> and <671>. The stability studies demonstrate that the components of the container closure systems are compatible with drug product.

Based on the stability data from three production scale batches of OSPHENA at long term (60 months) and accelerated (6 months) conditions, the proposed 24 months expiration dating period, when stored at room temperature, is granted.

For a complete description of the drug substance (characterization), composition, manufacture and control of the to-be-marketed drug product as well as the composition of the various formulations used during Phase 1, 2 and 3 clinical development refer to the Chemistry NDA review of Hitesh Shroff, Ph.D., Office of New Drug Quality Assessment (ONDQA), Division of New Drug Quality Assessment II, Branch IV.

Inspections of manufacturing sites are complete:

- (b) (4) received an ACCEPTABLE
- (b) (4) received an ACCEPTABLE
- (b) (4) eceived an ACCEPTABLE
- (b) (4) received an ACCEPTABLE
- PENN PHARMACEUTICALS LTD, the finished dosage manufacturer and release and stability tester, located in Tredegar, United Kingdom, received an ACCEPTABLE

The Office of Compliance issued an overall ACCEPTABLE on January 24, 2013. Labeling revisions submitted by the Sponsor on February 19, 2013 satisfactorily resolved previously noted revisions.

Per the ONDQA Chemistry reviewer, the NDA is recommended for Approval from a CMC perspective. The applicant has provided sufficient information to assure the identity, strength, purity and quality of the drug product.

Per the ONDQA Biopharmaceutics reviewer, Kareen Riviere, Ph.D., the NDA is recommended for approval from a Biopharmaceutics standpoint with the following dissolution method and acceptance criteria:

- Dissolution method: Apparatus II, 50 rpm agitation rate, 900 mL media volume, 37°C, 2% SDS in water
- Dissolution acceptance criterion: Q = (b) (4) at 60 minutes.

4. Nonclinical Pharmacology/Toxicology

The non-clinical pharmacology and toxicology information presented in the application was reviewed by Jeffrey Bray, Ph.D., Office of New Drugs (OND), Office of Drug Evaluations 3 (ODE 3), Division of Reproductive and Urologic Products (DRUP).

Ospemifene is a mixed estrogen receptor agonist/antagonist that demonstrates tissue selective activities, the drug class commonly referred to as selective estrogen receptor modulators (SERMs). Ospemifene potentially binds to both estrogen receptor α and β nuclear receptors.

Ospemifene has pharmacological activities in rats and monkeys consistent with estrogen agonism in the vagina, ovary, and bone; estrogen antagonism in the mammary gland and mixed agonism/antagonism in the uterus. In rats, mice, female dogs, and female monkeys, there were no unexpected toxicities noted. The main effects noted were related to the exaggerated pharmacological effects of ospemifene on reproductive organs. Organ weight, gross pathological and histopathological effects were noted on the ovary, uterus, vagina, mammary gland, liver, prostate, testis, and epididymis in most species and studies. The ovary, mammary gland, and male reproductive organs showed a predominantly

antagonistic profile, whereas the vagina and liver showed agonism. However, some studies showed cell and tissue-selective agonism. This was most clearly observed in the uterus of monkeys. In the rat, the profile was predominantly antagonistic. There were decreased ovarian weights with ovarian cysts with species- and cell-specific effects noted. 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. Sporadic findings were reported in the adrenal and pituitary and on hematopoiesis in rodents. In rodents and dogs, decreased male reproductive organ weights with atrophy of the prostate, testis, and epididymis were noted. All findings were at exposures comparable to human exposure at the proposed dose.

There were no significant findings from a battery of safety pharmacology assays which were designed to evaluate neurological, cardiovascular, pulmonary and renal effects.

Embryofetal toxicity (EFT) studies for ospemifene 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 resorptions 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 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 in viable pups born and increased post-implantation loss (total and %), and non-significant increase in number of litters with dead pups compared to control. The highest exposures obtained in reproductive toxicology studies were only 4% of human exposure with higher doses precluded by significant maternal toxicities and fetal losses.

No fertility and early embryonic development study was conducted or deemed necessary for the indicated population of postmenopausal women. Postmenopausal women who exhibit the signs and symptoms of vulvar and vaginal atrophy are generally older (approximately 10 or more years beyond the menopausal transition) than women experiencing vasomotor symptoms and are not at risk for conception.

The weight of evidence suggests that ospemifene is not genotoxic. Ospemifene was negative in the in vitro Ames and mouse lymphoma cell assays 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.

Ospemifene is carcinogenic to rodents based on the findings from the rat and mouse 2-year carcinogenicity studies. All treated rat and mouse groups had lower body weight gain and greater survival rates than control groups.

Hepatocellular and ovarian neoplasm were considered to be clearly related to drug in rats and ovarian and adrenal neoplasms were considered to be clearly related to drug in female mice. The male mouse study was terminated very early and per Dr. Bray not evaluable. In the carcinogenicity studies, increasing doses did not result in corresponding increases in drug blood levels, which explain the lack of dose-relationship for neoplastic findings. The exposure multiples in rats and mice were 1- and 5-fold, respectively, over clinical exposure at the proposed dose. Except for skin, both neoplastic and non-neoplastic treatment-related effects in estrogen target organs, such as testes, epididymis, ovary, uterus, mammary gland, bone, liver, adrenal, pituitary, spleen, thymus and thyroid were consistent with the established ospemifene pharmacology/toxicology, or other mixed estrogen agonist/antagonists. Adrenal, ovary, and pituitary tumors may be related to endocrine steroidogenic feedback loop disruption.

For a complete presentation and discussion of the Pharmacology-Toxicology program presented in the application refer to the Pharmacology/Toxicology NDA Review and Evaluation by Jeffrey Bray, Ph.D. Per the recommendation of Dr. Bray, "the nonclinical findings support Approval for the treatment of moderate to severe VVA in post-menopausal women at a daily oral dose of 60 mg."

5. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology [(OCP), reviewer LaiMing Lee, Ph.D.] reviewed 4 biopharmaceutics studies (including bioequivalence and food effect studies), 13 clinical pharmacology studies (including single and multiple dose PK, drug-drug interaction, hepatic and renal impairment studies), and 1 Phase II dose finding study. A population pharmacokinetic study evaluating age, renal function, and race was conducted and submitted by the applicant; it was reviewed by Pharmacometrics reviewer Jiang Liu, Ph.D. The risk for venous thromboembolism (VTE) in patients with Factor V Leiden was reviewed by Pharmacogenomics Reviewer Christian Grimstein, Ph.D.

Several formulations were evaluated during the clinical development program for ospemifene. These formulations (solution, capsule and tablets) were produced at multiple manufacturing sites including (b) (4), Penn Pharmaceuticals in the United Kingdom, and (b) (4) for the tablet formulations alone. Ospemifene 30 (Lot 0248A) and 60 mg tablets (Lot 0249A) were manufactured by Penn Pharmaceuticals for Phase 3 Study 15-50310. Ospemifene 60 mg tablets (Lot A07006) were manufactured by (b) (4) for Phase 3 Study 15-50821. The to-be-marketed (TBM) ospemifene 60 mg tablets will be manufactured by Penn Pharmaceuticals. The following Table 2 presents the various formulations used in the Phase 1, 2 and 3 trials in the clinical development program.

Table 2 Summary of the Ospemifene Formulations used During Clinical Development

Study Objective	Study Design	Treatments (Dose, Route, Formulation) [Product ID]	Population	Protocol No.
Bioequivalence of ospemifene in tablet and capsule formulations and to evaluate the bioavailability of ospemifene	Open-label, randomized, three-sequence, three-period, crossover	Single 60 mg, oral, Fasted, Tablet [(b) (4)0107-852]; Capsules [(b) (4)002]; Solution [(b) (4)001]	Healthy male	1506004
Bioequivalence of two ospemifene 60 mg tablets	Open-label, randomized, multi-center, two-sequence, four-period, replicated-treatment, crossover	Single 60 mg, oral, Fasted, Tablet [Penn Pharma 0249A (commercial tablet)]; [(b) (4)85518]	Healthy postmenopausal female	15-50926
Bioequivalence of two ospemifene 60 mg tablets	Open-label, randomized, two-sequence, four-period, replicated-treatment, crossover	Single 60 mg, oral, Fasted, Tablet [Penn Pharma 0249A (commercial tablet)]; [(b) (4)85481]	Healthy postmenopausal female	15-51028
Bioequivalence of two ospemifene 60 mg tablets	Open-label, randomized, two-sequence, two-period, crossover	Single 60 mg, oral, Fed, Tablet [Penn Pharma 0249A (commercial tablet)]; [(b) (4)85481]	Healthy postmenopausal female	15-51029
Comparative BA study of five 60 mg ospemifene tablet batches	Open-label, randomized, five-sequence, five-period, crossover	Single 60 mg, oral, Fasted, Tablet [Penn Pharma 0249A (commercial tablet)]; [(b) (4)A10016, A10017, A10018, A10019]	Healthy postmenopausal female	15-51030
Bioequivalence of two ospemifene 60 mg tablets	Open-label, randomized, balanced, two-sequence, two-period, crossover	Single 60 mg, oral, Fasted, Tablet [Penn Pharma 0249A (commercial tablet)]; [(b) (4)A07006]	Healthy postmenopausal female	15-51031
Comparative BA study of ospemifene under fasted and high-fat fed conditions	Open-label, randomized, balanced, two-sequence, two-period, crossover	Single 60 mg, oral, Tablet [(b) (4)0107-852], Fasted; Fed (High-fat)	Healthy male	15-50208
Extension to 15-50208, to assess effects of a normal light breakfast on the bioavailability of ospemifene	Open-label, nonrandomized, one-period, one-treatment	Single 60 mg, oral, Tablet [(b) (4)0107-852], Fed (Low-fat);	Healthy male	15-50208-02

Study	Dose	Formulation	Population	Protocol No.
Single dose	10, 25, 50, 100, 200, 400, 800 (mg)	Gelatin capsules	Healthy male	3044001
Repeated dose	25, 50, 100, 200 (mg once daily)	Gelatin capsules	Healthy postmenopausal female	1506003
Single dose and steady state pharmacokinetics	60 (mg once daily)	Tablet	Healthy postmenopausal female	15-50927
Mass balance study	60 (mg) containing 20.2 MBq of (^{3}H)-ospemifene	Solution	Healthy postmenopausal female	15-50206
Effect of impaired hepatic function on ospemifene pharmacokinetics	60 (mg)	Tablet	Healthy or hepatic impaired postmenopausal female	15-50820
Effect of impaired hepatic function on ospemifene pharmacokinetics	60 (mg)	Tablet	Healthy or hepatic impaired postmenopausal female	15-50920
Effect of impaired renal function on ospemifene pharmacokinetics	60 (mg)	Tablet	Healthy or renal impaired postmenopausal female	15-50921
Drug-drug interaction; Effect of ospemifene on warfarin pharmacokinetics (CYP2C9 inhibition)	Racemic warfarin; 10 (mg), Ospemifene; 60 (mg once daily)	Tablet (Warfarin and Ospemifene)	Healthy postmenopausal female	15-50614
Drug-drug interaction; Effect of ospemifene on omeprazole pharmacokinetics (CYP2C19 and CYP3A4 inhibition)	Omeprazole; 20 (mg), Ospemifene; 60 (mg once daily)	Tablet (Omeprazole and Ospemifene)	Healthy postmenopausal female	15-50719
Drug-drug interaction; Effect of ospemifene on bupropion pharmacokinetics (CYP2B6 inhibition)	Bupropion; 150 (mg), Ospemifene; 60 (mg once daily)	Tablet (Bupropion and Ospemifene)	Healthy postmenopausal female	15-50825
Drug-drug interaction; Effect of rifampin and ketoconazole on ospemifene pharmacokinetics (CYP3A induction and inhibition)	Ospemifene; 60 (mg), Rifampin; 600 (mg once daily) / Ospemifene; 60 (mg), Ketoconazole; 400 (mg once daily)	Tablet (Ospemifene, Rifampin and Ketoconazole)	Healthy postmenopausal female	15-50716
Drug-drug interaction; Effect of fluconazole and omeprazole on ospemifene pharmacokinetics (CYP2C9 and CYP2C19 inhibition)	Ospemifene; 60 (mg), Fluconazole; 200 (mg once daily) / Ospemifene; 60 (mg), Omeprazole; 40 (mg once daily)	Tablet (Ospemifene), Capsule (Fluconazole), Gastro-resistant tablet (Omeprazole)	Healthy postmenopausal female	15-50823
Thorough QTc study	Placebo, Ospemifene; 60, 240 (mg once daily), Moxifloxacin; 400 (mg once daily)	Tablet (Placebo, Ospemifene and Moxifloxacin)	Healthy male and female	15-50824

Source: Office of Clinical Pharmacology Review

Single dose pharmacokinetic parameters of the parent drug ospemifene were investigated in Study 15-51031, the pivotal bioequivalence study. Study 15-51031 was a randomized, open-label, two-sequence, two-period, crossover study conducted under fasted conditions in postmenopausal women for the purpose of determining whether or not 60 mg

ospemifene tablets from the Penn Pharmaceutical manufacturing site (Lot No. 0249A, the proposed to-be-marketed formulation used in Phase 3 Study 15-5031) and the (b) (4) manufacturing site (Lot No. A07006 used in Phase 3 Study 15-50821) were bioequivalent. Ninety-four subjects were equally and randomly assigned to one of two treatment groups and were given a single 60 mg dose of ospemifene manufactured by Penn or (b) (4) There was a minimum of 14 days for washout between treatment periods. A single 60 mg ospemifene tablet was taken with 240 mL of room temperature water after an overnight fast of at least 10 hrs. Subjects fasted for 4 hours after each drug administration and water consumption was restricted from 1 hour prior to dosing until 2 hours post-dosing.

Blood samples for determination of serum ospemifene concentrations were collected immediately prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, 72, and 96 hours post-dose. Subjects were confined to the research center during the first 24 hours after drug administration during the intensive blood sampling period and returned on an outpatient basis on Days 2 through 5 for additional blood draws and procedures. Ospemifene concentrations were determined by LC-MS/MS.

Ninety two subjects completed the study. However due to a major protocol violation in one subject, the final pharmacokinetic analysis was based on 91 subjects. The following Table 3 presents the single dose pharmacokinetic parameters, which are included in the proposed labeling, CLINICAL PHARMACOLOGY, subsection 12.3 Pharmacokinetics.

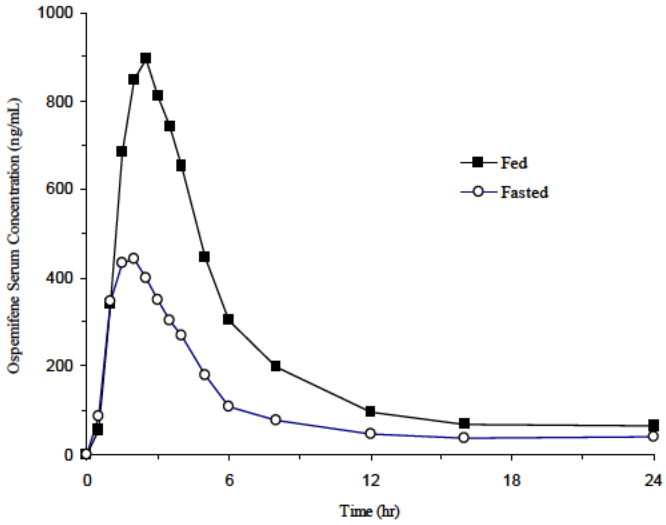
Table 3 Single Dose Mean (SD) PK Parameters of Ospemifene 60 mg Tablets, To-Be-Marketed Formulation

PK Parameter	Ospemifene (N-91)
$AUC_{0\text{-}96hr}$ (ng hr/mL)	3781 (1795)
$AUC_{0\text{-}inf}$ (ng.hr/mL)	4165 (1970)
Cmax (ng/mL)	533 (304)
Tmax* (hr)	2.0 (1.0-8.0)
$T_{1/2}$ (hr)	26.4 (6.7)
λ_z (1/hr)	0.028 (0.007)

*median (min-max)
Source: Office of Clinical Pharmacology Review

Figure 2 presents the mean (SD) serum-concentration-time profile following administration of a single dose of the to-be-marketed formulation of 60 mg ospemifene in Study 15-51031.

Figure 2 Mean (SD) Serum Concentration-Time Profile of Ospemifene [single oral administration of a 60 mg dose of the to-be-marketed formulation under fed (N-28) and fasted conditions (N = 91) in postmenopausal women participating in Study 15-51031]



Source: Office of Clinical Pharmacology Review

The results of Study 15-51031 demonstrated bioequivalence under fasting conditions between the to-be-marketed formulation used in Phase 3 Study 15-51031 produced by Penn Pharmaceutical and the (b) (4) formulation used in Phase 3 Study 15-50821. Study 15-50718, the Phase 3, 52-week extension study for assessment of endometrial safety used 60 mg ospemifene tablets manufactured by both Penn Pharmaceutical and (b) (4) Table 4 presents the comparative pharmacokinetic values.

Table 4 Result of Bioequivalence Study 15-51031

PK Parameters Mean (SD) for Ospemifene	Formulation for Study 15-50821	Formulation for Study 15-50310	Geometric Mean Ratio (90% CI)
Cmax (ng/mL)	501 (305)	533 (304)	0.95 (0.83, 1.09)
AUC_{0-96} (ng hr/mL)	3661 (1728)	3781 (1795)	0.96 (0.89, 1.05)
AUC_{0-inf} (ng.hr/mL)	3982 (1913)	4165 (1970)	0.97 (0.88, 1.05)

No multiple dose pharmacokinetic data is available for the ospemifene 60 mg to-be-marketed formulation from Penn Pharmaceuticals. Study 15-50927 was designed to obtain single and multiple dose pharmacokinetics for ospemifene. However the tablets used in Study 15-50927 was manufactured by (b) (4) 85518), which was not used in the clinical trials nor is it the intended to-be-marketed formulation. (b) (4) 85518 has been shown to be have lower exposure (20.7% lower in AUC0-inf and 34.4% lower in Cmax) compared to Penn 0249A (to-be-marketed formulation) in Study 15-50926.

The Sponsor conducted multiple studies to evaluate intrinsic and extrinsic factors that may affect the pharmacokinetics of ospemifene and the effect of ospemifene on other drugs.

The results of these studies are included, as appropriate, in proposed labeling sections 7 DRUG INTERACTIONS, 8 USE IN SPECIAL POPULATIONS and 12 CLINICAL PHARMACOLOGY. The studies include:

- ***Food effect***

  The two dedicated food effect studies were conducted in men using ospemifene tablets manufacture by (b) (4) (Batch 0107-852). These studies are not relevant to the to-be-marketed formulation of ospemifene. The effect of food in postmenopausal women administered the to-be-marketed ospemifene formulation was assessed by the OCP reviewer using a cross-study comparison of pharmacokinetic data from 5 bioequivalence studies (1 under fed condition and 4 under fasted condition). The pharmacokinetic parameters for ospemifene were similar across the four studies under fasted conditions. The results show that $AUC_{0\text{-inf}}$ and Cmax increased 1.7-fold and 2.3-fold, respectively, when ospemifene was administered with a high fat/high calorie meal. Tmax was similar at about 2 hrs. Half-life was similar and ranged from 24 to 29 hrs. In the two Phase 3 safety and efficacy clinical trials (Studies 15-50310 and 15-50821) and the long-term endometrial safety study (Study 15-50718), ospemifene was administered with food (no specific type indicated). The proposed label states that ospemifene should be taken with food.

- ***Renal impairment***

  The effect of renal impairment was evaluated in an open-label, single dose, parallel group Phase 1 Study 15-50921. Severe renal impairment and End-Stage Renal Disease (ESRD) did not significantly impact the systemic exposure of a single 60 mg dose of ospemifene (See Table 5). In subjects with severe renal impairment and ESRD, mean Cmax, $AUC_{0\text{-t}}$, and $AUC_{0\text{-inf}}$ for ospemifene were lower by 21%, higher by 19%, and higher by 20%, respectively. Half-life was the same at about 34 hours in patients with severe renal impairment and ESRD and normal renal function subjects. These results would be expected based upon the known clearance pathway for ospemifene, which is primarily through hepatic metabolism, and fecal and urinary excretion.

Table 5 Pharmacokinetic Parameters in Women with Severe Renal Impairment and End Stage Renal Disease versus Women with Normal Renal Functions

PK parameter*	Normal Renal Function (N=7)	Severe Renal Impairment + ESRD (N=8)	Severe/ESRD Renal Impairment versus Normal Renal Function PE (CI)**
$AUC_{0\text{-t}}$ (ng hr/mL)	7567 ± 2296	9395 ± 3965	118.7 (0.84, 1.68)
$AUC_{0\text{-inf}}$ (ng hr/mL)	8073 ± 2296	10141 ± 4144	119.6 (0.81, 1.76)
Cmax (ng/mL)	1106.1 ± 472.7	916.2 ± 525.2	78.6 (0.51, 1.22)
Tmax (hr)[1]	2 (1.0-6.0)	3.5 (2.0-8.0)	-
$T_{1/2}$ (hr)	33.6 ± 8.6	34.2 ± 6.1	103.0 (0.85, 1.25)

CL/F (mL/min)	132.3 ± 35.7	117.4 ± 56.8	83.6 (0.57, 1.23)

Severe (n=3), ESRD (n=5)
* mean ± SD
**point estimate and 90% CI of the least-squares geometric means ratio
[1]tmax: median and range
Source: Office of Clinical Pharmacology Review

- ***Hepatic impairment***

  The effect of mild and moderate hepatic impairment was studied in two Phase 1 open-label, single dose, parallel group studies, Study 15-50820 (Child-Pugh score determined mild and moderate impairment) and Study 15-50920 (Child-Pugh score determined moderate impairment). Subjects with normal hepatic function and patients with mild hepatic impairment had similar mean Cmax, AUC_{0-t}, and AUC_{0-inf} for ospemifene. In patients with mild hepatic impairment, mean Cmax, 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 (though not significant effect) on ospemifene exposure compared to mild hepatic impairment. In patients with moderate hepatic impairment, mean Cmax 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 effects of ketoconazole (a strong CYP3A4 inhibitor), rifampin (a strong CYP3A4 inducer), fluconazole (a CYP3A4/CYP2C9/CYP2C19 inhibitor), and omeprazole (a CYP2C19 inhibitor and substrate) on ospemifene***

  The effects of CYP3A4 inhibitor (ketoconazole) and CYP3A4 inducer (rifampin) on ospemifene were evaluated in open-label, randomized, three-period, crossover Phase 1 Study 15-50716. Treatments included:

  (1) 60 mg ospemifene after a standard meal as a single dose
  (2) once daily administration of 600 mg rifampin in the fasted state for 5 days and 60 mg ospemifene after a standard meal on 6th day
  (3) once daily administration of 400 mg ketoconazole after a meal for 4 days and 400 mg ketoconazole and 60 mg ospemifene on 5th day followed by 3 days once daily administration of 400 mg ketoconazole

  Ketoconazole moderately increased the concentrations of ospemifene in healthy postmenopausal women treated with ketoconazole 400 mg once daily for 5 days prior to and 3 days after a single dose administration of ospemifene 60 mg.

  The mean AUC_{0-inf} increased by 1.4-fold from 4578 to 6475 ng.hr/mL and Cmax increased by 1.5-fold from 644 to 872 ng/mL. Tmax was 2.5 hrs with ospemifene alone and with ketoconazole pre-treatment. Elimination half-life was similar at 24 hours, respectively. Continued CYP3A4 inhibition was maintained by giving three additional doses of ketoconazole after ospemifene administration.

  Rifampin moderately decreased ospemifene exposure in healthy postmenopausal women. The mean AUC_{0-inf} was decreased by 58% from 4578 to 1854 ng.hr/mL and Cmax was decreased by 51% from 644 to 301 ng/mL. Tmax and elimination

half-life remained essentially unchanged. Tmax was similar at ~ 3 hrs. Elimination half-life was similar at ~25 hrs. Rifampin was not given after ospemifene administration on Day 6 and during the PK sampling period; therefore, enzyme induction by rifampin may have been more significant. It is possible that ospemifene exposure may have been lowered more significantly if rifampin was given during the PK sampling period.

The effects of CYP3A4/CYP2C9/CYP2C19 inhibitor (fluconazole) and CYP2C19 inhibitor (omeprazole) on ospemifene were evaluated in open-label, randomized, two- and three-period, crossover Phase 1 Study 15-50823. Fourteen (14) postmenopausal women were administered a single 60 mg dose of ospemifene following a meal with and without pre-treatment with fluconazole and omeprazole. The fluconazole treatment period included 200 mg fluconazole (400 mg on Day 1) administered once daily under fasted condition for 8 days and on the 5th day one tablet of 60 mg ospemifene was administered under fed condition. The omeprazole treatment period included 40 mg omeprazole administered once daily under fasted condition for 8 days and on the 5th day, one tablet of 60 mg ospemifene was administered under fed condition. Subjects were genotyped as extensive 2C9 and 2C19 metabolizers.

Fluconazole significantly increased ospemifene exposure. The effect of fluconazole on ospemifene exposure was apparent with ospemifene $AUC_{0\text{-}inf}$ increasing 2.7-fold from 4288 to 11932 ng.hr/mL after fluconazole pre-treatment. Cmax increased slightly by 1.7-fold from 650 to 1028 ng/mL and Tmax was similar at ~ 3 hrs. $T_{1/2}$ increased significantly from 25.0 to 42.9 hrs with fluconazole inhibition.

The Sponsor identified fluconazole as a potent CYP2C9 inhibitor. Based upon the classification of CYP inhibitors in the current FDA's Draft Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (February 2012), fluconazole is an inhibitor of multiple enzymes - listed as a moderate CYP2C9, strong CYP2C19, and moderate CYP3A4 inhibitor. Despite the known inhibitory effects of fluconazole on CYP2C19 and CYP3A4, the Sponsor selected fluconazole as the perpetrator drug in the study of CYP2C9 inhibition. Due to fluconazole's inhibitory effect on multiple CYP enzymes, it not possible to conclude that the pathway for ospemifene metabolism is solely through CYP2C9.

The effect of omeprazole on ospemifene exposure was less significant than with fluconazole with ospemifene $AUC_{0\text{-}inf}$ increasing 1.2-fold from 3949 to 4568 ng.hr/mL after omeprazole pretreatment. Cmax increased slightly from 560 to 657 ng/mL. Tmax was similar at ~ 3 hrs. $T_{1/2}$ was essentially unchanged at ~24 hours

The Sponsor identified omeprazole as a strong CYP2C19 inhibitor. According to the above mentioned drug interaction guidance published in 2012, omeprazole is a moderate inhibitor of CYP2C19. The discrepancy in categorization of omeprazole is likely due to a previous classification of inhibitors in an earlier Agency guidance, where omeprazole was listed as a strong CYP2C19 inhibitor.

- ***The potential effect of ospemifene on CYP2C9 (with warfarin, a CYP2C9 substrate), CYP2B6 substrates (with bupropion, a CYP2B6 substrate) and CYP2C19 and CYP3A4 (with omeprazole).***

  The effect of ospemifene on CYP2C9 (using warfarin) was evaluated in open-label, two-period crossover Phase 1 Study 15-50614. Sixteen (16) healthy postmenopausal women were administered a single dose of 10 mg warfarin with and without pre-treatment of 60 mg ospemifene once daily for 8 days following a meal.

  The geometric least square means (90% CI) for test (warfarin + ospemifene)/reference (warfarin alone) ratio of S-warfarin $AUC_{0\text{-}inf}$ was 0.96 (0.91, 1.02). The Sponsor states in the application that repeated dosing of 60 mg ospemifene does not affect CYP2C9 activity. For Cmax, the LSM (905 CI) ratio was 0.97 (0.92, 1.02).

  The effect of ospemifene on CYP2B6 (using bupropion) was evaluated in an open-label, two-period, two-sequence, randomized, crossover Phase 1 Study 15-50825. Sixteen (16) healthy postmenopausal women were administered a single dose of 150 mg bupropion with and without pre-treatment of 60 mg ospemifene once daily for 7 days following a meal. Subjects were genotyped as not being homozygous for CYP2B6.

  The geometric mean $AUC_{0\text{-}inf}$ and C_{max} of bupropion decreased by 19% and 18%, respectively, with ospemifene co-administration. The Sponsor concludes that ospemifene has no impact on CYP2B6 activity and no dose modification is required if ospemifene and bupropion are co-administered.

  The effect of ospemifene on CYP2C19 and CYP3A4 (with omeprazole) was evaluated in open-label, two-period, crossover Phase 1 Study 15-50719. Twelve (12) healthy postmenopausal women were administered a single 20 mg dose of omeprazole with and without pre-treatment of 60 mg ospemifene for 7 days. Women who were genotyped as "not" poor metabolizers of CYP2C19 were included in the pharmacokinetic analysis.

  The ratios of the geometric means (90% CI) of the metabolic indices (with/without ospemifene) were 0.97 (0.77, 1.22) for 5- hydroxyomeprazole and 0.97 (0.66, 1.41) for omeprazole sulphone. The Sponsor states in the application that ospemifene does not have an effect on the metabolism of omeprazole and that repeat dosing of ospemifene does not significantly affect CYP2C19 and CYP3A4 activity.

- ***Other intrinsic/extrinsic effects***

  - ***Genetics***

    The Sponsor excluded Factor V Leiden carriers from Phase 2 and Phase 3 clinical trials. The OCP-Genomic Group (reviewer Christian Grimstein, Ph.D.) assessed whether 1) the risk estimation for venous thromboembolic events was biased due to the exclusion of Factor V Leiden carriers in the Phase 2 and 3 studies and 2) whether or not screening for Factor V Leiden is indicated for women who are eligible for ospemifene therapy.

    The risk of venous thromboembolism is approximately 2 to 3 fold higher in Factor V Leiden carriers compared to non-carriers, and is further increased if other known risk factors are present. Based on the estimated prevalence of Factor V Leiden and considering the increased risk associated with Factor V Leiden, few or no additional cases of venous thromboembolism would have been observed if Factor V Leiden carriers were included in Phase 2/3

trials. Dr. Grimstein's review determined that the current risk estimates are reasonable. He further concluded that screening for Factor V Leiden in women being considered for ospemifene therapy is not recommended given estimates that more than 1000 women would need to be screened in order to prevent a single case of venous thromboembolism.

- ***QT Prolongation***
  Thorough QTc Study 15-50824 was a randomized, double-blind, active and placebo-controlled trial in 200 healthy male (n=25) and female (n=25) subjects between 18 and 45 years of age. Subjects were randomized to receive daily 60 mg ospemifene, 240 mg ospemifene (supratherapeutic dose), moxifloxacin (active control) or placebo following a high-fat breakfast for duration of 7 days.

  For ospemifene 60 mg, ΔQTcI was -2.8 ms and the 90% CI for ΔQTcI was -4.3 to -1.2 ms. For the supratherapeutic dose 240 mg ospemifene, ΔQTcI was -3.5 ms and the 90% CI for ΔQTcI was -5.0 to -1.9 ms. The regulatory threshold of a 10 ms increase in QT was not exceeded; therefore, there is no safety concern for QT prolongation by ospemifene. For the reference drug moxifloxacin 400 mg, ΔQTcI was 5.4 ms and the 90% CI for ΔQTcI was 3.2 to 7.5 ms.

- ***Population PK***
  The OCP-Pharmacometrics Group (reviewer Jiang Liu) evaluated whether the ospemifene dose/exposure-response for efficacy and safety support the proposed daily 60 mg dose. The population pharmacokinetic analyses were conducted based on pooled data from sampling in Studies 15-50310, 15-50821, 15-50718, 15-50927, 15-50820, 15-50920 and 15-9021. A two-compartment model with first-order absorption processes was selected. Inter-subject variability was assessed on each of the PK parameters using the exponential error structure. Based on the OBJ, exponential error model was chosen for intra-individual variability. Age, race, manufacturing sites, body weight, BMI, ALB, ALT, BILI, CREAT and CLcr were tested as a covariate on PK parameters of CL/F. Age, race, manufacturing sites, body weight, BMI and ALB were tested as a covariate on V2/F. Linear and power models were applied to test continuous covariates and categorical model was applied to test categorical covariates.

  Dr. Liu concluded that the 60 mg dose was superior to the lower 30 mg dose with respect to changes in vaginal indices in addition to being superior to placebo for each co-primary endpoint. There was no dose –related increase in treatment emergent adverse events. No covariate was detected to have a clinically relevant effect on the pharmacokinetics of ospemifene. The CL/F estimate (9.16 L/hr) and the inter-individual variability for CL/F (36.3%) under the fed condition are smaller compared to those under the fasted condition (16.9 L/hr for CL/F and 42.7% for the inter-individual variability for CL/F).

OCP labeling recommendations, in particular those related to absorption of ospemifene, special populations and drug-drug interactions are discussed above in the body of the review. Refer to attached labeling for full details of sections 7 DRUG INTERACTIONS, 8 USE IN SPECIAL POPULATIONS and 12 CLINICAL PHARMACOLOGY.

For a complete presentation and discussion of the OCP development program presented in the application refer to the OCP NDA Review of LaiMing Lee, Ph.D., the OCP-Pharmacometrics Group NDA Review of Jiang Liu, Ph.D., and the OCP-Genomic Group NDA Review of Christian Grimstein, Ph.D. Per the conclusions of Dr. Lee, the Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3) finds the NDA to be acceptable from a Clinical Pharmacology perspective provided that an agreement is reached between the Sponsor and the Division of Reproductive and Urologic Products regarding the labeling language.

6. Clinical Microbiology

Not applicable to this NDA.

7. Clinical/Statistical - Efficacy

The primary review of the efficacy information in NDA 203505 was performed by Theresa van der Vlugt, M.D., OND/ODE 3/DRUP and Xin Fang, Ph.D., Office of Translational Science/Division of Biometrics III. For a very detailed discussion of design and conduct of the clinical trials including evaluated primary and secondary endpoints and their analyses the reader is referred to Dr. van der Vlugt' s and Dr. Fang's reviews.

The Agency's recommendations to Sponsors regarding clinical trials for products intended to treat the symptoms of vulvar and vaginal atrophy are presented in the 2003 Draft Clinical Trial Guidance. Even though the guidance specifically refers to Estrogen and Estrogen/Progestin Drug Products, the specific recommendations on clinical trial design and conduct as well as primary endpoint evaluation and assessment have been applied to all products for which a treatment of vasomotor symptoms due to menopause or a treatment of vaginal dryness or dyspareunia, symptoms of vulvar and/or vaginal atrophy, due to the menopause indication is sought. Symptoms of vulvar and vaginal atrophy other than vaginal dryness and dyspareunia may be pursued, but the Agency now advises that dyspareunia and dryness are the two symptoms for which clinical trials have successfully demonstrated efficacy.

For the indication of treatment of moderate to severe dyspareunia and/or moderate to severe vaginal dryness, symptoms of vulvar and vaginal atrophy due to menopause, the 2003 Draft Clinical Trial Guidance recommends one or more randomized double-blind, 12-week placebo-controlled trials to support efficacy. Studies should identify the lowest effective dose by including an ineffective dose as one of the doses studied. Enrollment criterion include postmenopausal women (defined by 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/ml or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy) who at baseline have self-identified a most bothersome moderate to severe symptom (the symptom consistent with the symptomatic indication sought) and on vaginal examination have no greater than 5 percent superficial cells on a vaginal smear, and have a vaginal pH >5.0. All such women with a uterus should have a negative endometrial biopsy at screening. To

evaluate efficacy for the indication of treatment of moderate to severe dyspareunia and/or moderate to severe vaginal dryness, symptoms of vulvar and vaginal atrophy due to menopause, the following co-primary endpoints are assessed:

- Mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being the most bothersome to her
- Mean change from baseline to week 12 in vaginal pH
- Mean change from baseline to week 12 in vaginal parabasal and superficial cells

The efficacy analyses should demonstrate statistically significant improvement versus placebo in the change from baseline to week 12 for each of the co-primary endpoints. Failure to demonstrate statistically significant improvement in any one co-primary endpoint is considered as failure to demonstrate efficacy. The indication is a symptomatic indication, vaginal dryness or dyspareunia, but linkage to the physical changes of vulvar and vaginal atrophy are made through the assessment of vaginal cells and vaginal pH. As indicated in the background, the Sponsor was advised throughout their clinical development program of the recommended clinical trial design, conduct, endpoint evaluation and analyses issues to be addressed for the successful demonstration of efficacy for the indication of treatment of moderate to severe dyspareunia and/or moderate to severe vaginal dryness, symptoms of vulvar and vaginal atrophy due to menopause.

Efficacy conclusions regarding OSPHENA were based on two Phase 3 clinical trials (Study 15-50310 and 15-50821). The Sponsor submitted information for the first 12 weeks of long-term safety Study 15-50718 as additional support for efficacy, however, this trial was not considered for determination of efficacy, because it did not study and evaluate all of the co-primary endpoints, as recommended in the 2003 Draft Clinical Trial Guidance and delineated above. The Sponsor was advised on three separate occasions, April 12, 2011 with Shionogi USA, Inc., September 29, 2009 with QUATRx Pharmaceuticals and April 29, 2008 with QUATRx Pharmaceuticals that the new molecular entity, ospemifene, should be supported by two adequate and well controlled Phase 3 studies for safety and efficacy and that efficacy will be based on the results of each pivotal Phase 3 study (15-50310 and 15-50821), analyzed separately and not on the basis of overall efficacy findings combined across the two Phase 3 studies.

Study 15-50310 was a multicenter, randomized (1:1:1), double-blind, placebo-controlled, three-group (ospemifene 30 mg, ospemifene 60 mg and placebo) parallel Phase 3 study conducted between January 16, 2006 and November 19, 2007 at 83 trial sites. Randomization was stratified by uterine status (intact vs. hysterectomized). The study enrolled 826 subjects. Only a sub-group of these subjects were included in the evaluation of efficacy [modified intent-to-treat (mITT)], as the Sponsor originally enrolled subjects with complaints of 5 symptoms of vulvar and vaginal atrophy (vaginal dryness, dyspareunia vaginal and/or vulvar irritation/itching dysuria and vaginal bleeding) and was intending to perform a composite analysis instead of analysis of the individual symptom. The protocol was amended April 24, 2007 to analyze only vaginal dryness and dyspareunia.

An additional issue with this study was the use of vaginal lubricants on an "as needed" basis during the treatment phase of this trial. The Agency had originally proposed that this study be designed as double-blind, double-dummy trial to compare oral ospemifene with a vaginal lubricant placebo with the intent being to demonstrate whether or not oral drug product demonstrated statistically significant improvement beyond that due to placebo vaginal lubricant. The Sponsor did not follow the Agency's recommendation and instead, as stated above, allowed the use of vaginal lubricants on an "as needed" basis in both arms of the study.

Study 15-50821 was a multicenter, randomized (1:1), double-blind, placebo-controlled, two-group (ospemifene 60 mg and placebo) parallel Phase 3 study conducted between April 04, 2008 and July 30, 2009 at 119 trial sites. Study 15-50821 enrolled 919 subjects. As it had for Study 15-50310, the Division advised the Sponsor, Hormos Medical, to conduct Study 15-50821 as a double-blind, double-dummy trial of oral drug product vs. vaginal lubricant placebo. The Sponsor indicated their reluctance to "force" use of vaginal lubricant on women and held that information can be extracted to address whether or not oral drug product treatment in combination with placebo vaginal lubricant demonstrates significant improvement beyond that or either oral place drug product or vaginal lubricant in both studies where vaginal lubricant had been allowed on an "as needed" basis. The Division indicated [April 11, 2011 meeting minutes with the Sponsor (Shionogi)] that the Sponsor should perform a secondary analysis on each study for the co-primary endpoint of vaginal dryness and dyspareunia using an ANCOVA model that includes an indicator for vaginal lubricant use (Y/N) at Week 12.

The subject disposition of the two studies based on the intent-to-treat (ITT) patient population is presented in the following Table 6.

Table 6 Subject Disposition in Studies 15-50310 and 15-50821, ITT Population

Disposition	Study 15-50310			Study 15-50821	
	Ospemifene 30 mg N (%)	Ospemifene 60mg N (%)	Placebo N (%)	Ospemifene 60mg N (%)	Placebo N (%)
Randomization	282 (100.0)	275 (100.0)	268 (100.0)	463 (100.0)	456 (100.0)
Completed Study	225 (79.8)	234 (84.8)	230 (85.8)	416 (89.8)	403 (88.4)
Discontinued Study	57 (20.2)	42 (15.2)	38 (14.2)	47 (10.2)	53 (11.6)
Subject withdrew	14 (5.)	14 (5.1)	12 (4.5)	8 (1.7)	19 (4.2)
Lost to follow-up	8 (2.8)	6 (2.2)	4 (1.5)	9 (1.9)	9 (2.0)
Adverse event	15 (5.3)	13 (4.7)	11 (4.1)	25 (5.4)	14 (3.1)
Protocol violation	14 (5.0)	7 (2.5)	9 (3.4)	1 (0.2)	2 (0.4)
Lack of efficacy	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	5 (1.8)	2 (0.7)	2 (0.7)	4 (0.9)	4 (0.9)

Source: Statistics Review based on Dataset ISE.ADDS, QS dataset in each individual study SDTM data set

Discontinuations were comparable between the ospemifene 60 mg group and placebo in both studies. No subject in either of these groups withdrew due to lack of efficacy.

The mean age of subjects participating in both Study 15-50310 and Study 15-50821 was 59. The majority of subjects in both trials were Caucasian 90.2 and 87.9%, respectively in

Study 15-150310 and Study 15-50821. Demographics were similar across treatment groups in both studies.

The Sponsor's analyses indicated that in Study 15-50310 both the 30 mg ospemifene and 60 mg ospemifene dosage strengths demonstrated a statistically significant difference vs. placebo (p= 0.0407 and p = 0.0136, respectively) for the co-primary endpoint of vaginal dryness, while only the 60 mg dose demonstrated a statistically significant difference vs. placebo (p = 0.0012) for the co-primary endpoint of dyspareunia. Both dosage strengths were highly statistically significant vs. placebo (<0.0001) in the analyses for the co-primary endpoints of mean change in vaginal superficial and parabasal cells as well as vaginal pH. For Study 15-50821, the Sponsor's analysis demonstrated that the 60 mg ospemifene was statistically significantly different from placebo for the co-primary endpoint of dyspareunia (p = <0.0001), but not for the co-primary endpoint of vaginal dryness (p = 0.0853). The 60 mg dosage strength was highly statistically significant vs. placebo (<0.0001) in the analyses for the co-primary endpoints of mean change in vaginal superficial and parabasal cells as well as vaginal pH.

The Statistical Reviewer, Dr. Fang, performed the Agency's analyses of the four co-primary endpoints for both studies using a modified intent-to-treat population (mITT). The mITT population included ITT population that met at baseline the requirement of pH>5, vaginal superficial cells ≤5% and the most bothersome moderate-to-severe symptom of vaginal dryness or dyspareunia. For missing values, a last-observation-carried-forward (LOCF) approach was used to replace missing values in the analysis population. In subjects with no post-baseline treatment values, baseline values were carried forward. If a subject did not have a baseline measurement, but had a post-baseline measurement, the change score was set to zero. In Study 15-50310, if the early termination visit occurred ≤35 days from the randomization visit, the missing value at Week 4 was replaced with values from the early termination records; otherwise the value was set to missing at Week 4. In Study 15-50821, the Week 4 visit window included treatment Days 2 through 57. Assessments after 14 days from the last dose were not included in the analysis for Study 15-50821.

In Study 15-50310, parabasal cells, superficial cells, and vaginal pH were evaluated using an analysis of covariance (ANCOVA) model. The model included fixed effects of treatment, uterus status, study center, and baseline value as covariate. The ANCOVA model in Study 15-50821 was similar except that there was no fixed effect of uterus status. In circumstance where the ANCOVA assumptions were severely violated, a rank-based ANCOVA was used including study center and uterus status. For the most bothersome symptom, the change from baseline to Week 12 in the severity of vaginal dryness and dyspareunia was analyzed using Cochran-Mantel-Haenszel (CMH) method controlling for study center (in both studies) and uterus status (only in Study 15-50310).

Type-1 error rate for the between dose comparisons was controlled by a step-down approach. Ospemifene 60 mg dose was tested first: if all four co-primary endpoints were statistically significant, then ospemifene 30 mg dose was tested. Because of the analyses of both vaginal dryness and dyspareunia, a Bonferroni multiplicity adjustment was performed by Dr. Fang.

The Statistical Reviewer's analyses are presented in the following Table 7.

Table 7 Mean (SE) Change from Baseline to Week 12 in Co-primary Endpoints for 30 and 60 mg Ospemifene vs. Placebo in Studies 15-50310 and 15-50821, mITT Population, Last Observation Carried Forward (LOCF)

Study 15-50310			
Most Bothersome Moderate to Severe Symptom at Baseline	OSPHENA 30 mg	OSPHENA 60 mg	Placebo
Dyspareunia			
N	124	110	113
Baseline Mean (SD)	2.65 (0.48)	2.74 (0.44)	2.73 (0.45)
LS Mean Change from Baseline (SE)	-1.22 (0.11)	-1.39 (0.11)	-0.89 (0.11)
Difference (95% CI) vs. placebo	-0.33 (-0.63, -0.03)[b]	0.51 (-0.81,-0.20)[b]	---
Nominal p-value	0.0968[a]	0.0012[a]	---
Percent Superficial Cells			
LS Mean Change from Baseline (SE)	9.36 (1.23)	10.88 (1.27)	2.73 (1.27)
Difference (95% CI) vs. placebo	6.63 (3.29, 9.97)	8.16 (4.73, 11.58)	---
Nominal p-value	0.0001[b]	<.0001[b]	---
Percent Parabasal Cells			
LS Mean Change from Baseline (SE)	-25.40 (2.37)	-34.44 (2.44)	5.84 (2.44)
Difference (95% CI) vs. placebo	-31.24 (-37.66, -24.82)	-40.3 (-46.9, -33.7)	---
Nominal p-value	<.0001[b]	<.0001[b]	---
Vaginal pH			
LS Mean Change from Baseline (SE)	-0.74 (0.09)	-0.97 (0.09)	-0.002
Difference (95% CI) vs. placebo	-0.74 (-0.98, -0.51)	-0.97 (-1.22, -0.73)	---
Nominal p-value	<.0001[b]	<.0001[b]	---
Vaginal Dryness			
N	95	113	100
Baseline Mean (SD)	2.53 (0.50)	2.5 (0.5)	2.4 (0.49)
LS Mean Change from Baseline (SE)	-1.24 (0.20)	-1.29 (0.09)	-0.92 (0.10)
Difference (95% CI) vs. placebo	-0.32 (-0.60,-0.05) [b]	-0.37 (-0.63,-0.11)[b]	---
Nominal p-value	-0.047 [a]	0.0136[a]	---
Percent Superficial Cells			
LS Mean Change from Baseline (SE)	9.10 (1.31)	11.16 (1.19)	2.33 (1.25)
Difference (95% CI) vs. placebo	6.77 (3.24, 10.30)	8.83 (5.48, 12.18)	---
Nominal p-value	0.0002 [b]	<.0001[b]	---
Percent Parabasal Cells			
LS Mean Change from Baseline (SE)	-19.56 (2.58)	-26.66 (2.35)	0.12 (2.47)
Difference (95% CI) vs. placebo	-19.67 (-26.64, -12.70)	-26.76 (-33.40, -20.13)	---

Nominal p-value	<.0001[b]	<.0001[b]	---
Vaginal pH			
LS Mean Change from Baseline (SE)	-0.55 (0.09)	-0.92 (0.09)	-0.16
Difference (95% CI) vs. placebo	-0.39 (-0.64, -0.13)	-0.75 (-0.99, -0.51)	---
Nominal p-value	0.0029 [b]	<.0001[b]	---
Study 15-50821			
Most Bothersome Moderate to Severe Symptom at Baseline	OSPHENA 30 mg	OSPHENA 60 mg	Placebo
Dyspareunia	NS		
N	---	301	297
Baseline Mean (SD)	---	2.67 (0.47)	2.67 (0.47)
Mean Change from Baseline (SE)	---	-1.55 (0.06)	-1.29 (0.07)
Difference (95% CI) vs. placebo	---	-0.36 (-0.53, -0.18)[b]	---
Nominal p-value	---	<.0001[a]	---
Percent Superficial Cells			
LS Mean Change from Baseline (SE)	---	12.35 (0.68)	1.69 (0.69)
Difference (95% CI) vs. placebo	---	10.66 (8.81, 12.52)	---
Nominal p-value	---	<.0001[b]	---
Percent Parabasal Cells			
LS Mean Change from Baseline (SE)	---	-40.57 (1.57)	-0.56 (1.59)
Difference (95% CI) vs. placebo	---	-40.0 (-44.3, -35.7)	---
Nominal p-value	---	<.0001[b]	---
Vaginal pH			
LS Mean Change from Baseline (SE)	---	-0.95 (0.05)	-0.08 (0.05)
Difference (95% CI) vs. placebo	---	-0.87 (-1.01, -0.73)	---
Nominal p-value	---	<.0001[b]	---

Most Bothersome Moderate to Severe Symptom at Baseline	OSPHENA 30 mg	OSPHENA 60 mg	Placebo
Vaginal Dryness	NS		
N	---	157	150
Baseline Mean (SD)	---	2.5 (0.50)	2.5 (0.50)
LS Mean Change from Baseline (SE)	---	-1.33 (0.08)	-1.11 (0.08)
Difference (95% CI) vs. placebo	---	-0.22 (-0.44, 0.003)[b]	---
Nominal p-value	---	0.0853[a]	---
Percent Superficial Cells			
LS Mean Change from Baseline (SE)	---	12.32 (1.03)	3.53 (1.06)
Difference (95% CI) vs. placebo	---	8.79 (5.91, 11.67)	---
Nominal p-value	---	<.0001[b]	---
Percent Parabasal Cells			
LS Mean Change from Baseline (SE)	---	-31.65 (2.13)	-4.11 (2.19)
Difference (95% CI) vs. placebo	---	-27.55 (-33.51, -21.59)	---
Nominal p-value	---	<.0001[b]	---
Vaginal pH			
LS Mean Change from Baseline (SE)	---	-0.95 (0.07)	-0.25 (0.07)
Difference (95% CI) vs. placebo	---	-0.71 (-0.90, -0.51)	---
Nominal p-value	---	<.0001[b]	---

[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.
Definitions: LOCF = last observation carried forward; SD = standard deviation; SE = standard error; LS = least square, NS = not studied

Source: Adapted from the Statistical Review (Tables 5 and 10) - Reviewer's analysis based on ISE analysis datasets ADMBS310, ADMBS821, ADPH, ADPC, and ADSC

Dr. Fang's analyses confirm efficacy for the 60 mg dose of ospemifene, which demonstrated statistically significant improvement vs. placebo in both studies for dyspareunia in conjunction with statistically significant improvement vs. placebo in the profile of vaginal superficial (increased percentage) and parabasal cells (decreased percentage) and vaginal pH (decreased). Efficacy for vaginal dryness was not demonstrated for the 60 mg dose for improvement with vaginal dryness. Efficacy for the treatment of vaginal dryness or dyspareunia was not demonstrated for Ospemifene 30 mg.

Dr. Fang performed exploratory analyses to determine the effect of lubricant use on the improvement of the co-primary symptom endpoint. Despite the Sponsor's contention that "The use of lubricant was minimal and declined with effective therapy at 60mg Ophena™", Dr. Fang's exploratory analyses showed that for the mITT population assessed for dyspareunia and vaginal dryness, the majority of the subjects used vaginal lubricant. Based on the absolute magnitude of the treatment effect (difference of 0.5 and 0.4 vs. 0.1 and 0.3 for dyspareunia in Studies 15-50310 and 51-50821 lubricant vs. no lubricant) in the

exploratory analyses based on a small sample size, Dr. Fang concluded that the overall exploratory subgroup analyses by lubricant group showed no significant difference between treatment groups for dyspareunia. Therefore, this reviewer believes that the use of lubricants on an "as needed basis" in the clinical trial does not preclude the conclusion that this product is efficacious for the treatment of dyspareunia due to menopause

8. Safety

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 evaluated ospemifene doses ranging from 5 mg/day to 90 mg/day. Of these 9 studies, 7 were placebo-controlled trials and included: the two 12-week, randomized double-blind Phase 3 trials for vulvar and vaginal atrophy, 15-50310 (30 and 60 mg ospemifene vs. placebo) and 15-50821 (60 mg ospemifene vs. placebo); Study 15-50310X, a 40-week extension of Study 15-50310 for women who had an intact uterus (30 and 60 mg ospemifene and placebo were evaluated); 15-50718, a 52-week trial of women who had an intact uterus who received either 60 mg ospemifene or placebo; and three Phase 2 studies, 1506002 (12-week evaluation of the effects of 30, 60 and 90 mg ospemifene and placebo on bone), 15-50717 (12-week evaluation of the effects of 5, 15 and 30 mg ospemifene and placebo superficial and parabasal vaginal cells and pH) and 15-50615 (6-week evaluation of 60 mg ospemifene and placebo). The remaining two studies were 1506001, a randomized double-blind active-controlled study of the effects of 30, 60 and 90 mg ospemifene and placebo on vasomotor symptoms, and Study 15-50312, a 52-week, uncontrolled open-label extension (60 mg ospemifene dose only) of 12-week Study 15-50310 for subjects who completed the parent study and were hysterectomized (i.e. without an intact uterus).

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.

Per the Sponsor's report, no deaths were reported during the ospemifene development program. In the 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). A total of 32 subjects reported at least 1 SAEs in the 60 mg ospemifene treatment group (2.6% of the 1242 subjects treated with that dose), while 7 reported at least 1 SAE in the 30 mg ospemifene treatment group (2.0% of the 352 subjects treated with that dose). There were no SAEs reported in 15 mg or 30 mg ospemifene treatment groups.

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%).

For products approved for the treatment of symptoms due to menopause (both vasomotor symptoms and symptoms of vulvar and vaginal atrophy), specific attention has been focused on the safety with respect to venous thromboembolic events (pulmonary embolism, deep venous thrombosis and thrombotic stoke) and uterine/endometrial events (in particular endometrial stromal/glandular proliferation, endometrial polyps, endometrial hyperplasia and endometrial adenocarcinoma and uterine sarcomas). To date only estrogen and estrogen/progestin combination products have been approved for symptomatic treatment associated with menopause. The Division has taken a similar focused safety approach (to that used for estrogen products) in its review of estrogen receptor agonists/antagonists and this was likewise applied to this application.

Per the Agency's review of the application, ospemifene 60 mg had a cerebral thromboembolic incidence rate of 0.72 per thousand women (1 case in 1379 subjects treated with 60 mg ospemifene) vs. 1.04 per thousand women in placebo (1 case in 958 placebo-treated subjects). The incidence rate of hemorrhagic stroke in the 60 mg ospemifene group was 1.45 per thousand women (2 cases in 1379 subjects treated with 60 mg ospemifene) vs. 0 per thousand women, respectively in placebo. With respect to deep vein thrombosis, the incidence rate for ospemifene 60 mg was 1.45 per thousand women (2 cases in 1379 subjects treated with 60 mg ospemifene) vs. 1.04 per thousand in placebo (1 case in 958 placebo-treated subjects). If OSPHENA is approved, the BOXED WARNING will identify OSPHENA as an estrogen agonist/antagonist with tissue selective effects and will include the statement, "There is a reported increased risk of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) who received daily oral conjugated estrogens (CE) [0.625 mg]-alone therapy over 7.1 years as part of the Women's Health Initiative (WHI)." This statement is consistent with class labeling for estrogen products. The incidence rate of stroke and deep venous thrombosis from the clinical trials for the 60 mg dose of ospemifene, as stated above, will be included following the estrogen class labeling statement to provide this information to the prescriber and patient.

The major safety concern for women using estrogen products has been the risk of endometrial hyperplasia and subsequent development of endometrial carcinoma. As stated, the development of endometrial cancer is a major safety focus of this review. Because the development of endometrial carcinoma is rarely seen in the one or two year clinical trials conducted to support long-term safety of estrogen products and virtually nonexistent in 12 week trials for efficacy in the symptomatic indications of menopause, the Agency has used the development of endometrial hyperplasia as a surrogate marker for the development of endometrial cancer.

The OSPHENA developmental program assessed the endometrial safety through measurement of endometrial thickness as assessed by transvaginal ultrasonography (TVU), as well as assessment of endometrial histology following scheduled endometrial biopsy at

baseline and 52 weeks, and a combination of TVU and endometrial biopsies done to assess bleeding.

The mean endometrial thickness at baseline was 2.107 ± 0.8179 across all ospemifene-treated subjects vs. 2.214 ± 0.8312 for placebo. The mean change in endometrial thickness at 12 weeks of treatment was 0.474 ± 1.4292 across all ospemifene-treated subjects vs. 0.040 ± 0.6281 for placebo and at 12-months the mean change in endometrial thickness was 0.800 ± 1.6893 across all ospemifene-treated subjects vs. 0.069 ± 1.2290 for placebo. Table 8 provides a summary of the mean change in endometrial thickness for all ospemifene-treated subjects.

Table 8 Summary of Endometrial Thickness at Baseline, 12 Weeks and 12-Months

Evaluation Time Point	**All Ospemifene Groups N = 1229**
Baseline	
N	1221
Mean (SD)	2.121 (0.8164)
12 Weeks	
N	953
Mean (SD)	2.569 (1.3929)
Mean Change	0.469 (1.4058)
12 Months	
N	391
Mean (SD)	2.847 (1.6328)
Mean Change	0.800 (1.6393)

Source: Adapted from NDA 203505, Integrated Summary of Safety - Table 81, page

It is clear to this reviewer that there is a progressive increase in the endometrial thickness in ospemifene treated subjects over time, the degree of which is not demonstrated in placebo subjects. This increase in endometrial thickness supports that ospemifene is having an agonistic or stimulatory effect on the endometrium. In women treated with 60 mg ospemifene in the placebo-controlled trials, 16.6% of subjects with post-baseline endometrial thickness assessments, had an increase in endometrial thickness greater than or equal to 4 mm at any time post baseline, while 8.4% had an increase in endometrial thickness greater than or equal to 5 mm at any time post baseline and 1.1% had an increase in endometrial thickness greater than or equal to 8 mm at any time post baseline. The calculated incidence rate of endometrial thickness ≥ 5 mm for subjects treated 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). This incidence rate is proposed to be included in labeling section 5 WARNINGS AND PRECAUTIONS, Subsection 5.2 Malignant Neoplasms.

Table 9 presents the summary of endometrial histology findings for endometrial biopsy assessments in the double-blind, placebo-controlled studies.

Table 9 Summary of Sponsor-Reported Endometrial Histology from Endometrial Assessment at Baseline, 12 Weeks and 12- Months in Double-Blind, Placebo-Controlled Phase 2/3 Clinical Trials

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 92.5)	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)
- 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

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
- 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)

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).

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

The Sponsor-reported endometrial histology profiles of women treated with 60 mg ospemifene demonstrate a level of proliferation more evident at 12 weeks (1.5% week proliferative, 2.5% active proliferation and 0.6% disordered proliferation) than 1 year (2% week proliferative, 0.3% active proliferation and 0.3% disordered proliferation). The Sponsor reported no cases of endometrial hyperplasia or endometrial carcinoma at 12 weeks or 12 months. However, Dr. van der Vlugt disagreed with the Sponsor's conclusion of no cases of hyperplasia and noted that one subject (Subject 15-50718-0016-0111) 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). This subject had approximately 9-months of OSPHENA 60 mg treatment. Dr. van der Vlugt counted this case in her review. The Sponsor did not count this case because the endometrial biopsy was obtained greater than 2 weeks after the last dose of study drug. 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 subject's endometrial assessment pattern strongly suggests progressive endometrial stimulation. I agree with Dr. van der Vlugt's assessment that this case should be counted and is included in the proposed labeling in section 5 WARNINGS AND PRECAUTIONS, subsection 5.2 Malignant Neoplasms.

Per the Sponsor, in the double-blind, Phase 2/3, placebo controlled studies, 9 subjects with endometrial biopsy sampling available for expert review were reported to have possible uterine polyps (7 subjects received ospemifene and 2 subjects received placebo). Dr. van der Vlugt's review concurs with a total of 6 cases of endometrial polyps (5 in 60 mg ospemifene-treated subjects and 1 in placebo-treated subjects) identified by the Sponsor's expert. The incidence rate for polyps of 5.9 per thousand women for ospemifene 60 mg vs.

1.8 per thousand women for placebo is included in the proposed labeling in section 5 WARNINGS AND PRECAUTIONS, subsection 5.2 Malignant Neoplasms.

One issue with respect to assessment of the endometrial histology in the ospemifene development program is that it was not entirely performed in a manner consistent with the 2003 Draft Clinical Trial Guidance, which 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. In the OSPHENA Phase 3 clinical trials, the 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. The Division believes that the step-wise approach used by the Sponsor, introduces the potential for bias for the evaluation conducted by the third pathologists who must evaluate previously read slides or recut samples. For this reason, the 2003 Draft Clinical Trial Guidance calls for initial reads by three independent evaluators. The Sponsor's evaluation of polyps deviated even more from our guidance. The initial read was made by the local lab, then a central lab and then re-adjudicated by an expert.

Overall, the endometrial histology findings, particularly with respect to the percentage of proliferative type endometrium and endometrial hyperplasia is not unlike the findings seen in the evaluation of very low dose estrogen products. The endometrial histology findings along with the transvaginal ultrasound findings with respect to endometrial thickness for ospemifene are consistent with a stimulatory or estrogen agonistic effect on the endometrium. The Division has taken the approach that unless proven otherwise, very low dose estrogen products and products having agonistic effects on endometrial estrogen receptors would retain estrogen class labeling for the BOXED WARNINGS, WARNINGS AND PRECAUTIONS AND DOSAGE AND ADMINISTRATION sections of labeling to include the use of progestins to reduce the risk of endometrial hyperplasia and adequate endometrial sampling (BOXED WARNINGS and WARNINGS AND PRECAUTIONS only) to assess women with undiagnosed or persistent recurrent abnormal genital bleeding. It is well established that the addition of a progestin to estrogen-alone therapy for 12 to 14 days per month reduces the risk of developing endometrial hyperplasia and endometrial cancer in users of unopposed estrogen. OSPHENA was not studied with a progestin (nor have any of the approved estrogen-alone products been supported by studies with progestin use for approval).

As stated previously, the development of endometrial carcinoma is rarely seen in one or two year clinical trials conducted to support long-term safety of estrogen products and virtually nonexistent. Even endometrial hyperplasia is infrequent in studies up to 2 years for very low dose estrogen products. This reviewer recommends that going forward, the Agency advise Sponsors of low dose estrogen products and estrogen agonist/antagonist products (and any other product that may have direct or indirect influence on the endometrial estrogen receptor) to study the product's effects on the endometrium without and with a progestin in long-term studies of duration substantially greater than the previously recommended standard 1- or 2-year safety study.

9. Advisory Committee Meeting

Advisory Committee input was not sought for the decision on this supplement.

10. Pediatrics

A full pediatric waiver for ages 0-18 was requested by Shionogi Pharmaceuticals with the rationale that the condition (menopause) does not apply to children. DRUP concurs with the Sponsor's assessment. Shionogi's request for a full pediatric waiver for OSPHENA was discussed at the December 05, 2012 Pediatric Research Committee (PeRC)/Pediatric Research Equity Act (PREA) subcommittee meeting. The committee determined that OSPHENA would be granted a full waiver.

11. Other Relevant Regulatory Issues

Inspections by the Office of Scientific Investigations (OSI)

The Division requested an inspection by the 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.

Of the three sites only Dr. Mabey received a FDA form 483 for infractions that included:

Study 15-50301

- Five (5) subjects 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.

Study 15-50821

- One 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.
- One 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." No addendum to the EIR was received. Dr. van der Vlugt determined that Subject 026 should not be excluded, as the deviation did not affect efficacy results.

Financial Disclosure

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. The missing financial disclosure information had no impact on efficacy findings because the Investigator and Sub-Investigators who were involved did not participate in Phase 3 placebo-controlled clinical trials.

Tradename Review

On September 13, 2012, the Division of Medication Error Prevention and Analysis (DMEPA) and the Office of Prescription Drug Promotion concluded that the tradename "OSPHENA" was acceptable.

12. Labeling

Major areas highlighted in the labeling of this product have been identified throughout this review. The Physician's Insert (PI) agreed to by the Agency reviewers [all review disciplines and Safety Endpoints and Labeling Development Team (SEALD)] and the Sponsor is attached to this Review.

The Patient Package Insert (PPI) was reviewed by the Division of Medical Policy Programs (DMPP), DMEPA and DRUP. Internal agreement was reached on the PPI on February 22, 2013 and this version was sent to the Sponsor who concurred on the same day. The agreed to PPI is attached to this review.

ONDQA and DMEPA have accepted the revised container and carton labeling received from the Sponsor on January 24, 2013.

13. Conclusions/Recommendations/Risk Benefit Assessment

I concur with the Biopharmaceutics, Chemistry, Nonclinical Pharmacology, Clinical Pharmacology, Clinical and Statistical Reviewers that NDA 203505 for OSPHENA can receive an Approval action.

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHELLEY R SLAUGHTER
02/25/2013